

Allergic rhinitis — an overview of a common disease

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Abstract

Allergic rhinitis (AR) is the most common chronic disease in childhood and yet is often ignored and/or misdiagnosed. It can present as part of the atopic spectrum of disorders and can affect not only the nose but also its connections, manifesting often with a multiplicity of symptoms, sometimes atypical.

If uncontrolled or inappropriately treated, AR can severely impair quality of life for children and their families. Growing evidence of its association with bronchial asthma is emerging: both as a risk factor for asthma development and a major factor in exacerbations. The use of evidence-based guidelines for AR therapy results in improved disease control.

Management is largely based on avoidance of the triggering allergen(s), the use of modern non-sedative antihistamines for mild disease, and of non-systemically bio-available nasal steroids for moderate/severe disease. Allergen specific immunotherapy, currently recommended for severe cases, is the only treatment modality potentially able to alter long term not only disease severity, but also progression. Immunotherapy is often unavailable to deserving patients and concern regarding risk/benefit and acceptability can hamper its use in children. Evidence on efficacy and safety of the more child-friendly sublingual route of administration is emerging, however further well-designed paediatric studies are needed.

Education of patients, carers and of practitioners in the nature of AR, the possible need for long term concordance with therapy and the optimal use of this is a vital part of disease management.

Keywords allergic rhinitis; diagnosis; immunotherapy; intra-nasal corticosteroids; quality of life; skin prick test; specific IgE; therapy

Introduction

Allergic rhinitis (AR) is the commonest chronic disease of childhood and a major health problem. Its prevalence varies worldwide with the highest levels in developed countries. It affects one in four school children (6–7 year olds) and one in two

teenagers (13–14 year olds). Time trend analysis by phase III of the International Study of Asthma and Allergies in Childhood (ISAAC) has detected a slight continuing worldwide increase in the prevalence of AR. This was most evident in the older children and in countries undergoing rapid socio-economic transition, suggesting that environmental impact on allergy development is not limited to the first few years of life.

The aetiology of AR is multi-factorial with genetic and environmental factors (tobacco smoke, pollution, infections, diet) contributing. In accordance with the concept of the “atopic march” AR often follows atopic dermatitis which manifests in the first few months or years of life. Early childhood eczema may promote subsequent allergen sensitization: malfunctioning of the skin barrier may allow uptake of environmental allergens via skin antigen presenting cells, with subsequent sensitization and thereafter migration of sensitized T-cells to the nose and airway. This has been at least demonstrated in a murine model. Thus early management of eczema may reduce the prevalence of environmental allergen sensitization and prevent subsequent rhinitis and asthma. However AR also occurs *de novo* in children without previous allergic manifestations and sensitization via the nose is a possibility. Local IgE production without evidence of systemic sensitization has been reported.

AR impacts on quality of life

Although not considered a severe disease its impacts on the overall physical and psychological wellbeing of the child is considerable. Family dynamics are also disrupted. Uncontrolled AR has been shown to affect children's quality of sleep impairing daytime concentration and school performance and attendance. In a case-control study conducted in the UK on 1834 15–17 year old students sitting GCSE examinations at the peak of the grass pollen season, pupils who dropped at least one grade in one of the three core subjects (English, Maths and Science) were more likely to have symptomatic AR with an odds ratio of 1.43 when compared to the controls. On-going allergic inflammation significantly reduces Rhinitis Health Related Quality of Life (HRQL) with a direct correlation with allergen exposure.

Symptomatic treatment with older generation sedating antihistamines further hampers examination outcomes and the overall ability of children to learn.

Definition

AR is an inflammatory process affecting the lining of the nose. In sensitized subjects exposure to both outdoor and indoor environmental allergens triggers an immunoglobulin E (IgE) — mediated inflammation characterized by an early and late hypersensitivity response. Histamine is the primary mediator of the early response whilst inflammation involving eosinophils and T-lymphocyte recruitment underlies the late phase response (Figure 1). Local IgE production has been advocated to explain the observation of typical clinical features of AR in a subgroup of patients with no evidence of systemic IgE sensitization. Paediatric studies on this topic are lacking.

