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Bronchodilators in wheezy under 2-year-olds: when and which (if any)?

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CLINICAL CASE

Amy is 13 months old and presented to the children's emergency department with a 5-week history of wheezing. Her parents explain that they have seen her general practitioner twice and attended the local walk-in centre three times over the last month. She has been prescribed antibiotics and salbutamol both of which Amy 'hates'. On examination, she had a dry cough with mild respiratory distress. She has occasional crepitations and widespread wheeze. Parents smoke 'outside the house' but neither has asthma. She is their first child. Clinically, she is well but parents would like to know whether inhalers will help.

INTRODUCTION

Birth cohort studies have demonstrated that approximately one-third of the children aged between 1 and 5 years suffer recurrent episodes of respiratory symptoms including wheeze. Wheezing prevalence in UK children has increased from twofold to threefold during the past 40 years but may have stabilised or even peaked in the early 1990s. Fortunately, a majority of young children with wheeze tend to have only transient symptoms and do not have subsequently increased risk of asthma or allergy in later life. Nevertheless, childhood wheeze presents a major burden of morbidity during preschool years and there is significant progression from some childhood wheeze to adult asthma. More than 25% of an unselected birth cohort of children had wheezing that persisted from childhood into adulthood or that relapsed after remission. Despite the relative commonness of childhood wheeze, controversy and confusion exist over which treatments are effective. Doctors and nurses caring for these children face a dilemma regarding the treatment. Although bronchodilators are of clear benefit in older children with asthma, the anatomy

and physiology in younger children are significantly different. In this article, we review the known physiology, the current evidence base and offer practical advice for those with a wheezy infant.

SOURCES AND SELECTION CRITERIA

We searched PubMed and Cochrane databases using the terms 'wheeze' AND 'bronchodilator' OR 'β-agonist' 'anticholinergic', 'ipratropium', 'adrenaline' or 'salbutamol' limiting the age range to children (or 'preschool children' where available) and selecting what we deemed to be clinically relevant articles. Citation searching of publications identified by database searches identified additional important recent related references. In addition, we drew on our personal archive of references and included pertinent evidence from older children and adults when data are lacking on infants.

THE DIAGNOSIS OF WHEEZE IN CHILDREN

A wheeze is a continuous high-pitched sound, with musical quality emitting from the chest during expiration. Several studies have shown that parental understanding and use of the word 'wheeze' is often at odds with that of clinicians.^{5–10} Confident retrospective diagnosis of wheezing in a child between wheezy episodes is a clinical challenge. Frequently, parents believe that wheeze is similar to 'gaspings', 'coughing', 'rattles', 'whistling' or 'rasping', whereas others defined wheeze as a different rate or style of breathing. Even among health professionals, studies have demonstrated inter-observer variations of wheeze by stethoscope examination and acoustic analysis.^{11 12} Personal experience has demonstrated that parents can usually give accurate and detailed descriptions of the type of respiratory noises their child makes in between episodes when asked to describe these in detail. However, it is

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vital to ask in detail about any reported respiratory symptoms to maximise diagnostic accuracy when reviewing a child.

PATTERNS OF WHEEZE

The complete differential diagnosis for wheezing episodes is extensive (box 1). Careful consideration of the pattern and nature of the symptoms including age at onset and variability of symptoms and signs is crucial before any treatment is undertaken; however, a thorough discussion of this is beyond the scope of this article. Once the nature of any respiratory noise has been defined, it is helpful to examine in detail the pattern and periodicity of wheezing episodes.

Current expert opinion suggests that wheeze in preschool children is best divided into two major types, that is, episodic viral wheeze and multiple-trigger wheeze.¹³ This discrimination is mostly of benefit in determining whether inhaled corticosteroids are likely to be of benefit rather than determining whether bronchodilators will be effective. Viral wheeze is defined as wheezing in discrete episodes and the child is well between the episodes. This is usually associated with clinical evidence of viral infection and is the

most common phenotype in preschool children. The first episode is frequently diagnosed as bronchiolitis infection. The common microbes identified are respiratory syncytial virus, adenovirus, rhinovirus, para influenza virus and human metapneumovirus.¹⁴ Episodic viral wheeze commonly should decline over time and disappear by 6 years of age. In contrast, multiple-trigger wheeze has not only discrete wheezing episodes but also symptoms between the episodes and is more likely to persist.¹⁵

