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# Inhalant Allergies in Children

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## KEYWORDS

- Pediatric allergy • Allergies in children • Allergic rhinitis
- Childhood asthma • Otitis • Inhalant allergy

Most otolaryngologists see pediatric patients and treat disorders associated with chronic upper respiratory inflammation (rhinitis, otitis, pharyngitis, and laryngitis) as a routine part of their practice. In 2009, otolaryngologists were surveyed by telephone as part of the Pediatric Allergies in America Survey. Otolaryngologists estimated that they saw 43 patients aged 4 to 17 years per week and that 41% were diagnosed with AR.<sup>1</sup> Pillsbury and colleagues<sup>2</sup> noted that AR was the most common International Classification of Diseases-9 code used by otolaryngologists in a workforce study conducted in 2000. Because allergy is a common contributor of upper airway inflammation, a working knowledge of pediatric allergy is beneficial in the evaluation and treatment of children presenting to otolaryngologists. Upper and lower airway inflammation is linked epidemiologically and physiologically.<sup>3</sup> Therefore, considering and appropriately identifying coexisting lower respiratory inflammation (eg, asthma) is also logical. Identifying asthma in otolaryngology patients is especially compelling because unmanaged asthma impairs quality of life and can be fatal. It is also likely that asthma is underdiagnosed and undertreated.<sup>4</sup> This article informs the otolaryngologist about the development, manifestations, and treatment of allergy in pediatric patients.

## GENETICS

Atopy is the predisposition to develop allergic diseases. The phenotype of allergy seems to have a complicated and variable genetic contribution. Gene-environment interactions have been identified,<sup>5</sup> and add another layer of variability to the development of allergic disease. There is no single genetic test to identify if an individual is likely to be atopic. Genetic studies looking at single nucleotide polymorphism have

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focused primarily on allergic inflammatory cells and mediators. Although hundreds of associations have been identified, each alone tends to be difficult to reproduce or represents only a small percentage of allergic individuals.<sup>6</sup> Large genome-wide association studies use a hypothesis-independent strategy to identify which genes are statistically different between an affected and nonaffected population. In asthma, genome-wide association studies have identified a small number of genes, such as *ORMDL3*,<sup>7,8</sup> of which the functions remain unclear. Currently, the allergy phenotype probably represents multiple and variable combinations of genetic predispositions many of which require a specific environmental interaction to be manifested. So far, the genes identified suggest alterations in both innate and adaptive immunity play a significant role in allergic disease.<sup>9</sup>

As suggested by the complicated genetics, family history of allergy is a risk factor, but inheritance does not follow a simple pattern. For AR, family history of atopy is one of several risk factors that include cigarette exposure; higher socioeconomic class; first-born or only child; and elevated total IgE (>100 IU/L) before age 6 years.<sup>10</sup> In the Danish twin study of asthma by Skadhauge and coworkers,<sup>11</sup> the proband-wise concordance of monozygotic males to develop asthma was 0.51 (0.39–0.63), whereas dizygotic opposite sex twins was only 0.07 (0.03–0.11). Another study showed that of those with one asthmatic parent, 26% developed asthma. Of note, maternal history was more predictive.<sup>12</sup> Although not definitive, asking about allergies in first-degree relatives is useful in the evaluation of a child with chronic upper or lower respiratory inflammation.

## IN UTERO

There have been multiple studies investigating if variables in pregnancy affect the later development of allergies including the time of year the child is born, maternal diet, or route of delivery. One study suggested that North American children born in the late fall have a higher risk of developing asthma.<sup>13</sup> This is attributed to the role of winter respiratory viruses, such as respiratory syncytial virus, occurring in the first few months of life increasing the risk of asthma. However, the authors are not aware of any recommendations advising timing of pregnancy based on allergy risk because studies are conflicting and the overall evidence insufficient. Restricting maternal diet in pregnancy from proallergic foods has been shown not to affect the development of atopy in the child.<sup>14</sup> Some studies have shown some protection from atopy in children delivered vaginally compared with those delivered by cesarean section.<sup>15</sup> The affect is attributed to the “hygiene hypothesis,” which is discussed later. IgE in cord blood has also been of interest. Nonspecific IgE is produced in utero starting around 11 weeks gestation, but specific IgE is first identified after birth. Initial reports of IgE levels in cord blood predicting atopy have not been supported in later prospective studies.<sup>16</sup>

Difficulties in identifying children at high risk for allergy beyond parental allergic history complicates research aimed at attempting to prevent the development of allergic disease.

## INFANCY: 0 TO 2 YEARS

Although inhalant allergy is not prevalent during the first 2 years of life, there are clues in infancy as to the risk of later developing inhalant allergic disease. Knowledge of these risk factors can be useful when trying to determine if an older child's rhinitis may be allergic. Many studies have also examined if there are ways to prevent or

reduce the development of allergic disease in children. A basic knowledge of the infant's developing immune system places the risk factors context.

