

Review Article

Critical evaluation of prognostic factors in childhood asthma

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Current knowledge of the natural history of asthma is improving through the establishment of a more precise definition of asthma linked with information from a number of large-scale longitudinal studies. Risk factors for the development of childhood asthma are now more clearly understood. They include gender, atopic status, genetic and familial factors, respiratory infections, and outdoor and indoor pollution (1). In the present review two types of asthma and their prognosis will be discussed:

(1) Asthma in preschool children and its risk factors for evolution towards persistent childhood asthma.

(2) Asthma in older children and its risk factors for evolution towards adult asthma.

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The asthma syndrome

There is convincing evidence that childhood asthma constitutes a spectrum of different conditions that are manifested by recurrent symptoms of bronchial obstruction, i.e. recurrent symptoms of wheezing and/or cough (2). As childhood asthma is made up of different phenotypes, we suggest that childhood asthma should be regarded as a syndrome: the asthma syndrome (Table 1). We also propose the definition of different types of asthma, although we agree that overlap exists and that the various asthmatic phenotypes can occur in the same patient, depending on their age and season of the year. We consider primary asthma as a type of asthma for which the etiology can be situated in the bronchi, i.e. bronchial hyperresponsiveness (BHR) to a number of triggers, such as allergens, viruses, and pollution. Secondary asthma is a type of asthma for which the etiology is situated outside the bronchi, such as in asthma maintained by chronic rhino-sinusitis or gastro-oesophageal reflux. In this latter type of asthma, BHR can be considered as a secondary phenomenon, indicating that treatment should be focused to pathologies outside the lower airways. Asthma with specific airway diseases is the existence of asthmatic symptoms (i.e. recurrent wheeze and/or

cough) in specific airway diseases such as cystic fibrosis, structural bronchial malformations, immune deficiencies, ciliary dyskinesia, and others. The division into different phenotypes of asthma refers not only to the different causes, but also to a different prognosis, suggesting that different treatment regimens might be used.

The classification is clearly illustrated by looking at asthma in children younger than 3 years of age. Evidence suggests that recurrent obstructive symptoms (i.e. recurrent wheezing) remit in a large number of these children who first develop these problems during the first 3 years of life. In these children, recurrent wheezing is usually evoked by viral infections, and low lung function parameters seem to be the main risk factors for these transient episodes. On the other hand, children who will go on to develop persistent wheezing beyond infancy and early childhood usually have a family history of asthma and allergies and present with allergic symptoms very early in life (2). Identification of specific inflammatory markers, such as eosinophil cationic protein (ECP) or soluble interleukin-2 receptor (IL-2R), for diagnosing persistent wheezing when the first lower respiratory symptoms occur, may be a necessary future step before the decision to institute strat-

egies for the prevention of persistent asthma can be made.

Risk factors for persistent asthma in children and adults

Gender

Male gender has been demonstrated to be a risk factor for asthma in children younger than 14 years of age, while being female is a risk factor for asthma in adults. However, from the current literature, the effect of gender on the outcome of asthma is not clear. Weiss et al. demonstrated apparent gender-related differences in the relationship between asthma and lung function: male patients had a higher incidence rate of asthma but female patients had a greater deficit in pulmonary function, suggesting a poorer long-term prognosis in female patients (3).

Atopic status

The expression of atopy is, in part, genetically determined, but is also dependent on exposure to different environmental triggers, including allergens, viruses, and pollutants. Early exposure to allergens seems to be a major trigger, but attempts at prevention by allergen avoidance have produced conflicting results (4). It is generally accepted that atopy is associated with a poorer prognosis of asthma during childhood (5). Subjects with eczema and positive skin-prick tests (SPTs) have asthma of greater severity, and the persistence of eczema has been associated with the persistence of asthma (6,7). Atopy was also associated with persistent wheezing in a cohort of babies at high risk for allergic diseases and was associated with an increased risk for both early and later childhood onset of wheezing (8). In a follow-up of a 1958 birth cohort, subjects who had asthma or wheezy bronchitis by 16 years of age were twice as likely to have a report of wheezing during the preceding year if they had hay fever, allergic rhinitis, or eczema (9). Furthermore, children experiencing persistent asthma beyond early life have increased serum immunoglobulin E (IgE) levels during the first year of life and are more likely than other children to be sensitized to foods (10,11). In a recent study, a clinical index, based on family history and atopic features, was proposed (Table 2) (12). In that study it was shown that in young children with frequent wheezing, the risk of developing asthma during school years was 76% if they had one positive major and at least two positive minor criteria. In youngsters suffering from infrequent wheezing, the risk was 59% when fulfilling the same positive criteria. More impor-

