# Wheeze in infants and young children

## Diagnoses and management options

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### 1. The interpretation of respiratory noises and other signs

(N.B. Throughout this article I use the standard terms *wheezes* and *crackles*, in place of the older terms *rhonchi* and *rales/crepitations*.[1])

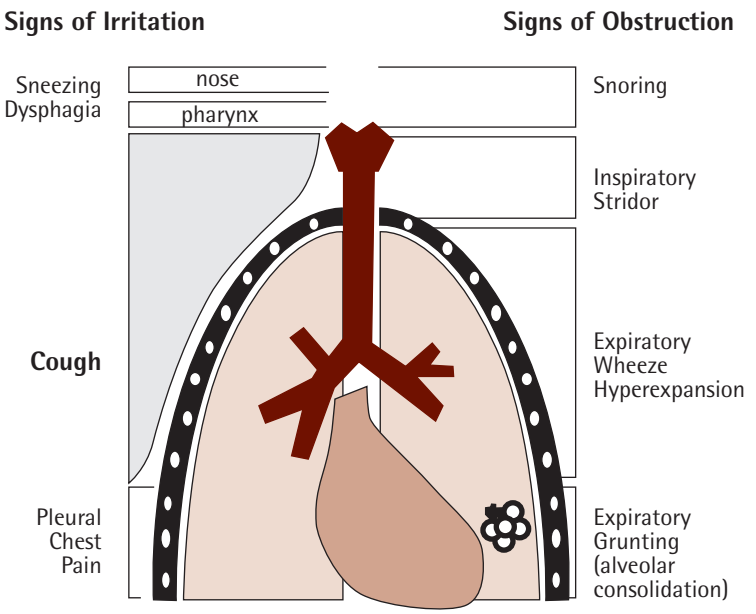
Wheeze is a sign of airway obstruction in intrathoracic airways (see diagram). It is a continuous sound that has a musical quality to it, particularly if it originates from a single airway. Increased air velocity through a narrow region lowers the internal pressure (the aerofoil effect) and narrows the airway further until the airway walls appose. Momentarily airflow stops until back pressure opens the airway up again. This cycle repeated many times per second generates a sinusoidal pressure wave and a musical tone. The vocal cords, the reed in a clarinet and a trumpeter's embouchure produce tones in a similar way. If multiple airways are involved, either several separate noises may be heard or they may blend with the breathing into a rasping polyphonic sound, much like an orchestra tuning up. Wheeze heard from the end of the bed is usually the latter type.

If only one airway is obstructed, e.g. from a foreign body in a main stem bronchus, or a tuberculous lymph node compressing a bronchus, there is often a single ('monophonic') wheeze. Sometimes you hear this only on one side of the chest, but in other cases you can hear the same noise throughout the chest.

Intrathoracic airways are naturally at their narrowest in expiration, when the entire chest cavity reduces in volume. Air is expelled from the intrathoracic airways through the extrathoracic trachea and upper airway into the atmosphere. On inspiration the lungs and intrathoracic airways are pulled open by negative intrapleural pressure and draw air out of the extrathoracic trachea, which narrows. This see-sawing of air between the intrathoracic and extrathoracic airways means that any pathological obstruction of the intrathoracic airways (for instance asthma) has its greatest effect on airflow during expiration, whereas obstruction of the extrathoracic trachea (for instance viral croup) has its greatest effect during inspiration. However as obstruction becomes more severe, the other, less affected phase of respiration may become noisy as well. In asthma or bronchiolitis not all airways are narrowed to the same degree, and some may be so obstructed that they only open and generate wheeze during inspiration.

