Natural history of asthma: Persistence versus progression—does the beginning predict the end?

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Environmental exposures during the early years and airway obstruction that develops during this time, in conjunction with genetic susceptibility, are important factors in the development of persistent asthma in childhood. Established risk factors for childhood asthma include frequent wheezing during the first 3 years, a parental history of asthma, a history of eczema, allergic rhinitis, wheezing apart from colds, and peripheral blood eosinophilia, as well as allergic sensitization to aeroallergens and certain foods. Risk factors for the development of asthma in adulthood remain ill defined. Moreover, reasons for variability in the clinical course of asthma—persistence in some individuals and progression in others—remain an enigma. The distinction between disease persistence and disease progression suggests that these are different entities or phenotypes. There is currently no consensus on whether disease progression requires either airway inflammation or airway remodeling or the combination of the two. For patients with irreversible airway obstruction, inflammation might, in part, be necessary but perhaps not entirely sufficient to induce the irreversible component, some of which could be attributed to alterations in the structure of the bronchial wall. Intervening with intermittent or daily inhaled corticosteroids in high-risk infants and children does not prevent disease progression or impaired lung growth. These findings, however, might not apply to adults, and further study in adults is needed to determine the effect of inhaled corticosteroid therapy on disease progression.

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Asthma is a multifactorial heterogeneous disorder, in essence a syndrome comprising different phenotypes that manifest similarly with cough, wheeze, shortness of breath, and chest tightness. Once considered to be simply a manifestation of intermittent bronchospasm and hypersecretion, the episodic symptoms of asthma are now known to occur on a background of persistent airway inflammation and airway remodeling.1 The patterns of inflammation and remodeling vary among individuals. Similarly, the clinical course of asthma varies substantially among individuals and is often quite unpredictable. Reasons for the variability in the clinical course of asthma—persistence in some individuals and progression in others—remain an enigma. Moreover, the temporal course and causes of chronic airway inflammation and remodeling, as well as the interplay between these key histopathologic changes in asthma, are poorly defined. This review will summarize our current understanding of wheezing disorders in infancy and childhood, the factors determining asthma development, the causes of asthma persistence and progression, the roles of inflammation and airway remodeling in disease progression, and the therapeutic implications of current knowledge. Unanswered questions and fertile areas for future research are identified.

NATURAL HISTORY OF ASTHMA FROM INFANCY TO ADULTHOOD

Wheeze before 3 years of age

Community-based longitudinal studies examining outcomes for early wheezers have provided insights into the development of asthma.2,7 Although these study results differ to a certain extent, possibly because of different study populations and measured parameters, some general patterns have emerged. Many children experience 1 or more wheezing episodes before the age of 3 years, often in association with a respiratory virus.8,9 Some have asthma, but the majority do not. For example, in the Tucson Children’s Respiratory Study, a longitudinal birth cohort study, the prevalence of wheezing with lower respiratory tract illness was 32%, 17%, and 12% in the first, second, and third years of life, respectively.8 Overall, one third of children had at least 1 respiratory tract illness with wheezing before the age of 3 years; 60% of these children were no longer wheezing at age 6 years.3 Four groups of children were identified at the age of 6 years (n = 826), as follows: (1) never wheezed (52%); (2) 1 or more respiratory tract illnesses with wheezing before the age of 3 years but no wheezing at age 6 years (transient wheezers, 20%); (3) no
wheezing before the age of 3 years but wheezing at age 6 years (late-onset wheezers, 15%); and (4) wheezing both before age 3 years and at age 6 years (persistent wheezers, 14%).

The persistent wheezers were more likely than other children to have mothers with asthma, increased serum IgE levels both in their first year and at age 6 years, and normal lung function in their first year but diminished function at age 6 years. By contrast, the transient wheezers were more likely to have mothers who smoked but not mothers with asthma; transient wheezers had diminished airway function both before age 1 year and at age 6 years and did not have increased serum IgE levels or skin test reactivity. The patterns of wheezing prevalence and lung function did not change significantly among these children from age 6 to 16 years.