tantly, 95% of young wheezy children with a negative index, never developed asthma between the ages of 6 and 13 years. In another study from Finland, concordant findings were found. In addition to the previous study, however, food allergy during the first 3 years of life was also a risk factor for developing persistent wheezing until reaching school age (13).

Studies on cord blood mononuclear cells have shown that subjects who will develop allergic symptoms have a characteristic pattern of response that includes decreased production of interferon- γ (IFN- γ), suggesting a T helper 2 (Th2)-type of predominance (14). Björkstén et al. showed that interleukin-4 (IL-4) production by peripheral blood mononuclear cells in early life may be predictive of the subsequent development of allergic symptoms (15).

In older children who are already suffering from established asthma, the association between atopy and the outcome of asthma during adulthood is not straightforward. Some studies have pointed to a negative effect and some to no effect. In a study by Peat et al. it was shown that non-smoking males with asthma had an excess decline in the forced expiratory volume in 1 s (FEV_1) compared to normal controls, but there was no association between individual regression slopes and atopic status, as measured by the total number of positive SPTs (16). In line with this observation, Roorda et al. reported that allergy in the child did not contribute to the prognosis of asthma from childhood to young adulthood (17).

Taken together, it seems that allergy is a risk factor for the development of persistent asthma in infants and young children. Once asthma has become established in the child, allergy appears not to be an independent determinant of prognosis into adulthood, suggesting that inflammatory processes in the airways run their own clinical courses, irrespective of the subject's atopic status.

Respiratory infections

Most wheezy episodes occurring in early life are caused by viral infection, in particular respiratory syncytial virus (RSV). Long-term studies have confirmed that bronchiolitis, the main clinical diagnosis caused by RSV infection in early life, is associated with continuing respiratory morbidity and airways hyper-responsiveness (18). Furthermore, in a recent study by Sigurs et al., it was shown that severe RSV bronchiolitis, requiring hospitalization, is linked to a subsequent increase in asthma and allergic reactions at 7 years of age (19). Taken together, there are now arguments suggesting that RSV lower respiratory tract ill-

Table 1. Different types of childhood asthma: 'The Asthma Syndrome'

Primary asthma
Viral-induced asthma
Allergic asthma
Non-specific asthma (caused by, e.g. pollution, exercise)
Secondary asthma
Asthma associated to upper airway pathology (rhino-sinusitis, adenoiditis)
Asthma associated to gastro-oesophageal reflux
Asthma with specific airway diseases

For further details refer to the text.

nesses in early childhood are an independent risk factor for the subsequent development of wheezing up to 11 years of age, and that severe RSV infections, requiring hospitalization, can induce persistent IgE-mediated hypersensitivity reactions up to 7 years of age (19,20). The exact mechanisms are unknown, but an RSV-induced Th2–Th1 switch has been shown (21). Interleukin-10 (IL-10) responses *in vitro*, during the convalescent phase, seem to have a predictive role for the development of recurrent wheezing after RSV bronchiolitis (22). The role of other respiratory viruses in the persistence of asthma is less clear, although it has been established that most young children suffering from viral-induced asthma will outgrow their disease by 5–7 years of age (2). However, the exact role of viral respiratory infections in the cause and persistence of asthma remains unclear. Bacterial infections of the airways seem not to be associated with features of asthma, although *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* have been identified as exacerbators of asthmatic symptoms (23,24). The role of these infections on the prognosis of asthma has never been studied. Recently, a number of studies were able to show that the usage of antibiotics is associated with an increased risk of developing asthma and allergic disorders, especially in children who are predisposed to atopic immune responses (25,26).