Intrathoracic airway obstruction also results in 'air-trapping' when all

*Figure 1. Anatomical origins of airway signs and symptoms*

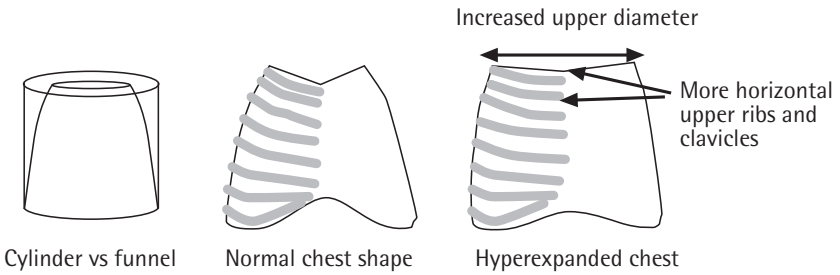


the air that is inhaled cannot be exhaled before the airway closes, or when the maximum rate of exhalation is limited and cannot keep pace with inhalation, or both. Air-trapping leads to progressive hyperexpansion of the lungs and intrathoracic airways. The increased diameter of the airways due to hyperexpansion acts to *reduce* the degree of obstruction in expiration. Expiration becomes easier, but the patient now has to work harder to breathe in. This increased effort is not due to obstruction, but to the elastic recoil of the already stretched, hyperexpanded alveoli and chest wall. Hyperexpansion stops progressing when a new state of balance is reached: expiration is mostly passive and inspiration involves a huge amount of work. Most of the clinical signs of increased work of breathing (accessory muscle use, indrawing, tracheal tug) reflect this increased inspiratory effort. Patients with asthma themselves complain of difficulty getting air in, even though we observe that it is their expiratory phase that is prolonged.

The clinical effect of these phenomena is to reduce breath sounds (decreased inspiratory flow and transmission to the chest) with a mixture bilaterally of inspiratory and expiratory wheezes from different airways, and prolonged expiratory phase. The effect of hyperexpansion is most visible in the equalization of diameter of the upper and lower chest in both the lateral and frontal dimensions, so that instead of an inverted funnel shape (Figure 2), the chest becomes more cylindrical or barrel shaped. (This can be difficult to detect in infants who may be naturally somewhat barrel-chested.) The clavicles and upper ribs are elevated medially and so are more horizontal.

Two other clinical symptoms are of note. ***Coughing*** is a sign of irritation of the airway epithelium anywhere from the vocal cords down to small bronchioles (see Figure 1). On its own it is *not* a sign of airway obstruction (cough without wheeze is rarely due to asthma). Airway irritation is part of many inflammatory disorders of the intrathoracic airways, extrathoracic trachea and larynx – asthma, bronchitis, bronchiectasis, viral croup, laryngitis etc. – as well as sometimes due to mechanical (foreign body) or chemical (inhaled particles or gas) irritation or increased cough receptor sensitivity.

*Figure 2. Hyperexpansion versus normal chest shape*




***Fine crackles***, once called crepitations, are characteristic of diseases with an alveolar and interstitial component. This is true of bronchiolitis due to RSV in young infants, and a very helpful ancillary sign in this disease, but it is not characteristic of asthma. However coarse crackles, which clear or change on coughing, are characteristic of mucus in large airways, which can occur in asthma.

## 2. Phenotypes of wheeze in infants and young children

Wheezing in children encompasses several different phenotypes, with differing aetiologies and natural histories, and it is fair to say that we are still struggling to understand and come to grips with how they differ and what the optimal medical approach should be in each case. However what we already know about wheezing in young children can help to clear up some of the misconceptions in this area. Here are the most common:

### *Most common misconceptions about wheezing in young children*

1. Children under two years old cannot have asthma because they do not have airway smooth muscle;
2. Wheezing under the age of one year is bronchiolitis until proved otherwise;
3. Asthma cannot be diagnosed in children under two years of age;
4. Infants with frequent wheezing require a preventer.

By the end of the first trimester of pregnancy, the early bronchial tree is covered in smooth muscle, and a neural plexus[2] (Misconception 1). Infants also have beta$_2$ agonist receptors, as bronchoconstriction can be induced by histamine and prevented by salbutamol.[3] Bronchodilator response, however, is variable in infancy, most likely because airway inflammation, with mucus and oedema play a greater role in obstruction of infant airways than bronchospasm. Infants, on account of their absolutely small size, have airways that are more readily obstructed from a variety of causes, and this is probably why they have a more complex differential diagnosis of wheeze than older children – it is not all bronchiolitis (Misconception 2). So whereas asthma *can be* diagnosed in some infants (Misconception 3), as we will see, it is true that asthma is *more difficult* to diagnose in infants because of the number of different causes of wheezing at this age. Preventive treatment may have some symptomatic benefit in selected infants and pre-schoolers but has no long-term effect on the natural history or long-term prevention of childhood asthma (Misconception 4).