In the atopic child, the bias of the immune system toward an allergic response is at least partially influenced by lymphocytes. Attention has been focused on T-helper cell lymphocytes because they direct much of the immunologic response to antigens. Stimulated T-helper lymphocytes produce different cytokine profiles that are broadly classified as Th1 or Th2 (a Th3 phenotype has also been described).<sup>17,18</sup> Th1 cytokines primarily influence the immune system to act against bacteria and include interleukin (IL)-2 and interferon- $\gamma$ . Th2 cytokines direct activity more appropriate toward parasites. The Th2 influence toward IgE and eosinophils also occurs in allergic inflammation. Th2 cytokines include IL-4, IL-5, and IL-13. At birth, T-helper lymphocytes are Th2 biased (or allergy biased), and as the immune system develops the T-helper cells change to a Th1 bias. The "hygiene hypothesis" suggests that challenges to the immune system early in life facilitate the shift to a Th1 bias, which protects against allergy. Infections early in life,<sup>19</sup> or increased risk of infections represented by exposure to siblings or by early entry into daycare,<sup>20</sup> have been associated with a decreased risk of later developing allergic disease. Some studies of T lymphocytes from infants at high risk for atopy have shown not only bias toward Th2, but also a decreased production of both Th1 and Th2 cytokines. It may be that the greater reduction of stimulated Th1 cytokines accounts for most of the imbalance compared with controls.<sup>21</sup> Paradoxically, as infancy has become more sanitized in developed countries, atopy has become more prevalent. The reason for the increase in allergy is likely to be more complicated than the "hygiene hypothesis" alone and multiple competing theories from changes in exposures, to nutrition, to air pollution exist.

Manifestations of allergy in infancy include food allergy and atopic dermatitis, which are both risk factors for the later development of inhalant allergy. Food allergy is commonly seen in infants and is frequently the first identifier of the atopic child.<sup>22</sup> Ten percent of 1 year olds have an elevated IgE to a food, most commonly milk or egg.<sup>23</sup> Infants with milk or egg food allergy are at increased risk for developing AR and asthma.<sup>23,24</sup> Atopic dermatitis is another marker of atopy in infancy. Atopic dermatitis in infancy frequently presents as pruritic eczema of the cheeks and flexural surfaces of the elbows and knees. Infants with atopic dermatitis have a 30% risk of developing asthma and a 35% risk of developing AR.<sup>25,26</sup>

Early sensitization to inhalant allergies in infancy occurs, but infrequently. Herr and colleagues<sup>27</sup> used a standardized questionnaire in 1850 infants at their 18th-month examination to identify children with AR-like symptoms defined as runny nose, blocked nose, and sneezing apart from a cold. Of the 1850 infants, 9.1% were found to have AR-like symptoms. All children were then assessed with a specific inhalant IgE screen, total IgE, and eosinophilia. There was no difference in eosinophilia or total IgE in the "AR-like symptoms" group compared with the "no AR-like symptoms" group. Inhalant-specific IgE was elevated in 5.5% with AR-like symptoms versus 2.7% ( $P = .04$ ) of those without symptoms. However, the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines include both specific IgE sensitization and symptoms in the definition of AR.<sup>28</sup> Only 9 of the 1850 children had both AR-like symptoms and elevated inhalant-specific IgE. In comparison, there were 43 of 1850 infants with elevated inhalant-specific IgE that were identified in the "no AR-like symptoms group." This suggests that AR is rare at 18 months of age and that screening infants for elevated specific IgE would lack specificity in identifying infants with clinical symptoms. Of interest, five of the nine infants with both AR-like symptoms and inhalant-specific IgE elevation were sensitized to dust mite.<sup>28</sup> Although AR is uncommon in infancy, viral rhinitis is prevalent. Children less than 6 years old average six to eight

“colds” annually with symptoms lasting 10–14 days.<sup>29</sup> Rhinovirus accounted for 46% of childhood upper respiratory infections in one study.<sup>30</sup> Distinguishing between AR and viral rhinitis is clinically significant because a physician might reasonably treat an infant with AR with antihistamines, but antihistamines have been demonstrated as ineffective compared with placebo in viral rhinitis.<sup>31</sup>

Lower respiratory inflammation in infants has a similar clinical dilemma in differentiating viral bronchiolitis from asthma. Viral bronchiolitis (wheezing and tachypnea) accounts for outpatient visits in 15% of infants and 3% are hospitalized.<sup>32</sup> The common causes include respiratory syncytial virus, rhinovirus, metapneumovirus, and coronaviruses. Viral-triggered asthma and bronchiolitis are difficult to distinguish from each other, but viral-triggered asthma tends to occur in children who have multiple wheezing episodes, are older than 2 years, and have a family history of atopy.<sup>33</sup> Once children are older than 2 years, an association between viral-induced wheezing and asthma risks (elevation in inhalant-specific IgE, maternal asthma history) becomes significant.<sup>34</sup> The clinical distinction between bronchiolitis and asthma affects pharmacologic treatment. Although bronchodilators and corticosteroids are mainstays of asthma treatment, neither bronchodilators<sup>35,36</sup> nor corticosteroids<sup>37</sup> have been shown to be effective in uncomplicated viral bronchiolitis (discussed later).