Children enrolled in a birth cohort in Manchester, England, were similarly classified by parentally reported wheezing history before age 3 years and by age 5 years (n = 463) into 4 groups of never wheezers (54%), transient early wheezers (25%), late-onset wheezers (5%), and persistent wheezers (17%). For those who had wheezed before age 3 years (persistent and transient early wheezers), poor lung function (assessed by specific airway resistance) at age 3 years predicted the persistence of wheezing at age 5 years. In a multivariate model the 2 independent predictors of persistent wheezing were increased airway resistance and allergic sensitization at age 3 years. By comparison, for children who had not wheezed before age 3 years (never wheezers and late-onset wheezers), neither lung function nor allergic sensitization predicted subsequent symptoms at age 3 years.

### Wheezing at school age and in adolescence

The German Multicentre Allergy Study assessed the role of early-life allergic sensitization and exposure to perennial allergens (house dust mite and dog and cat hair) in a cohort of 1314 children followed from birth to age 13 years. Symptoms resolved for most (90%) of the children who were repeated wheezers at 5, 6, or 7 years but who did not have atopy (specific IgE, <0.35 kU/L); importantly, these children retained normal lung function at puberty. Instead, those children who wheezed and also had atopy during the first 3 years of life showed loss of lung function at age 7 years. Lung function results were especially poor at ages 7 and 13 years for those with atopy and exposure to high levels of perennial allergens early in life.

In the longitudinal studies in New Zealand and Melbourne, lung function deficits were evident in children with asthma by 9 to 10 years of age and persisted into adulthood. The New Zealand birth cohort study followed more than 1000 children from age 9 years to age 26 years and examined persistence, remission, and relapse of wheezing. At the age of 26 years, among the 613 subjects with complete data, those with persistent or relapsing wheezing (27%) had a higher prevalence of sensitivity to house dust mite and cat allergen and of airway hyperresponsiveness, as well as lower lung function measurements than those whose wheezing did not persist or relapse (46%). In addition, those with persistent wheezing had lower lung function at each assessment relative to those without persistent wheezing.

The Melbourne Asthma Study prospectively followed, from ages 7 to 42 years, a randomly selected cohort of 479 children born in 1957 who had a past history of wheezing. The spectrum of wheezing severity in childhood tended to remain constant into adulthood: the children with milder symptoms, who wheezed with respiratory tract infection or bronchitis, tended to have no or very mild symptoms in adulthood, whereas those with asthma or severe asthma in childhood, who wheezed unassociated with respiratory tract infection, tended to have more troublesome symptoms in adulthood. Loss of lung function was evident by age 14 years among children with severe asthma but did not progress with time (Fig 1).

These studies suggest that for children with asthma, environmental exposures and lung function deficits that develop during the early years are important factors in the development of persistent asthma. As noted by Taussig et al, the fact that serum IgE levels in infancy and not umbilical cord blood IgE levels are associated with later persistent wheezing and asthma suggests that something occurs in the first year of life that either alters or unmasks a child’s propensity to respond to allergens.

### Risk factors for asthma development in childhood and adulthood

Established risk factors for the development of asthma in childhood include frequent wheezing during the first 3 years, a parental history of asthma, a history of eczema, allergic rhinitis, wheezing apart from colds, and peripheral blood eosinophilia of 4% or greater. In addition, allergic sensitization to aeroallergens and to certain foods is now recognized as a risk factor. For children 3 years of age and older with wheezing, the Tucson Respiratory Study Group developed a clinical index of asthma risk: the Asthma Predictive Index (API).

Although the positive predictive value of the API was modest (47.5% for the development of asthma at age 6 years), the negative predictive value was quite high because 91.6% and 84.2% of children with a negative API had not developed asthma by age 6 years and age 13 years, respectively. This index has been modified to serve as a predictive index for children age 2 years and older (Table 1).

Other factors that have been examined with regard to the risk of asthma development include exposure to tobacco smoke, pollution, antibiotic use, living on a farm, obesity, hospitalizations for respiratory disease, and genetic factors. The interplay between genes and environmental factors might have different outcomes depending on the age of the child, possibly explaining why effects of some factors vary between studies. For example, in a recent study by Kuiper et al, infants to the age of 2 years with a positive family history of asthma, the odds of wheezing ever and attacks of wheezing were increased by parental smoking and dust mite exposure, suggesting that these environmental factors modified the relation between positive family history and respiratory morbidity.