### *Bronchiolitis*

The term 'bronchiolitis' has a chequered history, which explains some

of the confusion. Taken literally, as inflammation of the bronchioles, it occurs in a host of different disorders. At one stage (particularly in the USA) bronchiolitis was used to describe any wheezing in young children, because diagnosing them with asthma had implications for insurance policies and future careers in the armed services. Currently the term in most Western countries is used to imply a specific acute condition associated with respiratory viruses (most commonly RSV but also rhinoviruses, parainfluenza virus, influenza virus and adenovirus) in midwinter and manifest by mild fever, wheeze, cough, respiratory difficulty, hyperexpansion, fine crackles and wheeze throughout the chest, and hypoxia. This condition occurs almost exclusively in infants and the majority of cases of severe bronchiolitis needing hospital admission occur in the first six months of life. [Bronchiolitis obliterans – permanent damage to the bronchioles following infection or other causes – and bronchiolitis obliterans with organising pneumonia – seen in transplant patients – are separate disorders]

From one to six months of age acute bronchiolitis is by far the most common cause of wheezing. By nine to 10 months of age it is becoming less common than some of the other causes. By the end of the first year of life, the most common condition is so-called transient infant wheeze.

### *Transient infant wheeze*

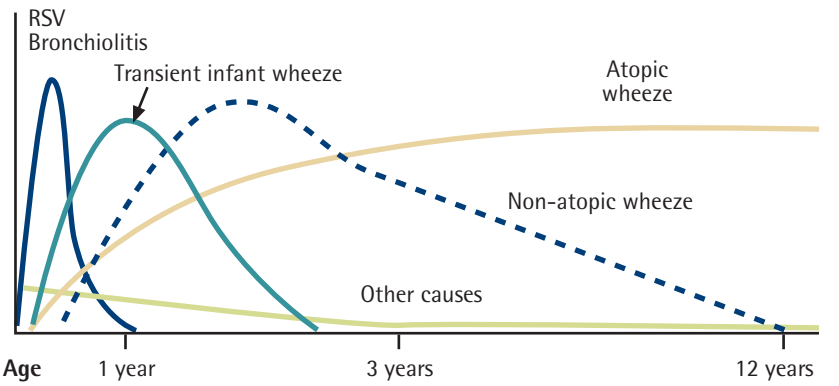
Transient infant wheeze is a term that has emerged from birth cohort studies and is still being defined. In the key study in Tucson, Arizona,[4] wheezing phenotypes were defined in retrospect at the age of six, when children were divided into those who had wheezed recurrently in the first three years of life and had grown out of it (Early Wheeze), those who had wheezed in the first three years and were still wheezing at six years (Persistent Wheeze), those who had first started wheezing after three years of age (Late Wheeze) and those who had never wheezed (Never Wheezed). Using sophisticated tests of infant lung function they were able to show that the Early Wheeze group:

1. had lower lung function than any other group shortly after birth (before the first wheezing episode);
2. have continued to have slightly lower function than predicted through into young adulthood,[5] suggesting their airways are anatomically smaller than average;
3. did not have any increase in family history of atopy or asthma or atopic markers at any age, compared to Never Wheezers;
4. did have an excess of maternal smoking in pregnancy compared to the other groups.

The Tucson group coined the term 'Transient Infant Wheeze' for this group of children. Other cohort studies have found similar, but not identical patterns.

It is believed that these children are largely non-atopic and are born with airways that are smaller than average, possibly as a direct influence of nicotine or other substances in tobacco smoke. They wheeze with infections in young life and stop wheezing as they grow bigger, but their lung function appears to be permanently affected. They may be at increased risk of COPD if they become smokers themselves. Whether or not they respond to asthma treatment is not established. One would expect the prevalence of this condition to depend on the local rate of maternal smoking in pregnancy.

*Figure 3. Occurrence of various wheezing phenotypes during childhood*




### *Other causes of non-atopic wheeze*

Bronchiolitis or pneumonia due to RSV in infancy increases the risk of recurrent non-atopic wheeze with infections, but this increased risk gradually falls off to undetectable levels by 12 years of age (dashed blue line in Figure 3). Rarely congenital cysts, bronchomalacia, inhaled foreign body, aspiration lung disease, cystic fibrosis, bronchial compression may cause wheezing in childhood, and these causes are also more common in infancy (green line in Figure 3).