Attenuating the development of allergy through environmental manipulation has not been very successful. A substantial number of studies have investigated restriction of food antigens or environmental controls to prevent inhalant sensitization, but these have yielded conflicting and often paradoxical results.

Because food allergy is frequently the first allergic manifestation in the atopic child and the prevalence of food allergy is increasing, multiple studies have investigated if restricting allergenic foods (eg, peanut products) from the infant’s diet would reduce the development of allergic disease. Dietary avoidance of highly allergenic foods was supported by a 1990 study of 1200 infants that correlated the number of solid foods introduced by age 4 months with eczema at age 10 years.<sup>38</sup> However, dietary antigen avoidance has not proved to be effective in most studies and a 2008 review in *Pediatrics* states, “for infants at high risk of developing atopic disease, there is evidence that exclusive breastfeeding for at least 4 months compared with feeding intact cow milk protein formula decreases the cumulative incidence of atopic dermatitis and cow milk allergy in the first 2 years of life.”<sup>39</sup> Beyond this, whether exposure to antigenic foods early in life promotes sensitization or tolerance is unclear.

The effect of breastfeeding in the development of asthma is controversial and studies conflict.<sup>39</sup> In a large cohort, breastfeeding seemed to reduce wheezing episodes in children less than 4 years, but in infants who had a family history of maternal asthma breastfeeding increased the risk of developing asthma after age 6 years.<sup>39,40</sup> However, a 2009 ISAAC II study of 54,000 children found no association between breastfeeding and allergy.<sup>41</sup> This type of disparity between study results is common in research examining the development of atopic diseases, but perhaps not unexpected given allergy’s complicated genetics and multiple environmental influences.

Preventing the development of inhalant allergies with environmental modifications has also yielded inconsistent results. Studies have looked at whether cat exposure in infancy might increase the risk of allergic sensitization to cat. In Sweden, most children with allergic asthma are sensitized to cat. Unexpectedly, a large study reported that having a cat in the home during infancy was associated with a decreased risk of developing asthma.<sup>42</sup> However, the influence of cat exposure seems to be opposite in high-risk groups. In a high-risk population defined by maternal asthma, having a cat in the home during infancy was associated with an increased risk of asthma.<sup>43</sup> Attempts to reduce house dust mite exposure to prevent atopic disease in high-risk infants have

yielded mixed results.<sup>44,45</sup> In the Manchester Asthma and Allergy Study wheezing was reduced with early intervention against dust mites.<sup>44</sup> The Isle of Wight study also found dust mite precautions reduced the development of allergy and asthma.<sup>46–48</sup> However, three other large studies showed no effect: the PIAMA study in the Netherlands,<sup>49</sup> the SPACE study in Europe,<sup>45</sup> and the CAPS study in Australia.<sup>50</sup>

Effective interventions to prevent development of allergic disease seem to vary by geographic location, ethnicity, socioeconomic class, and risk factors. Genetic tests may one day identify populations where allergic risk and effective prevention strategies are better matched.

Although preventing allergy through environmental control has shown mixed results, two controlled studies have shown that treating young children who have atopic dermatitis with antihistamines decreases the risk of developing asthma. Bustos and colleagues<sup>51</sup> treated children with atopic dermatitis, age 1 to 36 months, with daily antihistamine in a randomized, placebo-controlled trial. They reported 25% fewer diagnoses of asthma in the antihistamine group. The ETAC study treated 817 atopic dermatitis infants with either placebo or cetirizine. Fifty percent developed asthma in the control group, but 25% less in the cetirizine group when they had sensitization to dust or grass.<sup>52</sup>

Infants with food allergy or atopic dermatitis are at risk for later developing inhalant allergies, but inhalant allergies are uncommon in infancy. Successful prevention of inhalant allergy has remained elusive, but treating atopic dermatitis with antihistamines may have a modest but significant benefit. Asking about a family history of allergies, food allergy, and atopic dermatitis is likely helpful when considering if allergies contribute to upper or lower respiratory inflammation encountered in the older child.

## CHILDHOOD: 2 TO 17 YEARS

Inhalant allergy sensitivities generally develop after the third birthday.<sup>23</sup> There is rarely a need to test for allergies in children less than 4 years of age. Total and specific IgE increases rapidly in children from 3 to 6 years and peaks in the teenage years.<sup>23</sup> Prevalence and spectrum of inhalant IgE sensitization increase with age. Allergies in children play a well-defined role in nasal and conjunctival inflammation. However, the role of allergy in adenoid hypertrophy and eustachian tube function is less clear. For this section, allergic disease is separated by the different anatomic sites.