The risk factors for development of asthma in adulthood are not yet well defined. Occupational exposures result in at least 1 in 10 cases of asthma in adults. Other risk factors for adult-onset asthma identified in individual studies include airway hyperresponsiveness, atopic sensitization and airway hyperresponsiveness in childhood, low socioeconomic status, family history of asthma, both exsmoking and current smoking.
and female sex.27 Interestingly, compared with adults who had childhood-onset asthma, those with adult-onset asthma in one study, despite a significantly shorter duration of asthma, had similar impairment of lung function and requirement for and duration of oral corticosteroid therapy.28

**DISEASE PERSISTENCE VERSUS PROGRESSION**

**Airway remodeling and inflammation**

There are currently no standard definitions for what constitutes disease persistence as opposed to disease progression in asthma or criteria on how and when progression should be measured or evaluated.29,30 For the purpose of this review, disease persistence is defined as ongoing asthma symptoms, whereas disease progression is defined as a worsening of lung function, asthma symptoms, or both over time. All asthmatic patients have airway inflammation, with resultant altered airway function and symptoms. Most, if not all, have airway remodeling, including thickening of the reticular basement membrane (RBM), epithelial fragility, hypertrophy and hyperplasia of airway smooth muscle, deposition of extracellular matrix, and hypertrophy of mucus-secreting glands, as depicted in Fig 2.31

The onset and course of airway inflammatory changes and remodeling in children with asthma are as yet insufficiently characterized; however, increases in inflammatory cells, including neutrophils, eosinophils, and lymphocytes, are reported in all age groups studied, including infant wheezers.32-38 Increased neutrophil numbers are reported in bronchoalveolar lavage fluid, particularly in severe recurrent and viral-associated wheezing.36,37 Eosinophilic inflammation is evident in school-age children with asthma, especially in relation to allergic sensitization.39,40

Thickening of the RBM also appears to develop early. Although not evident in infants (median age, 12 months) with wheezing and reversible airway obstruction,41 RBM thickening is, however, apparent, together with eosinophilic inflammation, by a median age of 29 months in preschoolers with confirmed recurrent wheezing.42 Bronchial biopsy studies in children, most of them with severe or difficult asthma, consistently report RBM thickening.32,34,38,43,44

Thus although the individual course of asthma might vary, lung function loss is evident by 6 years of age in children with persistent asthma, together with the airway inflammation and remodeling profiles typical of adult asthma. It has been suggested that these characteristic pathologic features of asthma begin to develop between the ages of 1 and 3 years.42

**TABLE I. Modified Asthma Prediction Index: A clinical index to define asthma risk for children 2 years of age or older, per Guilbert et al.18 versus the original API (Castro-Rodriguez et al14)*

<table>
<thead>
<tr>
<th>Disease persistence</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>mAPI: Major criteria</td>
<td>Original API: major criteria</td>
</tr>
<tr>
<td>Parental history of asthma</td>
<td>Parental history of asthma</td>
</tr>
<tr>
<td>Physician-diagnosed atopic dermatitis</td>
<td>Physician-diagnosed atopic dermatitis</td>
</tr>
</tbody>
</table>

**Allergic sensitization to**

- mAPI: Minor criteria
- Original API: minor criteria

<table>
<thead>
<tr>
<th><strong>Disease persistence</strong></th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic sensitization to milk, egg, or peanuts</td>
<td>Allergic rhinitis</td>
</tr>
<tr>
<td>Wheezing unrelated to colds</td>
<td>Blood eosinophils ≥4%</td>
</tr>
<tr>
<td>Blood eosinophils ≥4%</td>
<td>Blood eosinophils ≥4%</td>
</tr>
</tbody>
</table>


mAPI, Modified API.* Differences between indices are shown in boldface. A positive mAPI was defined as the child meeting at least 1 major criterion or 2 minor criteria.

**Do persistent wheezers of childhood have disease progression or persistence?**

Some, but not all, persistent wheezers in childhood have disease progression. At age 16 years, children in the Tucson study who were categorized at age 6 years as persistent wheezers had significantly lower lung function than the never wheezers but, on average, no further decrease since age 6 years relative to their peers.10 Similarly, in the Childhood Asthma Management Program (CAMP) study,45 there was no decrease in mean lung function among children who entered the study at 5 to 12 years of age and were followed for 4 to 6 years. However, compared with children without asthma in the Harvard Six Cities Study, the children with mild-to-moderate asthma in CAMP showed reduced lung function, as measured by the ratio of FEV1/FVC, which was significantly lower for children with than those without asthma.46 The percentages of children with an abnormal FEV1/FVC ratio increased with age in CAMP.