### *Atopic asthma*

Finally there is the group of children with recurrent wheeze persisting to school age. Children with recurrent wheeze at school age commonly also have a parental history of asthma, or have signs of atopy, like eczema or allergic rhinitis, or have at least one positive skin prick test for an inhaled allergen. It is appropriate to call this atopic asthma or atopy-associated asthma (yellow line Figure 3).

In some such children the wheeze is only triggered by virus respiratory infections (intermittent or episodic asthma). In other children, wheeze is triggered by exercise, nighttime, cold air, allergens, etc. as well as occurring in more severe and prolonged bouts with virus infections (persistent asthma). Asthma becomes

more prevalent with age up to early school age and is more common in boys than in girls in childhood (this sex ratio reverses in adulthood). Some children first develop wheezing in late pre-school years, others develop wheezing as infants. It is my experience that many children with chronic persistent atopic asthma in late childhood, will have a history of wheezing going back to the first few weeks of life. Initially it will have been called bronchiolitis, and then viral wheeze, and finally asthma, but the parents will state that the symptoms were similar throughout.

### 3. Prediction of atopic asthma in infancy

Can we predict which infants with wheeze will end up being recognised as atopic asthma? The answer is: not entirely. However certain risk factors and situations increase the likelihood that a given infant with wheeze has (or one day will be diagnosed with) atopic asthma. The most important of these is a family history of asthma in parents or siblings. The likelihood of asthma is very high when both parents have definite asthma, however the risk is not zero if no family members have asthma. The next most important risk factor is atopic eczema, especially eczema in the elbow and knee flexures, in infancy. The third factor is the frequency of wheezy episodes associated with respiratory infection – the more often this occurs, the more likely the child is to have asthma. Fourthly, infants who have wheezing without respiratory infection – especially on exposure to cold air, or specific allergens, are more likely to have asthma. It is particularly useful to check these risk factors in children who present outside the bronchiolitis winter season, or after the first six months of life, or who do not have crackles in the chest to suggest bronchiolitis. Bronchodilator response may be tested by checking pulse, respiratory rate and effort and auscultatory findings before and 10–20 minutes after six puffs of salbutamol via spacer, or 2.5mg via nebuliser. A striking positive response is helpful in suggesting bronchospasm rather than just airway inflammation – the response should be reviewed more than once – however a negative response does not exclude asthma.

*Table 1*

| Major criteria | Minor criteria |
|---|---|
| 1. A parent has doctor-diagnosed asthma | 1. Doctor-diagnosed allergic rhinitis |
| 2. Doctor-diagnosed eczema. | 2. Wheezing apart from colds |
| | 3. Eosinophilia (>4% of differential). |

Castro-Rodriguez and colleagues[6] in the Tucson, Arizona group attempted to define an asthma predictive index at age three years based on some of the risk factors in Table 1.

Two predictive indices were assessed in children meeting at least one major criterion or at least two minor criteria:

A. *Loose predictive index:* any wheeze heard in the chest in first three years of life
B. *Stringent predictive index:* any wheeze heard in the chest in first three years plus parents rated wheeze in first three years of life as frequent.

*Table 2*

| | Prediction of active asthma at 13 years | Percent with active asthma at 13 years old | |
|---|---|---|---|
| **Index used** | **Odds ratio** | **Children with positive index** | **Children with negative index** |
| **Loose index** | 3.0 (1.9, 4.6) | 31.7% (28.1, 35.3%) | 13.5% (10.9%, 16.1%) |
| **Stringent index** | 5.7 (2.8, 11.6) | 51.5% (47.7%, 55.3%) | 15.8% (13.0%, 18.6%) |

*(Each measure is given with 95% confidence interval in brackets)*

You can see from the figures in Table 2 that the indices performed much better than chance at predicting which children would have asthma at 13 years, the stringent index increasing by almost sixfold the risk of asthma at 13. However, at most 50% of children with a positive index had active asthma at 13 years. On the other hand a substantial proportion (13–16%) of children with a negative index had active asthma at 13 years. A century ago a total asthma prevalence of that size would have been considered huge.