### *Upper Airway Inflammation and Allergies*

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#### *Allergic rhinitis*

AR is defined by the ARIA guidelines of 2008 as a chronic disorder of the upper airways that is induced by IgE-mediated inflammation after exposure of the nasal membranes in sensitized patients to a specific allergen.<sup>27</sup> The symptoms include nasal congestion, rhinorrhea, sneezing, nasal itching, and postnasal drainage.

AR has been traditionally categorized as seasonal or perennial depending on allergen sensitivity. The more recent ARIA guidelines of the World Health Organization include a classification that uses duration of symptoms and impact on quality-of-life parameters.<sup>53</sup> The duration of symptoms is either “intermittent” (symptoms for <4 days per week or for a duration of <4 weeks per year) or “persistent” (symptoms that occur >4 days per week and are present for >4 weeks per year). The effect on quality of life is subdivided into either “mild disease” (no impairment of daily activities, no sleep interruption, and no troublesome symptoms) or “moderate to severe disease” (one or more of the previously mentioned symptoms). Other guidelines (and the Food and Drug Administration [FDA]) divide AR into seasonal and perennial.<sup>54</sup>

AR is estimated to affect 60 million people in the United States, and its prevalence is increasing.<sup>55</sup> The prevalence of AR in children is possibly as high as 40%,<sup>56</sup> making it the most common chronic disease in the pediatric population. However, whether AR is self-described, physician diagnosed, or includes allergy testing affects the reported incidence and prevalence.<sup>27</sup> Additionally, there is profound geographic variability.<sup>57</sup> Most individuals develop symptoms of AR before 20 years of age, with 40% of patients becoming symptomatic by age 6 years. In adults diagnosed with AR, 40% have perennial AR and 20% have seasonal AR; an additional 40% have perennial AR with seasonal flare-ups.<sup>10</sup>

The recently published Pediatric Allergies in America Survey suggests that children are more likely to have seasonal allergies compared with perennial AR.<sup>1</sup> The most common triggers of nasal symptoms in the allergic children were pollen, dust, and animal dander. The single most frequently experienced nasal allergy symptom reported by parents was nasal congestion (52%), which was said to occur either every day (25%) or most days (27%) each week during their children's worst month for allergy symptoms. In addition to parental responses, the children 10 to 17 years of age were asked which nasal allergy symptoms they experienced every day or most days during their worst allergy month in the past year. Nasal congestion or stuffed-up nose (39%), repeated sneezing (36%), runny nose (35%), and watering eyes (20%) were frequently reported as occurring either every day or on most days of the worst month.<sup>1</sup>

Although AR is not life-threatening, it can be associated with significant morbidity through loss of productivity,<sup>58</sup> cognitive functioning,<sup>59</sup> missed school,<sup>60</sup> and impaired quality of life.<sup>61</sup> Many of these health-related quality-of-life issues seem to stem in part from sleep disturbances associated with AR.<sup>62</sup> In addition to impaired quality of life that AR elicits in patients, it can have a substantial economic impact including both direct costs to patients and indirect costs that include patient absenteeism and inefficient performance at school.<sup>60</sup> Walker and colleagues<sup>63</sup> compared national examination test performance in winter (practice) and summer (final) in grass-allergic and nonallergic students. Compared with controls, grass-allergic students were found to have a significantly increased risk to unexpectedly fail a test section in the summer (grass pollen season) that they had previously passed in the winter.

The diagnosis of AR in children is based on clinical evaluation and allergy testing. Allergy testing in the absence of clinical likelihood of allergic disease yields unacceptable false-positive rates illustrated by a positive skin prick test in 53.9% of 10,509 Americans randomly sampled in Third National Health and Nutrition Survey.<sup>64</sup>

The differential diagnosis of AR in children differs from adults. Children are more likely to have adenoid hypertrophy, nasal foreign body, or choanal atresia contributing to their nasal obstruction than adults. Polyps, deviated septum, and neoplasia are more likely causes of nasal obstruction in adults than children.

Treatment of AR in children is similar to adults.<sup>27</sup> Environmental control, pharmacologic therapy, and desensitization are the three main options for treating AR.

