

ANNOTATIONS

Infant wheeze: Is asthma a possibility?

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Abstract: Most infant wheeze is not asthma. Nonetheless, infants are able to develop reversible airway obstruction with or without allergic sensitisation, and asthma does occur at this age. The many other causes of infant wheeze, however, make asthma more difficult to distinguish from the background 'noise'. Consideration of risk factors and clinical features can enable some infants to be given a provisional diagnosis and, if their symptoms are disabling, a cautious trial of asthma treatment.

Key words: asthma; bronchiolitis; bronchodilator; infancy; infant; wheeze.

Introduction

Wheezy infants form a substantial proportion of children admitted to hospital. And yet our handle on infant wheeze is slippery – we lack consensus on how we understand, categorise and treat such infants. Although there are conflicting opinions and evidence, as clinicians we are compelled to make choices based on our current knowledge. The following is my approach.

What is 'Asthma'?

There is probably no other common medical condition for which precise definition is so elusive. We all recognise classical asthma. But there are fuzzy boundaries between normality, asthma and other airway conditions. Further, asthma is probably an endpoint of a number of pathways, and seems to consist of several phenotypes. The Global Initiative for

Asthma definition includes physiological and pathological components, which are not readily measured, particularly in young children.¹

Historically, asthma was a description of a symptom complex attributed to airway narrowing. Thomas Floyer in 1698 described asthma as 'a laborious respiration with lifting of the shoulders, with wheezing, arising from Compression, Obstruction or Coarctation of some branches of the bronchia, and some lobes of the bladders of the lungs'. Or, in current idiom:

Episodic wheezing and breathlessness that responds predictably to inhaled bronchodilator treatment.

This definition is helpful in clinical practice, and I regard more detailed definitions as defining subgroups. Interestingly, the two types of adult asthma Thomas Floyer recognised as 'continued' and 'periodic' correspond almost exactly to the subtypes of 'episodic (viral) wheeze' and 'multitrigger wheeze' in pre-school children described in the European Respiratory Society (ERS) Task Force report.

Note that:

- 1 'Episodic' signifies symptoms that come and go, not always predictably.
- 2 'Wheeze' is the cardinal symptom of bronchial narrowing.
- 3 'Breathlessness' distinguishes important from trivial wheeze.
- 4 Bronchodilator response suggests bronchospasm. It also demonstrates a means to relieve the child's distress.
- 5 Neither coughing nor atopy is a defining feature of asthma. Coughing without wheeze is unlikely to be due to asthma, and thus does not improve the sensitivity.² Atopy is a risk factor and defines a phenotype of asthma.

Bronchodilator response is difficult to establish in infants. During an episode, a table of wheeze, heart rate, respiratory rate, respiratory distress and pulse oximetry before and 10–15 min after 6 puffs of salbutamol via a spacer can be helpful. However, the assessment is subjective and needs repeating.

Key points

- 1 Infants can be given a tentative diagnosis of asthma, but there is a wide differential, requiring evaluation of specific clinical features and risk factors.
- 2 The confidence of asthma diagnosis increases with age, so that it is possible to predict childhood asthma from pre-school wheeze with moderate accuracy.
- 3 Treatment of asthma in infancy includes inhaled bronchodilators during acute episodes, avoidance of cigarette smoke, considering alternative day-care options and trial of inhaled steroids for disabling chronic symptoms.

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Does Asthma, as Defined, Occur in Infancy?

Reasons for past reluctance to diagnose asthma in infants included the old myths that infants do not have bronchial smooth muscle or β -receptors, concerns about unpredictability, and implications of the diagnosis for insurance and career choice. The ERS Task Force by consensus 'agreed not to use the term asthma to describe pre-school wheezing illness' because of insufficient pathophysiological evidence to relate this to childhood or adult asthma.³

However, three lines of evidence suggest that asthma may occur in infants.

- 1 *Anatomy and physiology.* Airway smooth muscle is present by the eighth week of gestation.⁴ Almost from birth, a proportion of infants will develop airway constriction after methacholine challenge, which can be reversed by inhaled β -agonists.⁵ The repertoire of airway manifestations undoubtedly changes as the immune system and airways grow, mature and encounter allergens and infections. However infants already have the *capability* for the reversible airway obstruction that we associate with asthma in older children.
- 2 *Cohort studies.* Most cohort studies of airway disorders, from the Tucson study on, have identified children who wheeze recurrently in infancy and continue to wheeze until 13 years or older.⁶
- 3 *Clinical retrospective.* Many older children with severe chronic asthma started wheezing in infancy, as the ERS Task Force agreed.³ Their hospital records often reveal a characteristic trail of successive admissions for 'bronchiolitis', 'virus-induced wheeze' and then 'asthma'. Parents will often say they thought it was asthma from the beginning.