An examination of individual data in CAMP reveals a subpopulation of children who had more pronounced disease progression: 26% of participants had a 1% per year or greater loss in postbronchodilator FEV1 percent predicted.47 Predictors of disease progression were younger age, male sex, and higher postbronchodilator FEV1 percent predicted at baseline. This subpopulation had more prominent eosinophilic inflammation during the washout period (at a single site where biomarker tests were performed).47 These findings suggest that indeed there might be inflammatory changes characteristic of disease progression in children. Despite the progressive lung function decrease, however, asthma was not clinically more severe among these children either at baseline or at the end of treatment.

**Disease persistence and progression among adults**

For adults, the rate of decrease of lung function over time, as measured by FEV1, is greater in those with asthma than in healthy subjects.38,40 Moreover, the rate of decrease among smokers is
greater in those with asthma than in those without asthma. The pattern of decrease in FEV\textsubscript{1} is heterogeneous, however. Not all patients experience disease progression, and progression is difficult to predict for any given patient. Although data from the New Zealand and Melbourne cohorts suggest that, on average, asthma severity tracks over time, asthma symptoms resolve for some pediatric and adult patients, remain stable for some, go into remission and then recur in adulthood for some, and progress (become more severe) for others. Risk factors for persistence of asthma into adulthood included house dust mite allergy, personal smoking, airway hyperresponsiveness in childhood, and female sex, whereas risk factors for asthma relapse included dust mite allergy, airway hyperresponsiveness, and early age at onset of asthma. On the other hand, risk factors for progressive loss of lung function have been reviewed by Ulrik and are summarized in Table II.

There is currently no consensus on whether disease progression requires airway inflammation, airway remodeling, or their combination. For patients with irreversible airway obstruction, inflammation might, in part, be necessary but perhaps not entirely sufficient to induce the irreversible component, some of which could be attributed to alterations in the structure of the bronchial wall termed remodeling. Arguably, irreversibility might be a consequence of structural and myogenic changes rather than a direct consequence of inflammation. Factors that have been associated with persistent airway obstruction (<50% predicted vs >80% predicted postbronchodilator FEV\textsubscript{1}) in patients with severe asthma include prolonged disease duration, peripheral blood eosinophilia, and bronchial wall thickening on high-resolution computed tomographic scanning. Despite these factors, the predictive value of any one component might not be helpful in the early identification of irreversible airway obstruction. However, an attractive hypothesis is that remodeling of the airways that develops potentially over years could evoke an irreversible airway obstruction phenotype, a phenotype of irreversibility.

Although most, maybe all, patients with asthma have some degree of airway remodeling, there is no direct association or correlation between physiologically relevant changes, as defined primarily by objective measures of airflow obstruction, and any single aspect of remodeling other than angiogenesis. The number of bronchial wall blood vessels appears to correlate with the severity of the asthma. However, neither the degree of thickening of the RBM nor the increase in airway smooth muscle mass correlates consistently with the duration or severity of asthma. Indeed, a number of patients have substantial remodeling but are able to maintain control of their asthma symptoms.

### TABLE II. Factors important for the outcome of asthma

<table>
<thead>
<tr>
<th>(ie, longitudinal changes in lung function)</th>
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<tbody>
<tr>
<td>More severe symptoms</td>
<td>Highly probable decrease</td>
<td></td>
</tr>
<tr>
<td>Long-standing asthma</td>
<td>Probable decrease</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>Probable decrease</td>
<td></td>
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<tr>
<td>Airway hyperresponsiveness</td>
<td>Possible decrease</td>
<td></td>
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<tr>
<td>Blood eosinophilia</td>
<td>Possible decrease</td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>Possible decrease</td>
<td></td>
</tr>
<tr>
<td>Newly diagnosed asthma</td>
<td>Possible decrease</td>
<td></td>
</tr>
<tr>
<td>Substantial β\textsubscript{2}-reversibility</td>
<td>Possible decrease</td>
<td></td>
</tr>
<tr>
<td>Low level of FEV\textsubscript{1}</td>
<td>Possible decrease</td>
<td></td>
</tr>
<tr>
<td>Chronic mucus hypersecretion</td>
<td>Possible decrease</td>
<td></td>
</tr>
<tr>
<td>Atopy</td>
<td>No effect</td>
<td></td>
</tr>
<tr>
<td>Early onset of asthma</td>
<td>No effect</td>
<td></td>
</tr>
<tr>
<td>Anti-inflammatory therapy</td>
<td>Probable increase</td>
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DIAGNOSTIC AND THERAPEUTIC IMPLICATIONS OF CURRENT KNOWLEDGE