Presentation

Classically AR is characterized by anterior or posterior watery rhinorrhoea (causing sniffing), sneezing, nasal blockage (mouth

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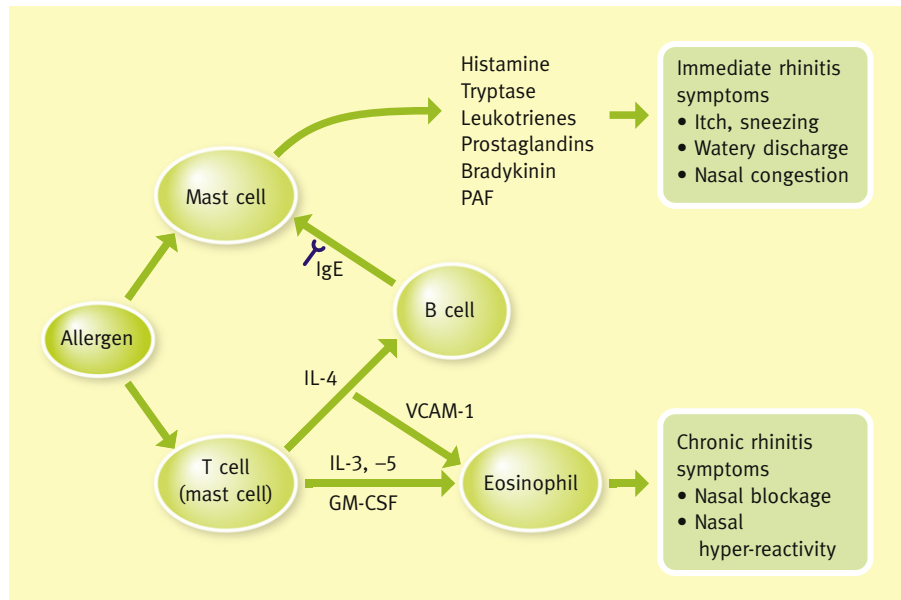


Figure 1 Illustration of the allergic early and late phase hypersensitivity response. Scadding GK et al: Clinical and Experimental Allergy 2008.

breathing) and/or itching, the latter often leads to nose rubbing (the allergic salute). Ocular symptoms are frequently associated, particularly in pollen allergy. They include eye itching, irritability, lacrimation, redness and conjunctival injection with occasional periorbital oedema and, in the most severe cases, corneal involvement (atopic keratoconjunctivitis and vernal keratoconjunctivitis). Allergic shiners (dark eye shadows beneath the lower eye lid), caused by blood and/or fluid accumulation in the infra-orbital groove, are also typical of childhood AR and in a recent study their degree of darkness has been associated with chronicity and severity of disease. Allergic children tend to have an extra skin fold or line under their lower eyelids (Denny–Morgan lines). Frequent throat clearing or hoarseness can be another feature.

The timing of symptoms in relation to allergen exposure (i.e. specific season or animal) is of primary importance as it is typical of AR (Table 1).

Differential diagnosis and co-morbidities

Classical AR is relatively easy to recognize but in children can have a multiplicity of presentations, including via associated co-morbidities. The age of the child can also be relevant to the

disease manifestation. In pre-school children for example nasal blockage and mouth breathing can sometimes be the only presenting symptom and recurrent viral colds and/or adenoidal hypertrophy are frequent misdiagnoses. Upper respiratory tract infections are more frequent in the first few years of life, whilst AR is more common in school children and adolescents (Table 2).

Adenoidal hypertrophy with or without sleep apnoea can often be associated with AR. Otitis media with effusion (OME) and eustachian tube dysfunction can be detected in children with AR. However the exact pathophysiological mechanisms underlining these associations are still poorly understood. In recent years oral allergy syndrome (OAS) has more often been reported by patients suffering with pollen-induced AR. In clinical practice it is not unusual to record a history of oral pruritus and/or local angioedema in response to fresh fruits and vegetables e.g. apples, hazelnuts, carrots, celery, in children presenting with allergic rhinitis, however data are still lacking on the paediatric prevalence of this problem.