Although counseling about environmental control of AR is recommended, clinical efficacy in controlled studies is often disappointing. Terreehorst and colleagues<sup>65</sup> performed a randomized placebo-control trial of dust mite mattress covers in 279 subjects allergic to dust mite. Although they did demonstrate decrease in dust mite counts, no clinical improvement in AR was detected between the groups. A recent Cochrane review suggested an extensive bedroom-based program including acaricides may "be of some benefit" in AR symptoms.<sup>66</sup>

Pharmacotherapy for AR consists of antihistamines, decongestants, intranasal corticosteroids, and leukotriene antagonists. The use of first-generation antihistamines

should be limited in children because of drowsiness, impaired learning,<sup>67</sup> and paradoxical hyperactivity. Pediatric formulations of second-generation antihistamines are found in **Table 1**, and although appropriate for allergy they have not shown benefit in viral rhinitis or otitis media. Topical antihistamines have indications starting at age 5 years for azelastine and age 6 years for olopatadine but compliance in children can be hampered by taste in the authors' experience. Decongestants and over-the-counter cough and cold preparations are not currently recommended in children under 2 years of age because of lack of proved efficacy and an association with rare cardiac fatalities in infants.<sup>68,69</sup>

Intranasal corticosteroids are indicated down to age 2 years. Concerns of reduced growth and adrenal axis suppression have led to differences in the lowest indicated age listed for different steroid molecules (**Table 2**). Paired papers published in *Pediatrics* in 2000 measured a 0.9-cm reduction in annual height gained with intranasal beclomethasone<sup>70</sup> and no difference in height with intranasal mometasone.<sup>71</sup> The FDA has recommended using the lowest effective dose and monitoring growth in children when prescribing intranasal steroids. Nasal steroids seem to reduce adenoid size and can be considered for moderate adenoid hypertrophy. However, it is unclear how long the nasal steroids have to be maintained to sustain the reduced adenoid size.<sup>72</sup> Other allergy medications for children include pseudoephedrine, chromolyn, ipratropium, and montelukast (**Table 3**). Montelukast is indicated for perennial AR in children down to age 6 months and may also have a beneficial effect on lower respiratory inflammation.

Desensitization by subcutaneous immunotherapy in children has been shown to be effective.<sup>73,74</sup> Risk, time, and expense of subcutaneous immunotherapy needs to be carefully matched to severity and ability to control allergic disease. Desensitization is unique in its beneficial effect on allergies after the treatment is discontinued, its affect on reducing additional sensitizations, and reduction in the development of allergic asthma.<sup>73</sup> Data on sublingual immunotherapy in children have been less convincing than adults. Roder and colleagues<sup>74</sup> published a systematic review of sublingual immunotherapy in children that identified seven high methodologic studies of which only one of seven showed efficacy. However, in 2009 and 2010 three large studies showed statistical results for sublingual immunotherapy for grass (**Table 4**).<sup>75-77</sup> Each of these three studies showed similar percentages of symptom

**Table 1**  
Second-generation antihistamines available for children in 2010

Second Generation		
Antihistamine	Formulations	Dose by Age
Cetirizine	5 mg/5 mL, 5- or 10-mg tablets	2-5 y, 2.5-5 mg 6-10 y, 5-10 mg
Fexofenadine	6 mg/mL, 30 ODT, 30, 60, 180	2-11 y, 30 mg/5mL bid ≥12 y, 60 mg bid or 180 mg qd
Loratadine	1 mg/mL, 5-mg chewable, 10 ODT	2-5 y, 5 mg daily (1 mg/mL) ≥6 y, 10 mg daily
Levocetirizine	2.5 mg/5 mL, 5-mg tablets	2-5 y, 1.25 po q AM 6-11, 2.5 mg po q AM >12 y, 2.5 to 5 mg po q AM
Desoradatine	0.5 mg/mL	6-11 mo, 1 mg daily 1-5 y, 1.25 mg 6-11 y, 2.5 mg daily >12 y, 5 mg po qd



<b>Table 2</b> Intranasal corticosteroids by age of FDA approval	
<b>Ages by FDA Approval</b>	<b>Intranasal Corticosteroid</b>
Age 2 y and older	Mometasone Fluticasone furoate
Age 4 y and older	Fluticasone prorionate
Age 6 y and older	Budesonide Triamcinolone Flunisolide Beclomethasone

improvement, strong placebo effects in the control groups, and promising safety profiles. Sublingual immunotherapy has not yet been FDA approved April 2011.

### **Allergic conjunctivitis**

Although ocular disease is not part of the respiratory system, the overlap between AR and allergic conjunctivitis is so great that it is often considered one disease: rhinoconjunctivitis. Bielory<sup>78</sup> summarizes several epidemiologic studies to estimate that there is 80% overlap, with 10% having AR alone and 10% having allergic conjunctivitis alone. The large ISAAC studies looked at rhinoconjunctivitis as single diagnosis and reported symptoms in 8.5% of 6 to 7 year olds and 14.6% in 13 to 14 year olds.<sup>57,79</sup> As such, children with AR should be assessed for allergic conjunctivitis and topical antihistamine or cromolyn eye drops considered.

