

Definitions and early natural history

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ASTHMA IS A DISEASE of mucosal and immunological development. It is recognised to be the result of a complex interaction between several cells, mediators and neural pathways, leading to an inflammatory response with airway hyperresponsiveness, wheeze, cough and breathlessness. It is usually identified by the presence of these respiratory symptoms in association with features of atopy. Despite this, defining asthma clinically, epidemiologically and physiologically remains a major dilemma. There is as yet no single test or gold standard.

Whichever criteria are used, the prevalence of wheeze, atopy and physician-diagnosed asthma are increasing in all populations around the world. Higher prevalence rates are reported in the more westernised countries, with wheezing occurring in over 30% of infants in the first year of life,¹ atopy in 40% of children,² and physician-diagnosed asthma in over 20% of children.¹

Significance of wheeze

All that wheezes is not asthma, but much is. Wheeze is a non-specific symptom resulting from lower-airway obstruction. Wheeze due to congenital or acquired structural abnormalities can usually be identified. However, most children who wheeze have no apparent structural abnormality — this majority group comprises those who will probably continue to have asthma and those with transient wheeze that is likely to cease within the first three to five years. About half of the early wheezers will have continuous episodes of wheeze and about half will have transient episodes.³ More than 80% of children with asthma begin wheezing in these early years,¹ but in 10%–20% of cases asthma onset occurs after the first four to five years of age.¹

Significance of cough

The management of a child with cough as the primary symptom is a common problem. Accumulating evidence suggests that cough in the absence of wheeze is rarely due to asthma.⁴ The prevalence of airway hyperresponsiveness in these children with cough is slightly more than in the general population, but much less than in children with asthma, and its significance is uncertain.⁵ Whether this group should be given treatment for asthma is unclear. They should not be given high-dose steroids.

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ABSTRACT

What we know

- Asthma is a disease of mucosal and immunological development.
- If a child's first episode of wheeze occurs in the first year of life, the child has about a 50% chance of developing asthma.
- If a child develops recurrent wheeze, the probability that it is related to asthma rises to about 80%.
- The presence of atopy, positive allergen skin-prick tests or elevated IgE antibody levels increases the probability of asthma to over 95%.
- Evidence of changes in lung function or of inflammation confirms a diagnosis of asthma.

What we need to know

- Can an algorithm be created for general practitioners to predict the likelihood of the development of asthma on the basis of presenting symptoms and relevant investigations?
- Is it feasible to use regular lung function testing or induced sputum samples to monitor the development of asthma in early childhood?
- How can we better understand in-utero programming for asthma?
- What characteristics of airway mucosal maturation are associated with the development of asthma?
- What deviations from normal immunological development are associated with the development of asthma?

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Significance of shortness of breath

Shortness of breath is associated with moderate to severe episodes of wheeze, but the symptom is highly dependent on the perception of the child and parents. It is useful as supporting evidence of airway narrowing.

Predicting the development of asthma

The probability of a diagnosis of asthma can be made progressively more reliably with increasing information. Stages in the confirmation of diagnosis are presented in the Box. The epidemiologist is usually dependent on the first one or two stages, the general practitioner on the first three, and the specialist or researcher has access to the fourth stage. It remains most difficult to make a definitive diagnosis in the young infant presenting with the first episode of wheeze. The Tucson group⁶ has developed indices to help GPs predict the likelihood of any episode of wheeze or frequent wheeze in the first three years being due to asthma.

Stages in confirming a diagnosis of asthma

First episode of wheeze

If a child's first episode of wheeze occurs in the first year of life, the child has a roughly 50% chance of developing asthma. If the first wheeze occurs in later years, there is a greater likelihood that asthma is the cause. Wheezing phenotypes include transient infant wheezing, non-atopic viral-induced wheezing, and persistent, generally atopic, wheezing.

Recurrent wheeze

If a child develops recurrent wheeze, the probability that it is related to asthma increases to about 80%, although a structural abnormality or viral-induced wheeze is still possible.

Atopy

The presence of atopy, as a clinical manifestation (eg, eczema, hay fever), positive allergen skin-prick tests or elevated IgE antibodies, increases the probability of asthma to more than 95%.

Altered lung function and inflammation

Confidence in the diagnosis of asthma increases to more than 99% when there is evidence of altered lung function (reversible airway obstruction, airway hyperresponsiveness or peak flow variability) or inflammation (observed in induced sputum, bronchoalveolar lavage or biopsy).