Outdoor air pollution

Only limited information is available on the role of outdoor pollution in the prognosis of childhood asthma, although it has been shown that

nitrogen dioxide and ozone may enhance the effects of allergens, possibly by increasing airway permeability (1). In one study covering a 20-year time frame, respiratory symptoms in general population cohorts of children were correlated with air pollution levels. No association was found between levels of pollutants and the incidence of asthma. However, a correlation was observed between pollutant levels and symptom persistence in those children already suffering from asthma (27). In a study by Britten et al., children who were raised in an industrial area of northern England were found to have a higher rate of asthma persistence than those in other locations. Those exposed to higher levels of air pollution were at higher risk for symptoms at age 15, but not at age 20 or 25 (28). Taken together, it seems, from the limited information we have, that outdoor pollution is not a risk factor for developing asthma, but it is a risk factor for persistence of symptoms in those children already suffering from asthma.

Cigarette smoking

Although passive exposure to cigarette smoke in young children is a risk factor for respiratory symptoms, childhood asthma, airway hyperresponsiveness, and diminished pulmonary function status, no definitive study has implicated passive smoking as a risk factor for the persistence of recurrent wheezing (29–31). On the other hand, it seems highly probable that passive smoking worsens the prognosis of asthma in young children, based on the observation that lung growth is diminished in the children of women who smoked during pregnancy (32).

Active smoking is associated with evidence of mild airway obstruction and slowed growth of lung function in non-asthmatic adolescents and, furthermore, active smoking during adolescence is associated with shortening of the plateau phase of the FEV_1 level that generally occurs between 20 and 30 years of age. Active smoking is therefore likely to have a more deleterious effect on lung growth and senescence in asthmatics than in non-asthmatics. However, in both children and adults, an effect of smoking additional to the effect of asthma on longitudinal changes in lung function, has been difficult to demonstrate. In retrospective studies, however, in adults with chronic obstructive pulmonary disease (COPD) (including asthma) an association was found between smoking and asthma persistence or recurrence (33). Therefore, although the evidence is scarce, it is difficult not to assume that active smoking has a negative effect on asthma prognosis, in both children and adults (34).

Table 2. A clinical index to define asthma risk

Major criteria	Minor criteria
1. Parental MD asthma*	1. MD allergic rhinitis*
2. MD eczema*	2. Wheezing apart from colds
	3. Eosinophilia (>4%)

Data derived from ref. 12. For further details refer to the text.

Bronchial hyper-responsiveness

The relationship between clinical asthma and BHR is less clear in early life than in older children or adults (35,36). Studies in which bronchial responsiveness to methacholine or histamine was measured early in life, but after the first wheezing episodes, showed no difference between normal infants and wheezy infants, indicating that wheezing during infancy is not associated with increased BHR (37). Information is now being generated on the role of BHR in infancy as a risk factor for the development of persistent childhood asthma (38). In the study by Clarke et al., both lung function and bronchial responsiveness to histamine were measured during the first months of life and before the development of significant respiratory symptoms in children of atopic parents. Lower levels of lung function were predictive of wheezing during the first year of life among males, whereas BHR was predictive of wheezing in females (38). Furthermore, BHR at 4 weeks of age was significantly associated with decreased lung function on spirometry and physician-diagnosed asthma at 6 years of age (39).

In older children, BHR is regarded as a hallmark of current symptomatic asthma and may precede the development of asthma. Furthermore, BHR is related to many features of asthma. They include the severity of symptoms, the medication needs, the fluctuations in lung function, and the number and state of activation of airway inflammatory cells, such as eosinophils and lymphocytes. Evidence from population studies suggests that BHR is a predictor of lower maximally attained levels of FEV_1 in early adulthood and associated with an accelerated decline in lung function in adulthood. In a study by Gerritsen et al. it was shown that children with a low PC10 histamine were significantly more likely to have current respiratory symptoms as adults than children with normal levels of responsiveness (40). Based on the available longitudinal studies on BHR it seems probable that BHR is associated with both impaired growth of lung function in children and accelerated decline in lung function in adults (34).