Allergic rhinitis and asthma

Asthma is the most commonly associated AR co-morbidity with an increased prevalence in children with allergic and with

Classic signs and symptoms of AR

- Paroxysmal sneezes
- Watery rhinorrhoea
- Nasal itch
- Nasal blockage
- Eye symptoms (itch, irritability, lacrimation, redness and peri-orbital oedema)
- Itchy throat and palate
- Symptoms present on allergen exposure
- Response to antihistamines

Table 1

Type of rhinitis in relation to different ages

Age	Allergic	Infectious	Other
Neonates and infants	+/-	++	++
Pre-school age	++	++	+
School age	+++	++	+
Pre-adolescent	+++	+	+

From Passali D et al: Consensus Conference of Allergic Rhinitis in Children. Allergy (54).

Table 2

non-allergic-rhinitis. AR has been detected in 78% of children with asthma and childhood AR was associated with a 2–7-fold increased risk of asthma in pre-adolescence, adolescence or adult life and a 3-fold risk of asthma persisting into middle age. Bronchial hyper-responsiveness (BHR) and impaired spirometric values have been observed in children with AR. Treatment of AR with pharmacotherapy seems to improve asthma control whilst allergen specific immunotherapy (SIT) for rhinitis may reduce progression to asthma.

Differential diagnosis

It is important to consider rarer conditions that can mimic AR. Primary ciliary dyskinesia (PCD) should be suspected when chronic rhinitis with muco-purulent secretion manifests from birth. Single sided nasal blockage in toddlers, particularly when associated with purulent discharge, can suggest the presence of a foreign body or unilateral choanal atresia (a malformation in which the nasal fossa does not open onto the aero-digestive system). Unilateral watery rhinorrhoea can be secondary to a CSF leak. The detection of nasal polyps in childhood suggests the possibility of cystic fibrosis and should instigate relevant investigations. Hormonal rhinitis can occasionally be detected in adolescents on oral contraceptives.

Classification

The Allergic Rhinitis and its Impact on Asthma working group (ARIA) re-classified AR in relation to symptom severity, duration and impact of disease on life. AR can be thus subdivided in intermittent (symptoms less than 4 days per week or less than 4 weeks) and persistent disease (symptoms more than 4 days per week or more than 4 weeks) and further characterized as mild or moderate/severe (Figure 2). This classification has been recently validated in children through an epidemiological survey involving 1275 children between 6 and 12 years.

The historical classification of AR as seasonal or perennial in relation to triggering environmental allergens is useful in some geographical regions and is important for pollen immunotherapy

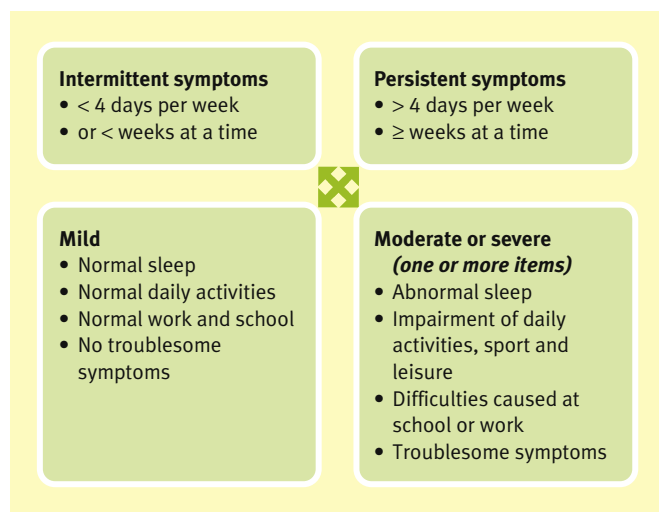


Figure 2 The ARIA classification — in untreated patients. Bousquet J et al: JACI 2001.

and has been maintained additionally in the British Society of Allergy and Clinical Immunology (BSACI) UK classification of AR.

Investigations

Clinical suspicion of an allergic cause for rhinitis can be confirmed by demonstration of IgE sensitization towards a relevant allergen indicated by the history. Skin prick tests (SPTs) to a likely panel of allergens (i.e. mites, relevant pollens, mould spores and pets) can confirm an AR diagnosis. SPTs, which are simple to perform and generally well tolerated in children, are not often available in primary care and cannot be interpreted when children are on regular antihistamines. Alternatively measurement of serum specific IgE can be used — but is more expensive, less immediate and no more sensitive.