### **Allergy and ear disease**

The relationship between otitis media and allergy has been the focus of several studies with a discrepancy of findings<sup>80</sup> suggesting either large regional differences or bias in associating otitis and allergic disease. The relationship between allergy and otitis media likely varies with the age of the children studied. In the authors' experience, inhalant allergy plays a smaller role in acute recurrent otitis media during infancy compared with chronic otitis media with effusion in 5- or 6-year-old children, especially when there is no infant history of eustachian tube dysfunction.

There is very little evidence that acute recurrent otitis media in infancy is associated with inhalant allergies. In 3549 case-controlled pairs, no increased risk of AR at age 6

<b>Table 3</b> Nonsteroidal, nonantihistamine allergy medications by age and dose	
<b>Other Allergy Medications</b>	<b>Dose by Age</b>
Pseudoephedrine	2–5 y, 15 mg q 6 h 6–12 y, 30 mg q 6 h
Cromolyn nasal spray (over the counter)	2 y and older
Ipratropium nasal spray	0.03% of 0.06%, 2 sprays q nostril 2–4 times per d 5 y and older for SAR
Montelukast	6–23 mo, 4 mg qd, granules 2–5 y, 4 mg qd, granules or chewables 6–14 y, 5 mg qd, chewables PAR age ≥6 mo Asthma age ≥12 mo SAR age ≥2 y

*Abbreviations:* Asthma, asthma maintenance; PAR, perennial allergic rhinitis; SAR, seasonal allergic rhinitis.

**Table 4**  
**Mean reduction in symptom scores of three grass sublingual preparations in three recent double-blind placebo-controlled trials**

Grass SLIT in Children Mean % Reduction of Symptoms: Active Versus Placebo			
Whan et al <sup>77</sup>	2009	20 µg × 5	28%
Bufe et al <sup>76</sup>	2009	15 µg Phlp5	27%
Halken et al <sup>75</sup>	2010	20 µg × 5	28%

years was detected for acute otitis media (odds ratio [OR], 0.98;  $P = .72$ ) or chronic otitis media (OR, 1.05;  $P = .84$ ) diagnosed before age 1 year.<sup>81</sup> However, the Melbourne Atopy Cohort Study of 448 children identified at high risk by having an atopic first-degree relative found an association with asthma. They showed that of the 59% who had at least one episode of acute otitis media when less than 2 years old there was a small to moderate increased risk for physician-diagnosed asthma at age 6 years (relative risk, 1.3; 95% confidence interval, 1.15–1.81).<sup>82</sup>

Allergic rhinitis may occur more frequently in children with chronic otitis media with effusion,<sup>80</sup> but common pharmacologic therapy for AR (antihistamines, decongestants, and nasal steroids) has not been shown to be effective.<sup>83</sup> One study found 89% of children aged 3–8 years with “glue ear” also had AR diagnosed by symptoms and either nasal eosinophilia or a positive skin prick test<sup>84</sup>; however, some of these children may have had nonallergic rhinitis with eosinophil syndrome and there may have been a referral bias. In contrast, another study showed a lower but statistically significant association of 16.3% versus 5.5% between chronic otitis media with effusion and AR defined by nasal symptoms independent of a “cold” and positive skin prick test compared with a control group. Interestingly, 16.3% would not be characterized as an elevated rate of AR in some epidemiologic studies of children.<sup>56</sup> This underscores how regional differences, age of subjects, and different definitions of AR make comparing outcomes across studies difficult. The American Academy of Otolaryngology Head and Neck Surgery’s 2004 practice guidelines for chronic otitis media with effusion specifically made no recommendation about allergies as a causal agent or effective treatment of chronic otitis media with effusion because of insufficient evidence.<sup>83</sup>

### **Adenoid hypertrophy and allergies**

The relationship between adenoid hypertrophy and AR is also unclear and there is little evidence linking adenoid hypertrophy with allergy. Nuhoglu and coworkers<sup>85</sup> compared adenoid size in AR and non-AR, finding that non-AR was more significantly associated with adenoid hypertrophy in a retrospective study of 108 children ( $P = .0001$ ). Marchisio and colleagues<sup>86</sup> found that the poor correlation between adenoid size and clinical nasal obstruction was worse in allergic children, presumably because of turbinate hypertrophy playing a larger role. However, adenoids from atopic children may be different pathologically and have showed increased IgE-positive macrophages and plasma cells compared with controls.<sup>87</sup> If turbinate hypertrophy is more frequently the cause of nasal obstruction in allergic children relative to adenoid hypertrophy, nasal steroid sprays or other management of the child’s allergies should be carefully considered in the treatment of their nasal obstruction.