Severity of the disease and lung function abnormality

Studies investigating the impact of severity and frequency of asthmatic symptoms have consistently shown that more severe or more frequent symptoms are associated with a worse outcome, i.e. lower level of lung function (34). From the Melbourne study it became evident that airways obstruction becomes more common as wheezing frequency increases and, furthermore, that those

subjects with frequent and persistent asthma in childhood continue to have abnormal lung function in mid-adult life (41). The value of lung function abnormalities in preschool children as a predictor of persistent asthma has been studied insufficiently.

Role of anti-inflammatory treatment

Anti-inflammatory therapy, especially inhaled corticosteroids, can effectively improve the clinical expression of asthma. Inhaled corticosteroids have been shown to reduce the chronic inflammation seen in the airways of asthmatic children. However, the influence of treatment on the long-term outcome of asthma is difficult to assess owing primarily to changes in treatment regimens over the years and the lack of controlled trials. Minimizing the degree of airway inflammation may, at least theoretically, lead to a more favorable growth of lung function in children with asthma. However, two longitudinal studies of childhood asthma concluded that pharmacotherapy had no influence on the outcome of the disease, but it should be noted that <25% of the children included in the studies were treated with inhaled corticosteroids (42,43). In contrast, in an open study by Agertoft & Pedersen, the FEV_1 improved significantly more with time during budesonide treatment, compared with the run-in period and with controls (44). Furthermore, in that same study, a significant, inverse relationship was found between the duration of asthma at the start of treatment with budesonide and the annual increase in FEV_1 during budesonide therapy. The authors concluded that early intervention with inhaled corticosteroids may prevent the development of non-reversible airway obstruction and reduce the risk of undertreatment. In a retrospective study by König & Shaffer, it was found that a delay in starting cromoglycate therapy had a negative effect on changes in spirometry, whereas a delay in starting inhaled corticosteroids had no detrimental effect on outcome (45). Although the designs of the studies by Agertoft & König are far from perfect, both studies do, however, lend support to the hypothesis that early intervention with anti-inflammatory therapy may improve the outcome, with regard to lung function, in children with asthma (44,45).

The question of a potential beneficial effect of therapy on the outcome of asthma in adults has been addressed in a number of studies, although some of these studies were not designed to investigate the role of therapy prospectively. In the study by Haahtela et al. it was found that early treatment with budesonide in adult asthmatics was

Table 3. Factors that may influence the prognosis of asthma in preschool children and in school children

Prognostic factor	Preschool children	School children	Reference
Gender	Male: worse prognosis	Female: worse prognosis	3
Atopy	Worsens prognosis	No influence (?)*	5–17
RSV infection	Worsens prognosis	No influence	18–22
Outdoor pollution	Unknown	Worsens prognosis	27, 28
Cigarette smoking (active or passive)	Worsens prognosis	Worsens prognosis	29–33
Bronchial hyper-responsiveness	Unknown	Worsens prognosis	34,38–40
Severity of asthma i.e. lung function abnormalities	Unknown	Worsens prognosis	34, 41
Anti-inflammatory treatment	Improves prognosis	Unknown	42–48
Increased markers of inflammation	Worsens prognosis	No influence	49–52

*(?) = contradictory results from the literature.

RSV, respiratory syncytial virus.

more effective than terbutaline in reducing airway responsiveness, improving peak expiratory flow rate, reducing respiratory symptoms, and reducing the need for supplemental β -agonists (46). In another study from the same authors it was also found that discontinuation of anti-inflammatory treatment often resulted in exacerbation of the disease (47). Comparable findings have been reported by Waalkens et al. on a smaller group of teenagers with asthma (48). Cessation of budesonide treatment resulted in an increase of symptoms, supplemental usage of bronchodilators, increased bronchial responsiveness, and a decrease in lung function parameters. Based on the available studies it is tempting to conclude that early intervention with anti-inflammatory treatment, primarily with inhaled corticosteroids, can positively alter the long-term outcome of asthma. However, positive changes in lung function and other markers of asthma severity, observed after 1–5 years of treatment, may not reflect the long-term prognosis of asthma. In general, evidence indicates that institution of anti-inflammatory

therapy early in the course of asthma, especially in children, is likely to improve the ‘short-term’ changes in lung function. However, despite general recommendations to use inhaled corticosteroids (i.e. different guidelines for treating childhood asthma), long-term controlled studies are needed to verify whether or not anti-inflammatory therapy can positively influence the natural history of asthma.