Can Causes of Wheeze be Discriminated in Infancy?

Although asthma almost certainly occurs in infancy, diagnosing it is more difficult and less confident than in an older child, and requires consideration of alternative causes of infant wheezing. The Tucson, Perth and Seattle cohort studies have given us considerable evidence that there are at least two, and perhaps more, major subgroups of infants with recurrent wheezing.⁷ Distinguishing subgroups is, however, different from diagnosing individuals, which remains probabilistic and tentative.

- 1 *Is it acute viral bronchiolitis?* Respiratory syncytial viral bronchiolitis causes wheeze, fine crackles and breathlessness in infants, predominantly 0–6 months old, during winter in temperate countries. Bronchiolitis can occur in infants 6–12 months old, and occasionally in summer (due to adenovirus and other viruses), but other wheezy conditions are becoming more common in these situations and require consideration. Fine to medium crackles throughout the chest are the hallmark of bronchiolitis; their absence should lead to suspicion of other causes.
- 2 *Is it one of the rare, specific causes of wheeze?* Wheeze that dates from near birth, is constant, or is highly regular and predictable suggests fixed, congenital airway obstruction. Aspiration lung disease may cause wheeze in an infant with malformations of the upper aerodigestive tract or neurodevelopmental

problems associated with impaired swallowing or airway protection. It is suspected particularly when wheezing occurs with feeds, choking or vomiting or in supine. Wheeze of sudden onset in a mobile older infant suggests the possibility of inhaled foreign body.

- 3 *Is it transient infant wheeze?* Confirmation of this requires resolution of wheeze by 2–3 years old. However, the possibility may be considered in an infant with recurrent virus-triggered wheeze who has no personal or family history of asthma or atopy and whose mother smoked in pregnancy.
- 4 *Is it asthma?* I consider the possibility of asthma in an infant who has episodic wheeze and shortness of breath and who has risk factors including:
 - i Parents or siblings with asthma
 - ii Eczema, especially around elbows and knees
 - iii Other allergies or eosinophilia
 - iv Interval symptoms of wheeze with cold air or allergen exposure

In such an infant a *trial* of bronchodilators is warranted. A definite bronchodilator response suggests that bronchospasm, a key feature of asthma, is present. In the above clinical context asthma is the only condition likely to cause bronchospasm, although there is conflicting evidence about whether or not infant bronchodilator response, taken on its own, is predictive of asthma.^{8,9} A negative or indefinite response could be repeated. However, a trial of bronchodilator should not be a sentence and should not lead to ongoing treatment in the absence of a clear response.

Distinction is often not straightforward when the risk factors themselves are not definite (e.g. possible eczema on the cheeks) or the child has features of another condition (bronchiolitis, transient infant wheeze and asthma are all common and overlap). How well can we predict future asthma in an infant? The available studies address *pre-school* wheezing.

Prediction of School-Age Asthma from Pre-School Wheezing

Castro-Rodriguez *et al.* attempted to predict later asthma in the Tucson cohort study using a predictive index.^{10,11} A child who met criteria for the stringent index would have had at least three episodes of wheezing in the first 3 years of life and would have (i) eczema; (ii) a parent with doctor-diagnosed asthma; or (iii) two of the minor criteria (doctor-diagnosed allergic rhinitis, wheezing apart from colds, or $\geq 4\%$ peripheral blood eosinophils).

Children with a positive index had a 77% likelihood of having asthma at 6–8 years of age and 50% at age 11–13 years. Children with a negative index had a 10% likelihood of having asthma at age 6–8 years and 15% at age 11–13 years.

Overall, about 1 in 5 children with asthma at 11–13 years of age had had wheezing in their first 3 years of life.

So although asthma *can occur* and *can be suspected* in infancy, the diagnosis is tentative. This can be expressed to parents like this: 'Your child's pattern of wheeze and the asthma in your family suggest that he/she is likely to have further episodes of wheeze and may have asthma. Reliever inhalers may be useful in a future episode. As your child gets older it will become clearer whether or not he/she has asthma'. This is more

informative and helpful than saying 'It's a viral wheeze and we can't diagnose asthma at this age'. It is my experience that when the 'asthma' word has at least been considered the parents are more likely to get education about wheeze and plans for treatment of future episodes than when 'viral-induced wheeze' is the only consideration.

Asthma Treatment in Infancy

Day care and smoking exposure should be addressed in any infant with recurrent wheeze. Asthma treatment trials in infancy have suffered from very variable selection criteria and conflicting results. A recent meta-analysis concludes that infants with recurrent wheezing improve with inhaled steroids.¹² However, even in older pre-school children, inhaled steroids have shown only modest effects on persistent symptoms, and no protection against future chronicity or airway re-modelling.¹³ A relatively high threshold for using inhaled steroids in infancy – persistent disabling symptoms or very severe episodes – seems sensible.