If associated with a major risk factor (parental history of asthma or eczema) or two of three minor risk factors (eosinophilia, wheezing without colds, allergic rhinitis), 59% of children with any wheeze and 76% of those with frequent wheeze subsequently developed asthma. In contrast, over 95% of children without these risk factors did not develop asthma.

Severity of asthma is defined as "infrequent episodic" (75% of children with asthma), "frequent episodic" (20%), and "persistent" (5%).⁷ An acute attack may be mild, moderate or severe.

Natural history

There is increasing evidence that asthma may be induced prenatally in genetically predisposed children. Elevated IgE levels, reduced interferon gamma and impaired T-cell maturation in cord blood have been found to be associated with subsequent development of asthma.^{8,9} The mechanism of this in-utero programming is yet to be defined.

This evidence of early onset is supported by measurements of lung function in the first four weeks of life. Measurements of maximum airflow at functional residual capacity using the rapid thoracic compression technique in a Perth cohort have demonstrated that low flow rates in the first month of life are associated with wheezing illnesses in childhood and asthma through to 11 years of age.^{10,11} By contrast, in the Tucson cohort,¹ lower-lung function was less clear in the persistent wheezers but more marked in transient wheezers. The reasons for this difference are not clear.

Bronchial hyperresponsiveness at one month of age is associated with reduced lung function in later childhood and continuing asthma, but not bronchial hyperresponsiveness at six years of age. However, bronchial hyperresponsiveness

at six years of age is associated with asthma at 11 years of age.¹² Bronchial hyperresponsiveness in the early weeks of life is therefore a non-specific indicator of abnormal airway function, while bronchial hyperresponsiveness at later ages, particularly if persistent, is more specifically related to asthma.⁵

Bronchiolitis and wheeze in the first year of life are associated with pre-existing reduced airflow rates.¹³ Children with these conditions continue to have reduced forced expiratory flow rate in later childhood, but do not show significant reductions in other lung function indices or increased prevalence of asthma (unpublished data). By contrast, bronchiolitis that is severe enough to cause hospitalisation during the first two years of life is more likely to be an early indication of asthma.¹⁴

Transient wheezing in the early years may be associated with maternal smoking during pregnancy and reduced lung function. The wheezing appears to be a manifestation of respiratory infection in infants with narrowed airways. It is yet to be determined whether the natural history of transient and mild persistent wheezing is changing with time.

Better descriptions of the patterns of wheeze and improved understanding of the natural history of wheeze, atopy, mucosal and immunological development will help us better define and diagnose asthma.

References

- Martinez FD, Wright AL, Taussig LM, et al. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995; 332: 133-138.
- Zhao TB, Wang HJ, Chen YZ, et al. Prevalence of childhood asthma, allergic rhinitis and eczema in Urumqi and Beijing. *J Paediatr Child Health* 2000; 36: 128-133.
- Van Asperen PP, Kemp AS. The natural history of IgE sensitisation and atopic disease in early childhood. *Acta Paediatr Scand* 1989; 78: 239-245.
- McKenzie S. Cough — but is it asthma? *Arch Dis Child* 1994; 70: 1-2.
- Sears M, Jones D, Holdaway D, et al. Prevalence of bronchial reactivity to inhaled methacholine in New Zealand children. *Thorax* 1986; 41: 283-289.
- Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000; 162: 1403-1406.
- Isles A, Robertson C. Position statement. Treatment of asthma in children and adolescents: the need for a different approach. *Med J Aust* 1993; 158: 761-763.
- Clough JB, Keeping KA, Edwards LC, et al. Can we predict which wheezy infants will continue to wheeze? *Am J Respir Crit Care Med* 1999; 160: 1473-1480.
- Prescott SL, Macaubas C, Smallcombe T, et al. Development of allergen-specific T-cell memory in atopic and normal children. *Lancet* 1999; 353: 196-200.
- Young S, Sherrill DL, Arnott J, et al. Parental factors affecting respiratory function during the first year of life. *Pediatr Pulmonol* 2000; 29: 331-340.
- Young S, Arnott J, O'Keefe PT, et al. The association between early life lung function and wheezing during the first two years of life. *Eur Respir J* 2000; 15: 151-157.
- Palmer LJ, Rye PT, Gibson NA, et al. Airway responsiveness in early infancy predicts asthma, lung function and respiratory symptoms by school age. *Am J Respir Crit Care Med* 2001; 163: 37-42.
- Young S, O'Keefe PT, Arnott J, Landau LI. Infant lung function, airway responsiveness and respiratory symptoms before and after bronchiolitis. *Arch Dis Child* 1995; 72: 16-24.
- Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. *Am J Respir Crit Care Med* 2000; 161: 1501-1507. □