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The wheezing infant

Michael Silverman

Wheeze is a symptom and not a diagnosis. It is extremely common in infancy; 20–30% of children have experienced recurrent episodic wheezing by the age of 12 months. Wheezing may result from widespread peripheral airway narrowing or, less commonly, from localized central disease. Excluding recurrent viral wheezing and asthma-like symptoms, all other specific causes of wheezing (e.g. cystic fibrosis, congenital airway disorders, chronic lung disease of prematurity) affect only 2–3% of the population. Although wheezing disease preceded by acute viral bronchiolitis early in infancy features prominently in most articles on childhood asthma, it affects, at most, 1% of the population. The increased prevalence of reported wheezing in industrialized countries until the mid-1990s, accompanied by an increase in the number of hospital admissions for wheezing, represents a true increase in the problem rather than simply increased awareness. In the UK, wheezing in pre-school children accounts for about 25% of acute hospital admissions in childhood, and almost 50% during epidemics of respiratory syncytial virus (RSV) infection.

Risk factors

There are major differences in the risk factors for wheezing in infants and for asthma in schoolchildren (Figure 1), which indicate that wheezing in infancy has a different basis.

- In infant wheezing, exposure to environmental tobacco smoke during fetal life and postnatally is strongly implicated.
- Atopy does not seem to be a predisposing factor in wheezy infants in the community, but it may be implicated in children who are admitted to hospital with more severe disease. Research on cohorts of infants show that there is no simple relationship between aero-allergen exposure and sensitization. Nevertheless, atopic asthma is uncommon in the first year of life.
- In infants with recurrent wheezing, bronchial responsiveness is no different from that in healthy controls (in contrast with the situation later in life).
- Brief or no breast-feeding during the first few weeks of life increases the risk of wheezing in infancy, possibly because of reduced protection against viruses. The effect is small, however, and does not extend to later atopic asthma.

Pathology

Little is known about the histopathology and immunopathology of wheezing in infants. Acute viral bronchiolitis in the first 6 months of life is an inflammatory disorder characterized by a massive influx

of neutrophils into the lung, detectable by bronchoalveolar lavage (BAL) in ventilated infants. Infants who die exhibit widespread epithelial shedding, particularly in the peripheral airways, and obstruction of the airway by mucus and inflammatory cells.

Studies of inflammatory processes in the lungs by mini-BAL during anaesthesia for non-pulmonary surgery have shown:

- pro-inflammatory cytokines (e.g. sICAM-1) are raised in the infants of smoking parents
- inflammatory cells are raised for up to 2 weeks after a viral upper respiratory tract infection
- inflammatory cells are absent between episodes in patients with viral wheeze, but eosinophils and mast cells persist in patients with atopic asthma.

Acute episodes of wheezing in infancy are characterized by hyperinflation and an increase in airway resistance. Abnormal lung function persists during symptom-free intervals; there is increased airway resistance, and reduced forced expiratory flow can be demonstrated by the squeeze technique. (In the squeeze technique, the sleeping infant lies in an inflatable jacket that encases the chest and abdomen. When the jacket is inflated rapidly at the end of a normal tidal inspiration, the thoraco-abdominal compression causes forced exhalation. Flow is measured at the mouth with a flowmeter attached to a face-mask.) In infants, there is little physiological evidence of a bronchodilator response to β_2 -agonists or antimuscarinic bronchodilator agents given by aerosol. This lack of response does not result from an absence of bronchial smooth muscle in infancy, nor a deficiency of β_2 -adrenergic receptors, because β -agonists block the action of nebulized bronchoconstrictor agents during bronchial challenge in infants.

Clinical features

It is important to determine the duration, pattern and severity of wheeze, and to identify provoking factors. The pattern (particularly whether symptoms occur between acute viral episodes) is important in management. There are two main patterns.

- Acute episodic wheeze and cough are commonly associated with respiratory viral infection and punctuated by mainly symptom-free intervals. Rhinoviruses, RSV, coronaviruses and the recently identified metapneumovirus are commonly implicated.