### **Lower Airway Inflammation in the Allergic Child**

Although there are many causes of inflammation in the lower airway including infections, asthma is the archetypal disease of chronic lower respiratory inflammation in the allergic child. However, not all asthmatic children have allergies. Like many other

complex chronic diseases, asthma is a single name for a spectrum of disease. Hundreds of genes likely influence the pathogenesis of asthma, many of which are influenced by environmental interactions.<sup>88</sup> Asthma varies clinically in onset, severity, triggers, and response to therapy. Asthma comprises a range of heterogeneous phenotypes that differ and overlap in presentation. Although we may be on the cusp of tailoring the diagnosis and treatment of asthma using genetic markers, in 2011 asthma is approached clinically by selecting treatment based primarily on severity and triggers (eg, exercise-induced asthma or allergic asthma).

Awareness of asthma is important for otolaryngologists because of the epidemiologic link between chronic upper and lower airway inflammation.<sup>27</sup> Asthma is underdiagnosed, impairs quality of life, and even mild persistent asthma is potentially life threatening.<sup>4</sup> The ability to identify asthma, initiate treatment, and ensure appropriate continued care should be the goal of every specialist who cares for children that are known to be at increased risk of this common disease.

Asthma is influenced by both genetic and environmental factors. Family and twin studies have indicated that genetics play an important role in the development of allergy and asthma. Twin studies suggest that approximately 60% of asthma susceptibility is caused by genetic factors, with indicators of allergic sensitization, such as serum IgE levels, also demonstrating heritability.<sup>89</sup> Genome-wide linkage studies and case-control studies have identified 18 genomic regions and more than 100 genes associated with allergy and asthma.<sup>9</sup> Recently, the gene *ORMDL3* has been identified as exhibiting a highly significantly association with asthma, a finding that has been replicated in several populations.<sup>90</sup>

Although genetic predisposition is clearly evident, environmental factors also play a large role in asthma susceptibility and are likely to underlie the increases that have occurred in recent decades.<sup>91</sup> Observations of migrating populations and of Germany after unification have strongly supported the role of local environmental factors in determining the degree of expression of asthma within genetically similar populations.<sup>92</sup>

During early childhood, certain viruses have been associated with the development of the asthmatic phenotype. In a landmark 2008 study, Jackson and colleagues<sup>93</sup> showed that wheezing with rhinovirus at age 3 years was more predictive of asthma at age 6 years (OR, 25.6) than aeroallergen sensitization (OR, 3.4). Respiratory syncytial virus, rhinovirus, influenza, and parainfluenza are among viral pathogens associated with wheezing in the first few years of life.<sup>94</sup>

In contrast, exposure of an infant to a substantial number of infections, as suggested by the hygiene hypothesis, is seen as protective against the development of the asthma phenotype.<sup>95</sup> Although this theory has been supported by some studies of allergy prevalence,<sup>96</sup> it has been partially refuted by recent studies of asthma prevalence suggesting that although large family size (more than four children) is associated with a decreased risk of asthma, birth order is not involved.<sup>97</sup>

Wheezing and asthma are not synonymous in children. Although some 50% of preschool children have wheezing with viral respiratory infections, only 10% to 15% have a diagnosis of asthma by the time they reach school age.<sup>98</sup> Wheezing in early infancy and childhood has been divided into three courses: (1) transient wheezing, (2) persistent wheezing, and (3) late-onset wheezing.<sup>99</sup>

Transient wheezing in early infancy has been well characterized, with decreased airflow rates on pulmonary function testing at birth, onset of wheezing within the first year, and resolution by mid-childhood with no lasting effects on pulmonary function.<sup>98</sup> Transient wheezing is the most prevalent form of early wheezing and accounts for 60% of the children who wheeze in infancy. It has no significant relationship to atopy

but maternal smoking during pregnancy has been identified as a variable significantly associated with this phenotype.<sup>100</sup> It is suspected that these children have smaller airways, which seems to be associated with maternal smoking, and as they grow the episodic narrowing of the already small airway by viral-induced inflammation becomes asymptomatic.<sup>98</sup>

Children with persistent wheezing can be subdivided into nonatopic and atopic. Nonatopic persistent wheezing comprises 20% of wheezy children under the age of three years and is associated with the first episode of wheezing occurring less than 1 year of age.<sup>98</sup> It is believed that this phenotype may be caused by an alteration in the regulation of airway tone leading to viral-induced wheeze.<sup>101</sup> The atopic persistent wheezing phenotype is found in 20% of children who wheeze during the first 3 years of life and symptoms typically present after age 1 year. Risk factors associated with atopic wheeze include male gender, parental asthma, atopic dermatitis, eosinophilia at 9 months, and a history of wheezing with lower respiratory tract infections.<sup>101</sup> This phenotype is also associated with early sensitization to food or inhalant allergens<sup>102</sup> and reduced lung function at age 6 years (compared with children with no history of wheezing with lower respiratory illnesses).<sup>98</sup>

Late-onset wheezing (wheezing absent before age 3 years, but present at age 6 years) seems to represent another phenotype. These children are more likely to be male, have mothers with asthma, be sensitized to allergens, and have early rhinitis than children who never wheezed. Late-onset wheezing represented 15% of children in one cohort.<sup>98</sup>

Wheezing may also have less common noninflammatory causes, such as an airway foreign body, subglottic cyst, hemangioma, or vascular ring.