These allergy investigations have a high negative predictive value but their specificity is not as high. Sensitization does not always translate to clinically relevant disease and the results should always be interpreted in the light of the clinical history. A recent evolution of specific IgE testing is the ability to measure specific IgE towards the molecular components of an allergen. Being able to understand the exact profile of sensitization in AR sufferers can be useful to discriminate between primary and cross-reactive positivity when contemplating immunotherapy. This is presently available in specific allergy centres only.

Therapy

The aim of AR treatment in children is to provide safe and effective relief of symptoms. There is evidence that outcome is improved when evidence-based guidelines are applied. The ARIA guidelines are currently the most widely used in Europe for AR treatment. A recent revision published in 2010 answers specific paediatric questions. A stepwise therapeutic approach is suggested (Figure 3).

Allergen avoidance is recommended across the spectrum of disease severity. Hay fever sufferers are asymptomatic outside the pollen season, and avoidance of domestic pets shows clear benefits; single interventions for indoor HDM reduction gave equivocal results or lack of benefit. Food allergy rarely causes isolated rhinitis-but can be relevant in small children with additional gastro-intestinal problems, asthma and/or atopic eczema.

New generation non-sedative anti-histamines: are recommended alone for the treatment of mild to moderate AR and can be used in combination with intranasal steroids (INS) when treating moderate to severe disease. Sedating anti-histamines have no place in AR treatment.

Intranasal steroids (INS): are superior to anti-histamines (oral or topical), to anti-leukotrienes and to the combination of anti-histamine and anti-leukotriene in meta-analyses. They are recommended for moderate to severe disease, nonetheless clinicians are often reluctant to use INS in children because of concern re systemic side effects. These concerns are unnecessary when the latest molecules are used as their systemic bioavailability is extremely low. Mometasone furoate (MF) and Fluticasone propionate (FP) have been extensively studied in children and no adverse effects on cortisol levels, the hypothalamic-pituitary-adrenal (HPA) axis or