Risk factors for wheezing in infants and asthma in schoolchildren

Risk factors	Wheezing in infants	Asthma in schoolchildren
• Cigarette smoke		
<i>In utero</i>	+++	?
In childhood	++	+
• Viral infection	++++	++
• Atopy	±	+++
• Aero-allergen exposure	0	+++
• Brief or no breast-feeding	+	–
• Low birth weight	+	+
• Attendance at day nursery	++	–
• Child has older siblings	++	–

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• Chronic symptoms include day-to-day wheeze and troublesome dry, night-time cough. Acute episodes may also occur. There may be atopic features. (Chronic cough, in the absence of reported wheeze, is epidemiologically and clinically a condition separate from wheezing and asthma; the term 'cough-variant asthma' is unhelpful in infants.)

When diagnosing wheeze in young children, the main areas of confusion are with inspiratory sounds from the upper airway (including stridor) and with rattly chest sounds. In the absence of simple, routine measurements of lung function in infants, wheezing is assumed to be equivalent to intrathoracic airway obstruction.

The clinical features of tachypnoea with lower intercostal indrawing, hyperinflation and widespread expiratory wheeze vary according to the severity of the airway obstruction and probably its site. Inspiratory crackles may be heard in children with acute viral infections, but persistence between episodes suggests an alternative diagnosis (e.g. bronchoalveolitis, fibrosis). Features of atopic disease (e.g. eczema) should be sought, because their presence may have prognostic significance.

Assessment of severity – referral to hospital for evaluation is necessary if any of the following are present:

- progressive deterioration in clinical condition
- breathlessness that prevents sleep or feeding
- persistent tachycardia (> 120 beats/minute)
- obvious signs of distress
- hypoxia severe enough to cause cyanosis (or $\text{SaO}_2 < 92\%$ by oximetry).

Differential diagnosis – features that raise the possibility of an alternative diagnosis (Figure 2) include:

- perinatal respiratory disease or neonatal symptoms
 - extreme prematurity
 - vomiting, possetting or dysphagia
 - inspiratory noises or expiratory noises other than wheeze.
- Other features that indicate alternative diagnoses or major complications include:
- persistent failure to thrive
 - hypoxia between episodes
 - focal signs on auscultation (recurrent or persistent)
 - inspiratory wheeze or stridor
 - abnormal voice or cry.

Investigations

- Chest radiography should be performed on the first presentation of any infant with acute severe airway obstruction requiring secondary care (see below). Subsequent episodes should be investigated only if there are unusual features.
- If the differential diagnosis is unclear, high-resolution CT can exclude structural disorders such as airway compression).
- Bronchoscopy may be performed when focal stricture or a foreign body is suspected, and microlaryngoscopy when an upper airway anomaly is possible. Bronchography is rarely needed, to detect tracheal and large airway abnormalities such as tracheo-bronchomalacia).
- A sweat test should be performed when cystic fibrosis is suspected.
- Immunological investigations are seldom helpful. A host defence defect may present with wheezing, but is more likely to be associated with recurrent febrile episodes, suppurative lung

Uncommon causes of chronic or recurrent wheezing in infants

Developmental anomalies

- Bronchomalacia (localized or generalized) and tracheal anomalies
- Bronchial compression syndromes (e.g. vascular anomalies, bronchial or pericardial cyst)
- Congenital heart disease (left–right shunt)
- Tracheal granuloma, stricture or polyp (after mechanical ventilation)

Host defence defects affecting the airways

- Cystic fibrosis
- Ciliary dyskinesia
- Defects of immunity

Post-viral syndromes

- Obliterative bronchiolitis
- Airway stricture or granuloma

Recurrent aspiration

- Gastro-oesophageal reflux
- Disorders of swallowing (neuromuscular disease, mechanical disorders)
- Tracheo-oesophageal fistula
- Laryngeal cleft

Perinatal inflammatory lung disease

- Chronic lung disease of prematurity
- Congenital infection

These causes combined may account for 2–3% of wheezing episodes in infants. The most common cause of wheezing in infancy is recurrent episodic wheeze, which occurs in 20–30% of infants.