That is currently about the best we can do, using the risk factors we know about in young children to predict later asthma.

#### *Risks that apply to all wheezing disorders*

Parental smoking, besides being a risk factor for transient infant wheeze, is also a risk factor for the development of bronchiolitis and asthma. Viral infections not only cause bronchiolitis but trigger exacerbations of transient infant wheeze and asthma. Thus smoking is a non-specific risk factor and viral infection a non-specific trigger for wheezing and these do not greatly help to distinguish causes of wheezing.

*Exemplary cases*

1. Imagine a four-month-old child with acute wheezing and respiratory difficulty, presenting in July following one day of runny nose. Neither parent has asthma, neither smokes and the child has no eczema. The child has severe respiratory distress, a barrel chest, and wheeze and fine crackles throughout the chest.
   *You should not have too much difficulty diagnosing bronchiolitis in this situation.*

2. Another child is nine months old and has had their third episode of acute wheezing and respiratory difficulty, this time presenting in February following one day of runny nose. Neither parent has asthma, but mother smoked heavily during pregnancy, and still does. The child does not have eczema. The child has mild respiratory distress, is mildly hyperexpanded and has wheeze (but no crackles) heard throughout the chest.
   *This is a child who we might expect to have transient infant wheeze.*
3. A third child, aged nine months, presents in February with his third episode of wheezing and increased respiratory effort, following one day of runny nose. In between these episodes he sometimes gets wheezy on cold days. Both parents are on preventive treatment for asthma, but neither smokes. Two siblings have asthma. The child has been treated for flexural atopic eczema. The child has mild respiratory distress, is hyperexpanded with wheeze but no crackles heard throughout the chest.
   *I hope you will agree this child is most likely to have atopic asthma, and it would be reasonable to give a trial of bronchodilator, as explained above, to see if he has bronchospasm.*

These scenarios are deliberately contrived to display all the relevant risk factors and features; in practice, of course, cases are rarely so clear-cut. However the cases do illustrate the point that (a) asthma can occur and be diagnosed in infancy (Misconceptions 1 and 3) and (b) not all wheezing in infancy is bronchiolitis (Misconception 2). In a case with some risk factors for asthma, it is reasonable to explain to the parents that there are risk factors for future wheezing, and to say that it will become clearer with time whether the child has asthma or not. It may be worthwhile in older infants to trial a bronchodilator. However, see below.

The fourth misconception needs some further explanation.

### 4. Treatment of wheezing or asthma in infancy

Many studies of asthma treatment have been undertaken in infants, both of bronchodilators and of preventers including sodium cromoglycate and inhaled steroids. Studies of bronchodilators in children under two years of age have been mixed and do not show clear benefit.[7] Inhaled steroids seem to improve symptoms in high risk atopic children with frequent wheeze after the age of one year, but results in infants have been very mixed[8] (Misconception 4). In my search of studies trialling inhaled steroids in children under 24 months I have found three positive and two negative studies. One possible reason for conflicting results is that different groups have studied groups of wheezy infants with a different mix of atopic, and non-atopic infants. *It is clear, however, from two major studies, that inhaled steroids in infants or young children do not alter the natural history of the disease nor reduce the risk of later asthma,*[9,10] In one of these, the PEAK study,[9] after two years of treatment of young children, observations during a further year off inhaled steroids showed that all improvements in lung function and clinical parameters during treatment reverted quickly to resemble the children who had been on placebo over the two years.

**Inhaled steroids in infants or young children do not alter the natural history of the disease nor reduce the risk of later asthma**

Fortunately severe chronic asthma is rare in infancy. There are occasional infants with wheeze who have strong asthma risk factors (asthma in parents and/or eczema in child) and whose symptoms are disabling (frequent wheeze associated with respiratory distress). In these cases we sometimes feel compelled to trial inhaled steroids. We should explain to parents of such children that at this point studies of treatment are not conclusive in children under 12 months of age. During the trial of treatment parents should document symptoms and response daily. If there is no certain benefit after a few weeks, then the treatment should be discontinued.