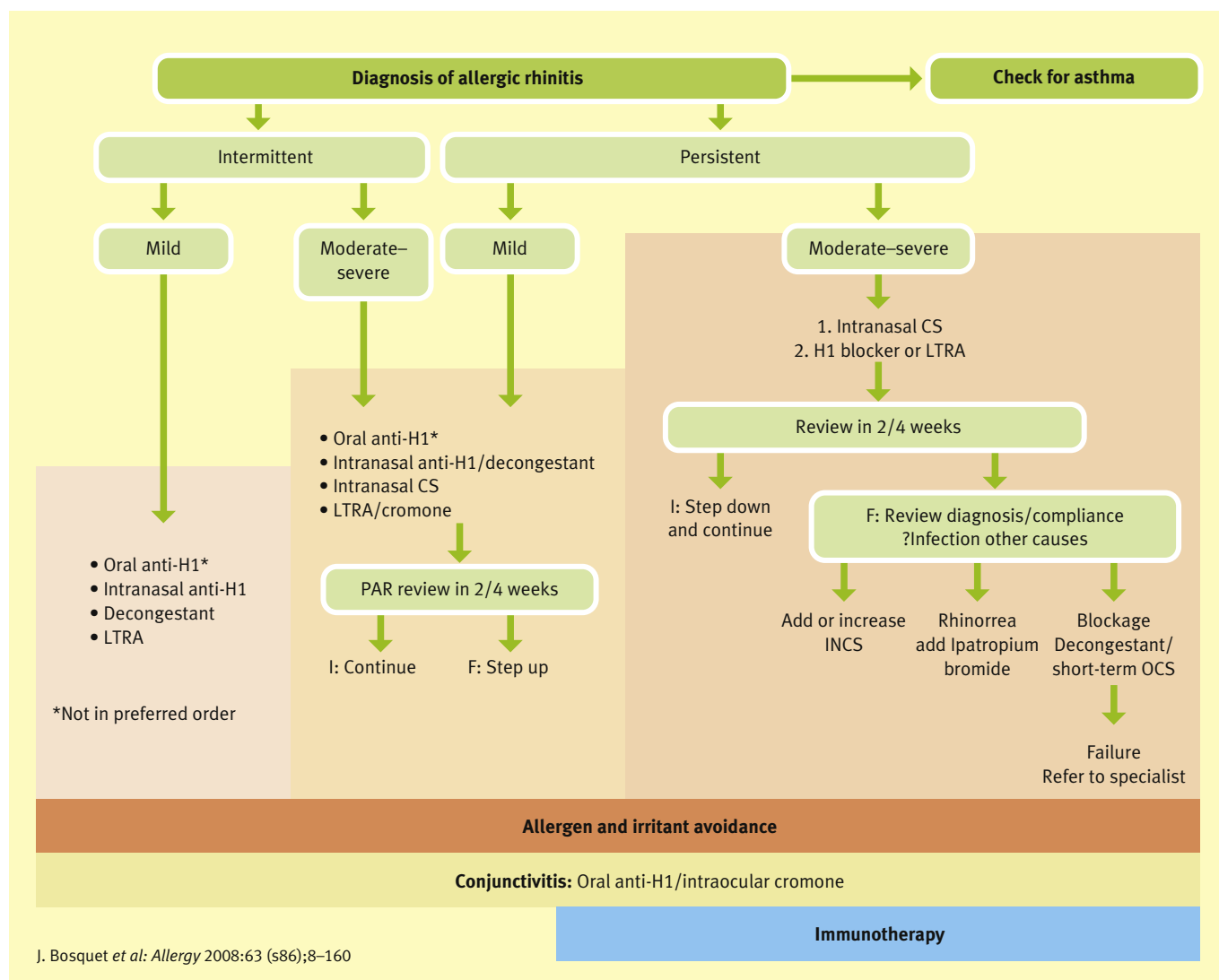


Figure 3 Allergic rhinitis treatment. Adapted and modified from Bousquet et al: *Allergy* 2008.

growth over 1 year have been detected. Fluticasone furoate has similarly low bioavailability (Figure 4).

Nasal biopsies in adults after 1 year of regular use do not show any evidence of mucosal atrophy. INS improve innate immunity via beneficial effects on muco-ciliary clearance, and have shown benefits when used in acute rhinosinusitis, so continuation during URTI is recommended.

INS may reduce ocular symptoms and also bronchial hyper-reactivity, probably by reduction of inflammation-induced neural reflexes. There is some evidence that INS can benefit asthma, but randomized, controlled prospective trials are needed of the addition of long term INS to regular inhaled corticosteroid both for efficacy and safety.

Monitoring of children's growth is a simple and sensitive means of assessing systemic effects of glucocorticosteroids.

Saline douching: this is often omitted by AR guidelines but is effective in reducing symptoms of AR as well as those of rhinosinusitis, where douching is guideline-recommended. Isotonic solutions are well-tolerated, inexpensive, easy to use, with no

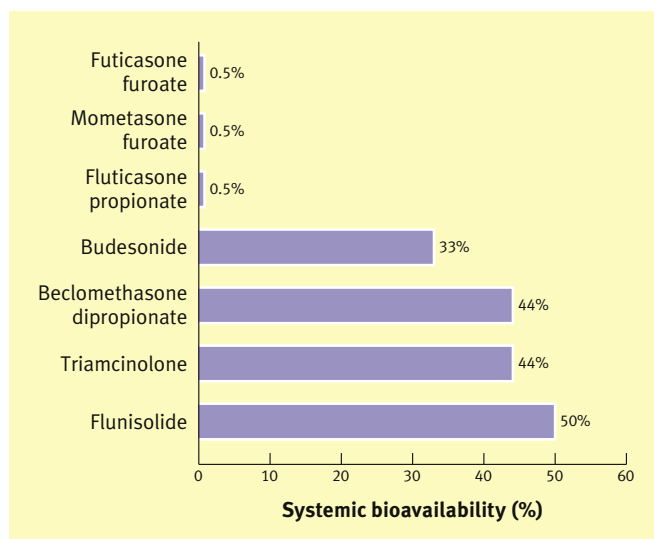


Figure 4 Low systemic bioavailability of newer intranasal steroids.

evidence showing that regular, daily use adversely affects health. Other **complementary therapies** such as homeopathy, acupuncture, butterbur and herbal medicines are not recommended.

Leukotriene receptor antagonists: have shown similar efficacy to anti-histamines, with slightly greater efficacy when the two were combined. ARIA 2010 recommends the use of anti-leukotrienes in children with seasonal AR and in pre-school children with persistent AR. Their use is also suggested in children with AR and concomitant asthma where concerns exist about the use of glucocorticoids.