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disease and infections of the upper respiratory tract (particularly recurrent severe otitis), gastrointestinal tract and skin.

- A diagnosis of gastro-oesophageal reflux may be supported by a 24-hour oesophageal pH study, a trial of antireflux therapy or video-fluoroscopy. A contrast swallow is not sensitive, but may help distinguish other causes of recurrent aspiration.
- Oximetry is used to monitor arterial oxygen saturation during acute episodes. Oxygen saturation (SaO_2) less than 92% during quiet sleep, or in a quiet awake state, suggests airway obstruction requiring admission to hospital.
- Measurement of lung mechanics is confined to research institutions.

Management

Avoidance of trigger factors: cigarette smoke is probably the most important avoidable factor. Viral infections are seldom avoidable, but attendance at day nurseries and overcrowding in the presence of older siblings increases the risk of viral infections in infancy. Breast-feeding reduces the risk of wheeze. Reduction of aero-allergen sources (e.g. house dust mite) and not keeping furry pets in the home may be worthwhile if there is a strong family or personal history of atopy, but paradoxically may increase allergen sensitization in children in low-risk families. Reducing aero-allergen exposure has no effect on viral wheeze. There is little

Drug treatment in wheezy infants

Bronchodilators

Inhaled β_2 -agonists may be effective in relieving symptoms in infants with chronic lung disease of prematurity; though there is little formal evidence to support their routine use in acute episodes of wheeze, they become increasingly effective as the infant gets older. β_2 -agonists may be more effective when given by metered-dose inhaler and spacer than by jet nebulizer. Nebulized adrenaline may be more effective than selective β_2 -agonists, but comparative studies have not been performed. Ipratropium bromide is no more effective than β_2 -agonists in wheezy infants.

Corticosteroids

In episodic viral wheeze (without interval symptoms), there is no evidence of chronic inflammation. In clinical trials, regular prophylaxis with high-dose topical inhaled corticosteroids (in pre-school children beyond infancy) does not alter the severity or frequency of acute viral episodes. High-dose inhaled or oral corticosteroids given at the onset of an acute viral wheezy episode have no clinically significant effect. In clinical trials, infants with chronic symptoms (between and during viral episodes) benefit from long-term prophylaxis with inhaled corticosteroids; the severity of both interval symptoms and episodes is reduced. No benefit is gained from short-course oral corticosteroids in acute severe episodes managed at home; their benefit in children in hospital is unproven.

Other agents

There is no evidence to support the use of sodium cromoglycate or theophylline in infancy. Antibiotics are not required in the routine management of wheezy infants. Atypical infections (e.g. *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*) may be more common than suspected in infancy, and treatment with erythromycin is therefore appropriate if indicated.

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evidence to support altering established feeding practices in infants with wheezing, or in those at high risk of asthma.

Education – information about the nature and management of wheezing should be given to the parents according to their wants and needs. The value of ‘training programmes’ in improving the health of wheezy infants has not been established. Written information, particularly about drug therapy, should always be offered to parents to reinforce verbal messages.

Therapeutics

Drugs used in the management of wheezy infants are listed in Figure 3. Most published clinical trials based on short-term physiological outcome with single doses of bronchodilators administered by jet nebulizer in hospital have shown no significant benefit. Regular therapy at home using, for example, spacers and metered-dose inhalers has been little studied, and the range of devices used for aerosol administration has hardly been explored. The efficacy of treatment seems to increase with age and when intercurrent symptoms accompany acute wheezy episodes. There is no evidence to support use of regular ‘preventer’ therapy with topical corticosteroids or sodium cromoglycate in infants who suffer isolated episodic wheeze with viral infections. Instead, each individual episode should be treated promptly as below (Figure 4).

Despite the absence of good clinical data, published management schemes and protocols for infants resemble those used for older children. However, much closer control is required over infant therapy, because acute episodes can progress with alarming rapidity and the parents of young infants generally have little experience on which to base clinical judgements.