Inflammatory markers as predictors of asthma persistence

In young children, ECP and IL-2R were found to be helpful in predicting the outcome of asthma, as increased levels were associated with a persistence of symptoms (49,50). In a study by Clough et al. it was found that increased age at presentation, personal atopy, and raised soluble IL-2R are all associated with an increased risk for persistent asthma (50). In older children, the prognostic value of these markers was insufficiently studied. However, Wenzel et al. demonstrated that airway inflammation persists in severe symptomatic asthmatics despite the use of high-dose corticosteroid therapy and improvement of clinical symptoms. This observation (i.e. a discrepancy between clinical evolution and levels of inflammatory markers) suggests that markers of inflammation might be of little help in predicting the clinical and long-term course of asthma (51). A concordant finding was recently published by Van den Toorn et al. (52). These authors were able to demonstrate elevated levels of exhaled nitric oxide in adolescents with a past history of asthma but in complete clinical remission during the year preceding the study. Taken together, these data suggest that the clinical history of asthma seems to be independent of the disappearance or persistence of signs of airway inflammation. The exact mechanisms that are responsible for the switch-off of clinical asthma seem to be different from those that switch off airway inflammation.

Table 4. Risk profile of the young (preschool) child and older child for developing persistent childhood and adulthood asthma

Profile of a preschool child with an increased risk of developing childhood asthma
Male
Obvious signs of atopy (i.e. eczema)
Severe RSV bronchiolitis during infancy
Passive smoking
High levels of inflammatory markers (ECP, IL-2R) in serum
No or delayed anti-inflammatory treatment
Profile of an older child with an increased risk of developing adulthood asthma
Female
Severe asthma with persistent lung function abnormalities
Severe degree of bronchial hyper-responsiveness
Passive or active smoking
Living in a polluted area

ECP, eosinophil cationic protein; IL-2R, interleukin-2 receptor; RSV, respiratory syncytial virus.

Analysis of risk factors: Conclusions

It still remains difficult to predict the outcome of bronchial asthma in an individual patient. However, a number of factors have been described that enable a reasonable prediction of the prognosis of asthma, although extensive variability exists. The ideal prognostic factor, or combination of factors, remains very difficult to determine in an individual patient. In young children, two major types of asthma can be distinguished: non-allergic asthma and allergic asthma (53). Non-allergic asthma is most frequently triggered by viral infections and has its origin in the existence of narrower airways. In general its prognosis is favorable and most children will grow out of it during the first 4–6 years of life, although the prognosis can be worsened by exposure to cigarette smoke and probably by exposure to pollutants. In contrast, the prognosis of allergic asthma seems to be less favorable, as many youngsters will not grow out of it, especially those with a high degree of allergy in combination with a severe RSV infection during the first year of life. A few studies highlight the potential value of lung function testing and measurement of BHR in predicting the prognosis of young wheezing children, and these factors deserve further study.

In most older asthmatic children, symptoms of asthma are triggered and maintained by allergic reactions. However, the degree of allergy seems to have no influence upon long-term prognosis. In older children, the prognosis is negatively influenced by the degree of lung function abnormalities, the degree of BHR, and active smoking. It still needs to be elucidated if anti-inflammatory therapy is able to improve the long-term prognosis.

In Table 3, different factors are shown which might influence the prognosis of asthma in pre-school children (i.e. in the evolution towards childhood asthma) and in school children (i.e. in the evolution towards adult asthma). Furthermore, 'a risk profile' based on possible risk factors is shown in Table 4.

Parents want to know if their children will outgrow their asthma and at what age. For physicians it remains very difficult to answer this question accurately, predicting the exact prognosis in individual patients. A number of features of a child's asthma can help us, but many aspects still require investigation. Currently, clinical features of the child's asthma give us incomplete information for predicting the prognosis. In this respect, further study of immunological markers (inflammatory markers) and/or genetic markers of the different phenotypes of bronchial asthma

should help us to predict the child's prognosis more accurately.

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