The treatment should be stopped if there is no clear benefit to the child.

Multiple-Choice Questions

1 Which one of the following *is true* about asthma in relation to infants?

Asthma . . .

- A cannot occur because of absence of bronchial smooth muscle
- B cannot be diagnosed due to the complex differential diagnosis
- C cannot always be confidently diagnosed but may be suspected
- D should not be diagnosed because treatment is only supportive
- E can only be diagnosed by a definite bronchodilator response

Critique: The correct answer is C.

- A Bronchial smooth muscle is developed by 8 weeks gestation, and neonates can respond to both bronchoconstrictors and bronchodilators.
 - B The differential diagnosis is complex but usually there are clinical pointers in the history and exam to the more likely diagnosis.
 - C Correct. Asthma may be difficult at times to distinguish from transient forms of wheezing, but factors like infantile eczema, recurrent symptoms, interval symptoms and immediate family history of asthma should arouse suspicion of this possibility.
 - D Infants can be treated with bronchodilators and inhaled steroids, although the degree of benefit is debated and is probably modest.
 - E Bronchodilator response may be difficult to assess clinically in infancy because of imperfect dose delivery, subjective assessment and perhaps the proportionately greater influence of inflammatory oedema on narrowing of a small airway.
- 2 A 5-month-old baby, Jack, normal at birth and growing and developing well, presents to the hospital with acute wheezing

and breathlessness. Jack has had three previous similar episodes and is sometimes mildly wheezy when laughing or in cold air. Jack's 6-year-old brother has asthma. Both parents smoke and did so during pregnancy, but the grandmother does not. Both parents work, and Jack attends a large city day-care centre every morning. On examination Jack has audible expiratory wheeze, rapid breathing with increased effort, and auscultatory wheeze on inspiration and expiration with no crackles. *Which one of the following is the most likely cause of the wheezing?*

- A Aspiration lung disease
- B Infantile-onset asthma
- C Transient infant wheeze
- D Acute RSV bronchiolitis
- E Non-specific virus wheeze

Critique. B is the correct answer

- A There are no risk factors for aspiration lung disease, such as craniofacial, oesophageal, laryngeal or neurodevelopmental problems.
 - B Correct. There are fairly strong risk factors for asthma – several episodes, interval symptoms with laughing and cold air exposure, and immediate family history of asthma. This makes B the *most likely* cause in the scenario given.
 - C Although the mother smoked in pregnancy, and the child's airway growth may well have been affected, smoking is also a risk for most types of wheeze in infants. In transient infant wheeze maternal smoking is characteristically the only risk factor, whereas this child also has risk factors for asthma.
 - D Acute viral bronchiolitis does not fit with recurrent episodes, interval symptoms and the lack of crackles in the chest.
 - E Viruses are non-specific triggers of wheezing – in acute bronchiolitis and episodes of asthma and transient infant wheeze, besides other conditions. However, here it is the clinician who is non-specific rather than the wheeze itself. We have categories and clinical pointers or risk factors to most forms of wheeze in infancy, although these are often not sought or recognised. Where the diagnosis remains unclear I encourage people to be descriptive about the clinical features and the risk factors and list the most likely possibilities. This produces clearer thinking and anticipatory guidance than diagnosing 'non-specific viral wheeze'.
- 3 After resolution of the current episode with the aid of bronchodilator treatment, the parents of Jack, in question 2, ask for advice regarding his ongoing management. Which one of the following would be the *least likely* to help Jack?
- A As required beta-agonist via spacer
 - B Parents accept help to quit smoking
 - C Provision of day care by grandmother
 - D Regular twice-daily inhaled steroids
 - E Management plan for future episodes

Critique. Correct answer D.

- A Has obviously helped in hospital, and would be expected to help with symptom relief, provided it is not being overused.
- B Smoking exposure is an ongoing risk for increased respiratory infections, wheezing, and asthma severity, besides direct damage to the airways.
- C Exposure to many children in a busy day-care centre means a high level of virus exposure. Early day-care centre attendance has been shown to be variously protective against, or a

risk factor for, childhood asthma. However, when a child is *already having recurrent viral-triggered wheezing episodes* one is not dealing with asthma prevention but with management of recurrent wheeze, possibly asthma. In this situation more virus exposure will lead to more frequent episodes of wheeze.

- D Correct. Regular twice-daily inhaled steroids may or may not help this child. There are some interval symptoms but they are mild, and the efficacy of inhaled steroids is modest against interval symptoms, and very small against virus-triggered episodes. This may be a future consideration if the child's interval symptoms get worse and the previous measures have not helped.
- E On occasions, infants get severe and life-threatening episodes of asthma, and parents should be given information about what to do, what to give, and when and whom to call for help.

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