Domiciliary therapy for day-to-day chronic symptoms – mild symptoms that do not disturb sleep or feeding may not require therapy. In patients with troublesome chronic symptoms, a step-wise approach to treatment should be considered, starting with intermittent inhaled bronchodilator and progressing through low-dose inhaled corticosteroid to high-dose inhaled corticosteroid and, if necessary, oral prednisolone on alternate days as for older children. There is no evidence to support the use of sodium cromoglycate in infants. In infants with very troublesome, persistent airway obstruction, alternative diagnoses should be excluded. Any infant who requires any form of corticosteroid therapy should be managed jointly by a primary care physician and an expert in paediatric pulmonary disease.

Acute episodes – management of infants with episodes of acute severe airway obstruction is summarized in Figure 4. A trial of bronchodilators and corticosteroids is worthwhile (despite limited evidence of benefit in clinical trials), except in those with acute bronchiolitis (first episode of wheeze in an infant < 6 months old), in whom neither is useful (though preliminary evidence suggests that nebulized adrenaline may be useful, as in rescue therapy in a hospital setting). If used, bronchodilators (β_2 -agonist or antimuscarinic agent) should be administered by an oxygen-driven jet nebulizer and face-mask, using a standard childhood dose. Infants should be assessed by oximetry and clinical observation 15–30 minutes later and the treatment modified if necessary. Heart rate monitoring is important, because bronchodilator therapy may lead to tachycardia. A repeat dose should be used only if there is clear evidence of efficacy.

Oxygen therapy may be required in infants with an Sao_2 by pulse oximetry of less than 92% during quiet sleep or the quiet awake state. Intravenous therapy or nasogastric feeding should be considered in children who are too breathless to drink; however, a nasogastric tube may increase airway obstruction and trigger coughing by irritating the pharynx. Hyponatraemia secondary to inappropriate antidiuretic hormone secretion is a rare complication of severe acute bronchiolitis (and infantile pneumonia). Monitoring of body weight and serum sodium concentration is required.

Mechanical ventilation may be needed if exhaustion or a gradual increase in oxygen requirement occurs. Paco_2 is seldom used as a single indicator of the need for ventilatory support in infants.

Prognosis

Symptoms are generally confined to the pre-school years, particularly in children with simple episodic wheeze associated with viral infections. Recent data suggest that the long-term outcome in these infants is good; after 25 years, they have only slightly more symptoms than a control population. Acute episodic viral wheeze in infancy appears to be almost completely independent of later atopic childhood asthma. Hospital-based cohorts of wheezy infants differ from the general population; a slight excess of atopy is seen. Prognosis is worse in these children and in those who suffer more than four attacks of wheezing in their pre-school years.

Management of episodes of acute severe airway obstruction in infancy

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Prognosis may also be worse in infants with a very low birth weight (< 1500 g) and in those in whom there is evidence of eosinophil activation (raised serum eosinophil cationic protein production or urinary eosinophil protein-X excretion) during acute episodes.

Adolescents and young adults with a history of wheezing lower respiratory illness in the first 2 years of life are prone to productive cough and to a slight reduction in lung function. Recently, a link has been shown between chronic obstructive pulmonary disease in late adult life and lower respiratory illness in infancy; disturbance of lung development during fetal life may be the important common factor.

There is no reason to believe that infants who begin wheezing with acute viral bronchiolitis will fare differently from others with acute episodic wheeze. RSV bronchiolitis does not damage the lungs in the long term, though other viruses (particularly certain adenoviral subtypes) may do so, leading to chronic obliterative bronchiolitis. Other chronic post-viral syndromes are described following acute severe viral pneumonia or bronchiolitis in infancy,

including focal damage to large airways (e.g. granuloma, strictures), bronchiectasis (generalized or localized), and abnormalities of growth and development that may lead to focal hypoplasia (McLeod's or Swyer-James syndrome).

Mortality from acute wheezing disease in infancy is low. Most deaths in acute episodes occur in infants compromised by congenital heart disease or underlying pulmonary disorders such as cystic fibrosis or chronic lung disease of prematurity. ♦

FURTHER READING

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