### 5. Prevention of asthma

Full discussion of the inception of asthma and possible preventive factors is beyond the scope of this article. Some of the interesting findings of different groups have been:

1. Children in highly industrially polluted, socioeconomically depressed Leipzig had much less asthma than ethnically similar children in wealthy Munich. Car ownership and ozone exposure is higher in Munich.
2. Children in Alpine regions of Europe had less asthma if they spent time in the cow shelter or drank unpasteurised milk in their first year, and particularly if their mother did so during pregnancy.
3. Very young infants in Estonia had different bowel organisms (lactobacilli and bifidobacteria) than ethnically similar children in nearby Sweden (E.coli) – probably due to differences in diet – and the latter developed more allergies.
4. High exposure to cats and dogs early in life decreases the risk of later sensitisation to those and other allergens, particularly among atopic individuals, but has no effect on the incidence of wheezing by four years of age.
5. Sensitisation to house dust mite increases the risk of asthma, but early exposure does not necessarily increase the risk of asthma.
6. Having a large sibship or attending daycare in infancy (which usually occasions more frequent respiratory viral infections) increases the incidence of wheezing in infancy but decreases the risk of wheezing by school age.

7. Other protective factors in some but not all studies: exclusive breastfeeding (New Zealand), BCG vaccination (Taiwan), schisosomiasis, measles (Guinea-Bissau).
8. Other factors being explored: diet – vegetables and fruit, fish, vitamin D, paracetamol and antibiotic use in infancy.

Polymorphisms (naturally occurring variations of a single DNA base) of some immune regulation genes alter the response to some of the factors listed above – e.g. early exposure to dogs reduces the risk of asthma in children with the TT or CT variant at position 159 of the CD14 gene, but not in children with the CC variant.

Counselling of strongly atopic families about preventive strategies is not prudent at present, until we have better understanding of these factors. There are a host of other reasons for encouraging breastfeeding, whether or not there are risk factors for atopy.

### Competing interests

The author has, in the past five years, received funding to attend symposia from companies that have an interest in medications for asthma, which is dealt with in this paper.

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## The NHS workforce planning disaster

*'The job of predicting the staff needs of the NHS has been a "disastrous failure" with "little if any thought [being] given to long term strategic planning," says a report by the cross party Health Select Committee. MPs partly blame the demanding targets set by government for the chaotic hiring and firing of staff that has been seen in the NHS during the past 12 months. This, together with a huge injection of cash for the NHS, led to what they call a "boom and bust" approach to workforce planning.*

*"The huge growth in funds provided by the Government, together with the demanding targets it set, ensured that the increase in staff far exceeded the NHS Plan. Many new staff were recruited from overseas. In 2005 there were signs that the NHS was spending too much. Boom turned to bust. Posts were frozen; there were some, albeit not many redundancies, but, most worryingly, many newly qualified staff were unable to find jobs and the training budget was cut," says the report.*

*Despite the government publishing what the committee described as an "excellent blueprint" for workforce planning in 2000 and mapping out its plans to expand the health workforce in the NHS Plan, health authorities had inadequate numbers of people with the expertise needed to forecast workforce needs accurately.*

*The report also blames large pay increases, which it says have not been matched with similar increases in productivity, and "an appalling lack of coordination between workforce and financial planning" for the current situation. Criticism was levelled too at "micromanaging" from the Department of Health and "constant reorganisation including the establishment of Workforce Development Confederations within 3 years."'*

*Kmietowicz Z. BMJ 2007;334:653.*

## Making sense of 'risk' for patients

*'Although NNT provides useful information for clinicians to enable them to compare the benefits and risks of interventions for a specific patient, this format was the least likely to encourage patients to take medication in our study.*

*In this study, we sought to differentiate between the persuasiveness of the method in which data are presented and the method that patients found best in helping them understand their risks and benefits. The decision to treat cardiovascular disease risk factors with drugs is in effect a "lifetime sentence" with both potential benefits and harms. It would be unethical for this decision to be made without informed consent. Certain formats of providing information may be more persuasive than others, but may not necessarily be the best way to help patients fully understand risks and benefits.*

*The greatest challenge is how to support decision making by providing information that is meaningful. It is therefore imperative that information on risk is communicated in ways that are understandable and acceptable to patients and also considered accurate by primary care practitioners. This study contributes to our knowledge on how to achieve this objective.'*

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