Allergen specific immunotherapy (SIT)

This is at present recommended for severe AR uncontrolled by pharmacotherapy. Good evidence exists of its ability to reduce symptom severity in pollen-induced paediatric AR.

SIT can be administered either via the subcutaneous or the sublingual route. In Europe at present only 1–5% of children suffering with AR are treated with SIT: 75% receiving Subcutaneous Immunotherapy (SCIT) and 25% Sublingual Immunotherapy (SLIT).

Treatment benefit must always be carefully weighed against risks. A recent review shows efficacy of SCIT, with an effect size which is higher in those studies where adolescents were included and confirms a very low incidence of severe adverse reactions. No fatal events were reported. However the vaccines were delivered in a carefully controlled 'study' environment and in appropriately selected patients. Adrenaline use was reported in 13 studies (0.13% of the 14,085 injections given), a reminder that SCIT is still not completely risk free.

SLIT in children has been recently reviewed and efficacy in hay fever reported, whereas data on HDM desensitization is non-concordant. Local oral reactions are common and usually transient, systemic reactions occasionally occur but no fatalities have been reported. A meta-analysis of 49 SLIT studies, including 15 paediatric ones with over 1400 children, again suggests a higher effect size in the paediatric group.

SIT is the only therapeutic modality that has a disease modifying effect not only during the treatment period but also in subsequent years. Moreover it is possibly able to prevent new sensitizations and the progression of rhinitis to asthma. The landmark randomized prospective 10 year Prevention of Asthma Study (PAT) demonstrated that new asthma was reduced in the children receiving SCIT for hay fever, compared to those treated by pharmacotherapy alone – but has been criticized for being un-blinded. There is an on-going trial of the effectiveness of grass pollen SLIT in the prevention of asthma.

Conclusion

Allergic Rhinitis (AR) can sometimes be unresponsive to treatment, leading to troublesome symptoms and impacting on daily activities and quality of life. It is important to consider the possible causes for such difficult-to-treat cases. Firstly, adherence to therapy must be checked as poor concordance leads to treatment failure. Providing written guidance in the form of information leaflets on specific allergen avoidance, the correct technique in the application of nasal preparations and explanation of potential side effects is often helpful. Clear written

treatment plans are a useful tool, particularly when several preparations are simultaneously prescribed. AR can sometimes co-present in association with other forms of rhinitis (or rhinosinusitis) leading to increased severity. Associated co-morbidities should be considered in the differential diagnosis in order to determine the most appropriate therapeutic approach. For patients with difficult to control allergic disease allergen specific immunotherapy should be considered. Grade A evidence via meta-analysis confirms the efficacy of both subcutaneous and sublingual immunotherapy which is the only treatment modality with the ability to alter the long-term course of the disease. ♦

FURTHER READING

- 1 Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008 Apr; **63**(suppl 86): 8–160.
- 2 Ait-Khaled N, Pearce N, Anderson HR, Ellwood P, Montefort S, Shah J. 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 Jan; **64**: 123–48.
- 3 van den Oord RA, Sheikh A. Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis. *BMJ* 2009; **339**: b2433.
- 4 Almqvist C, Li Q, Britton WJ, et al. Early predictors for developing allergic disease and asthma: examining separate steps in the 'allergic march'. *Clin Exp Allergy* 2007 Sep; **37**: 1296–302.
- 5 Rondon C, Canto G, Blanca M. Local allergic rhinitis: a new entity, characterization and further studies. *Curr Opin Allergy Clin Immunol* 2010 Feb; **10**: 1–7.
- 6 Meltzer EO, Blaiss MS, Derebery MJ, et al. Burden of allergic rhinitis: results from the Pediatric Allergies in America survey. *J Allergy Clin Immunol* 2009 Sep; **124**(3 Suppl): S43–70.
- 7 Blaiss MS. Allergic rhinitis and impairment issues in schoolchildren: a consensus report. *Curr Med Res Opin* 2004 Dec; **20**: 1937–52.
- 8 Juniper EF, Guyatt GH, Dolovich J. Assessment of quality of life in adolescents with allergic rhinoconjunctivitis: development and testing of a questionnaire for clinical trials. *J Allergy Clin Immunol* 1994 Feb; **93**: 413–23.
- 9 Santos CB, Pratt EL, Hanks C, McCann J, Craig TJ. Allergic rhinitis and its effect on sleep, fatigue, and daytime somnolence. *Ann Allergy Asthma Immunol* 2006 Nov; **97**: 579–86.
- 10 Walker S, Khan-Wasti S, Fletcher M, Cullinan P, Harris J, Sheikh A. Seasonal allergic rhinitis is associated with a detrimental effect on examination performance in United Kingdom teenagers: case-control study. *J Allergy Clin Immunol* 2007 Aug; **120**: 381–7.
- 11 Roberts G, Mylonopoulou M, Hurley C, Lack G. Impairment in quality of life is directly related to the level of allergen exposure and allergic airway inflammation. *Clin Exp Allergy* 2005 Oct; **35**: 1295–300.
- 12 Vuurman EF, van Veggel LM, Uiterwijk MM, Leutner D, O'Hanlon JF. Seasonal allergic rhinitis and antihistamine effects on children's learning. *Ann Allergy* 1993 Aug; **71**: 121–6.
- 13 Scadding GK, Durham SR, Mirakian R, et al. BSACI guidelines for the management of allergic and non-allergic rhinitis. *Clin Exp Allergy* 2008 Jan; **38**: 19–42.
- 14 Durham SR, Gould HJ, Hamid QA. Local IgE production in nasal allergy. *Int Arch Allergy Immunol* 1997 May; **113**: 128–30.