Most children with asthma experience their first wheezing episode during their first 5 years of life, yet early identification of the children at greatest risk of asthma is a challenge for clinicians. Objective measures of disease activity are limited and difficult to perform in preschool children. Thus for very young children with recurrent wheezing, using a clinical index that incorporates risk elements, such as the modified API (Table I), might be the best indicator of probable asthma. Newer diagnostic tests, such as exhaled nitric oxide determinations, a surrogate marker for airway inflammation, might prove valuable in the assessment of young children for possible asthma.
If multiple wheezing episodes have occurred, can subsequent episodes be prevented, and more importantly, can the natural history of asthma be altered and the progression to asthma be halted? Efforts thus far at primary prevention of asthma through manipulation of environmental factors have had mixed success but have shown promise, although longer periods of follow-up are needed.66-68

With regard to symptom control, studies support the effectiveness of daily therapy with fluticasone18,19,67 or montelukast58 in controlling asthma symptoms in preschool children. However, early institution of intermittent or daily inhaled corticosteroids has not proved effective in halting disease progression in childhood asthma. Two recent reports suggest no effects on asthma has not proved effective in halting disease progression in children. However, inhaled budesonide provided better asthma control but no improvement in lung function compared with that resulting from use of placebo or nedocromil.65 Not surprisingly, for infants at high risk of asthma, intermittent 2-week therapy with inhaled corticosteroids did not provide short-term benefit during wheezing episodes, nor did it have any effect on the progression from episodic to persistent wheezing.70

For adults, early intervention with inhaled corticosteroids might reduce the loss of lung function over time. In a small pilot study, early treatment with inhaled budesonide produced sufficient lung function improvement to allow low-dose maintenance therapy for adults with mild asthma.41 More recently, in a large multinational trial that randomized patients 5 to 66 years old with recent onset of asthma (<2 years), mostly mild persistent asthma, to daily budesonide therapy or placebo for 3 years, the mean FEV1/FVC ratio among adults decreased by 0.58% among those receiving budesonide, which was significantly less than the 1.74% decrease among those receiving placebo.72,73 Interestingly, the effect of budesonide in lessening loss of lung function was not significant among adolescents and was less marked among children less than 11 years old than among adults.

Several therapeutic and prognostic implications can thus be derived from the current knowledge of the natural history of asthma. Young children with infrequent episodes of wheezing typically have resolution of symptoms.2 School-aged children who wheeze but do not have atopy have a good long-term prognosis, and thus the need for daily controller therapy for these individuals should be carefully considered.7 Assessment of allergic sensitization and, when possible, lung function in preschoolers with wheezing can identify those with atopy and reduced lung function who are at risk of persistent disease.11 However, recent studies provide strong evidence that intervening with intermittent or daily inhaled corticosteroids in high-risk infants and children does not prevent disease progression69 or impaired lung function.60 These findings might not apply to adults,12 and further study in adults is needed to determine the effect of inhaled corticosteroid therapy on disease progression.

AREAS OF FUTURE RESEARCH

Areas where further research is needed to address remaining questions include determining how wheezing patterns correlate with histopathologic findings and a better understanding of the characteristics and determinants of asthma progression. Study is needed of the contribution of the small airways to remodeling and disease progression, in addition to the relationships among remodeling, inflammation, and airway hyperresponsiveness and whether there exists any element of cause and effect. Furthermore, investigators need to address whether physiologically relevant airflow remodeling can result from aberrant injury and repair rather than unique exposures. In this case avoidance of exacerbations in susceptible individuals would be tantamount to preventing disease progression. In addition, the biology of airway smooth muscle is an important area of investigation because there is now evidence suggesting a role of airway smooth muscle in regulating bronchomotor tone, in perpetuating airflow in asthma, to daily budesonide therapy or placebo for 3 years, the

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