The most common cause of asthma symptoms in children less than 5 years old is viral infections. There is no single test or risk factor that predicts who will progress to asthma. Instead, a predictive index may be used based on the cohort data that separated transient wheezing from persistent and late-onset wheezing. Castro-Rodriguez and colleagues<sup>103</sup> created a predictive index for ages 2 to 3 years that conferred a 76% chance of asthma by age 6 and a greater than 95% chance of not having asthma by age 6 if negative. Guilbert and colleagues<sup>104</sup> modified these criteria for the PEAK study for clinical use. The index used in the PEAK study was recommended by the 2007 National Institutes of Health (NIH) asthma guidelines and is as follows: children between ages 2 and 4 years who have had more than three episodes of wheezing (one physician diagnosed) within 1 year and who have met either one major criteria (parental asthma, physician-diagnosed atopic dermatitis, or inhalant allergen sensitization) or two minor criteria (wheezing unrelated to colds, food sensitization, or eosinophilia >4%). Children positive for this index had fewer asthma exacerbations and decreased burden of disease if treated with inhaled corticosteroids compared with placebo, but early inhaled corticosteroids failed to prevent asthma development.<sup>105</sup>

Because atopic children with rhinitis are well represented in otolaryngology clinics and at increased risk for asthma, asking about recurrent wheezing and considering treatment in children who meet the index's criteria would benefit these patients. A check list is provided in **Table 5**. Other important risks for childhood asthma include sensitization to the smaller inhalant allergens by age 6 to 8 years and maternal history of asthma. Smaller inhalant allergen travel preferentially to the lungs by virtue of their size and include cat, alternaria, dust mite, and cockroach.

The 2007 NIH asthma guidelines divides asthma into age groups of 0 to 4 years, 5 to 11 years, and older than age 12 years. Asthma is classified into intermittent and persistent disease. Persistent asthma is stratified into mild, moderate, and severe. Children can be classified based on frequency of wheezing, night time awakenings, frequency

Table 5 Asthma risk checklist for pediatric otolaryngology patients with rhinitis or allergies		
Yes	No	Question
		Has your child had greater than four episodes of wheezing in the last year?
		Has a physician diagnosed wheezing in your child in the last year?
		Did your child have wheezing in absence of a "cold" in the last year?
		Has the child's father ever been diagnosed with asthma?
		Has the child's mother ever been diagnosed with asthma?
		Has your child ever been diagnosed with atopic dermatitis?
		Does your child have a food allergy or did they have a food allergy?
		Has your child tested positive for allergies?
		Does your child use an inhaler or nebulizer sometimes?
		Did your child wake up with coughing or difficulty breathing in the last month when they did not have a "cold"?
		Does your child wheeze or become abnormally short of breath with exercise?

of inhaled  $\beta_2$  agonist use, and exacerbations lasting greater than a day. Once classified, simple charts recommend the initial treatment for each age group.<sup>4</sup> Asthma is a heterogeneous disease and response to treatment needs to be assessed. In most children, optimally managed asthma should result in no missed school, rare use of rescue inhalers, no emergency room visits, and no hospitalizations. Treating asthma also reduces asthma mortality. The number of corticosteroid inhalers used annually is inversely proportionally to the chance of death in those with asthma.<sup>106</sup> The 2007 NIH Asthma Guidelines, including charts for classifying severity, stepwise approach to management, and recommendations for altering therapy based on standardized assessment of the control of asthma control, are available free online. The NIH Asthma Guidelines are written to improve the diagnosis and management of asthma by primary care physicians and can be easily incorporated by otolaryngologists.

## SUMMARY

Children with rhinosinusitis and rhinoconjunctivitis are at risk for inhalant allergies. Allergies often contribute to upper and lower chronic respiratory inflammation. This population of children is likely well represented among otolaryngology patients. Inhalant allergies are uncommon in infancy, but food allergy, atopic dermatitis, and allergic disease in a first-degree relative are important risk factors. The differential diagnosis and treatment of AR and allergic asthma are different in children than adults and change with the age of the child. The prevalence of viral rhinitis and viral bronchiolitis should be carefully considered in young children suspected of inhalant allergies.

Inhalant allergies play a significant role in rhinitis and the associated conditions of allergic conjunctivitis and asthma, but it is less clear how inhalant allergies affect other upper respiratory conditions, such as eustachian tube dysfunction and adenoid hypertrophy. Familiarity with the diagnosis and treatment of pediatric inhalant allergy offers an opportunity substantially to improve the quality of life of allergic children.

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