- 15 Greiner AN, Hellings PW, Rotiroti G, Scadding GK. Allergic rhinitis. *Lancet* 2011 Dec 17; **378**: 2112–22.
- 16 Bertelsen RJ, Carlsen KC, Carlsen KH. Rhinitis in children: co-morbidities and phenotypes. *Pediatr Allergy Immunol* 2010 Jun; **21**(4 Pt 1): 612–22.
- 17 Bozkurt MK, Bozkurt B, Artac H, Arslan N, Reisli I. Vernal keratoconjunctivitis—a rare but serious comorbidity of allergic rhinitis and eustachian tube dysfunction. *Int J Pediatr Otorhinolaryngol* 2010 Jan; **74**: 60–3.
- 18 Chawes BL, Bonnelykke K, Kreiner-Moller E, Bisgaard H. Children with allergic and nonallergic rhinitis have a similar risk of asthma. *J Allergy Clin Immunol* 2010 Sep; **126**: 567–73.
- 19 Masuda S, Fujisawa T, Katsumata H, Atsuta J, Iguchi K. High prevalence and young onset of allergic rhinitis in children with bronchial asthma. *Pediatr Allergy Immunol* 2008 Sep; **19**: 517–22.
- 20 Burgess JA, Walters EH, Byrnes GB, et al. Childhood allergic rhinitis predicts asthma incidence and persistence to middle age: a longitudinal study. *J Allergy Clin Immunol* 2007 Oct; **120**: 863–9.
- 21 Jacobsen L, Niggemann B, Dreborg S, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy* 2007 Aug; **62**: 943–8.
- 22 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 Sep; **126**: 466–76.
- 23 Bufe A, Roberts G. Specific immunotherapy in children. *Clin Exp Allergy* 2011 Sep; **41**: 1256–62.
- 24 Larenas-Linnemann D. Sublingual immunotherapy in children: complete and updated review supporting evidence of effect. *Curr Opin Allergy Clin Immunol* 2009 Apr; **9**: 168–76.
- 25 Radulovic S, Calderon MA, Wilson D, Durham S. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst Rev* 2010. Issue 12. Art. No.:CD002893.

Practice points

- Allergic rhinitis (AR) is an IgE-mediated inflammation of the nasal mucosa characterized by nasal itching, sneezing, obstruction and rhinorrhoea. Association with other allergic diseases is often seen
- Diagnosis is based on a comprehensive clinical history, including targeted questions to ascertain the presence of possible related co-morbidities, and thorough clinical examination. This is supported by positive skin prick tests and/or serum specific IgE which corroborates the history
- Although often considered merely a nuisance, evidence exists that uncontrolled AR severely impacts on children's sleep, psychological/physical wellbeing and academic performance
- AR appropriate treatment improves symptoms and co-morbidities with optimal results when guidelines are applied