LUNG DEVELOPMENT AND ANATOMY IN EARLY HUMAN LIFE

Lung development and physiology during fetal and early life have been extensively studied. Despite these studies, some important fallacies still persist among doctors and students alike, most notably a presumed lack of bronchial smooth muscle during early life. Lung development in the human fetus is divided into four overlapping stages after the initial embryonic stage (0–7 weeks) as pseudo-glandular stage (7–17 weeks), canalicular stage (16–26 weeks), saccular stage (24–36 weeks) and alveolar stage (36 weeks to term).¹⁶ Airway smooth muscle is clearly present from 8 weeks' gestation when desmin is expressed.^{16 17} By 16 weeks, maturation of the innervation is advanced with two major nerve trunks running the entire length of the bronchial tree. β_1 and β_2 receptors are known to be present all through the fetal airway including small airways. An extensive and intricate varicose network of bronchial smooth muscle with functional nerve fibres persists throughout infancy and then into adult life.¹⁸ The presumption that bronchial smooth muscle is lacking during infancy, therefore, seems to owe its origin to clinical studies wherein bronchodilators were shown to be ineffective, rather than to any anatomical or histological studies.

HISTORY AND PHYSICAL EXAMINATION

As with any clinical scenario, a good history and a detailed clinical examination are important. There is no evidence regarding the usefulness of physical examination between episodes of wheeze in children under 2 years of age. Work of breathing can crudely and indirectly indicate degree of airway narrowing. The presence or absence of wheezing is frequently used in clinical severity scores of younger children. This sign must be interpreted with caution as reductions in airflow associated with increasing airway obstruction may result in a reduction in audible wheeze. Identification of unusual or atypical features may suggest another underlying condition (box 1).

LUNG FUNCTION TESTS AND INVESTIGATIONS FOR WHEEZE

There is no evidence that chest radiographs help in the diagnosis or management of preschool children with wheeze.¹⁹ In most young infants, airway calibre

Box 1 Differential diagnosis of chronic or recurrent wheezing in infancy (modified from 15)

- ▶ Developmental anomalies
- ▶ Tracheo-oesophageal fistula and related disorders
- ▶ Bronchomalacia (localised or generalised)
- ▶ Stovepipe trachea
- ▶ Bronchial compression syndromes
- ▶ Vascular ring
- ▶ Anomalous origin of the right subclavian artery
- ▶ Bronchial or pericardial cyst
- ▶ Congenital heart disease (L–R shunting)
- ▶ Granuloma or polyps
- ▶ Host defence defect
- ▶ Cystic fibrosis
- ▶ Ciliary dyskinesia
- ▶ Defects of immunity
- ▶ Severe combined immune deficiency
- ▶ Combined IgA and IgG2 deficiency
- ▶ Postviral syndromes
- ▶ Recurrent viral infections
- ▶ Obliterative bronchiolitis
- ▶ Airway stricture or granuloma or lymphadenitis
- ▶ Recurrent aspiration
- ▶ Gastro-oesophageal reflux
- ▶ Disorders of swallowing
- ▶ Neuromuscular disease
- ▶ Mechanical disorders
- ▶ Perinatal disorders
- ▶ Chronic lung disease of prematurity
- ▶ Congenital infection

is likely to be the most important determinant of wheeze.²⁰ Infants (8–20 months) with recurrent wheeze are shown to have reduced airway function when compared with healthy controls.²¹ Reduced airway function when present in early infancy was associated with persistent wheeze at 11 years of age, and this relationship was found to be independent of the effect of increased airway resistance and atopy in childhood.²² Although there has been an increase in the number of different methods to measure lung function in young children by forced expiratory flows, including thoracic compression technique,²³ tidal breath analysis,²⁴ interrupter resistance measurements,²⁵ multiple-breath gas washout and lung volumes,²⁶ exhaled nitric oxide,²⁷ analysis of induced sputum²⁸ and airway hyperresponsiveness,²⁹ this has not been of clinical use because of an uncooperative age group. Currently, there are no investigations that are proven to help with the diagnosis or management of wheeze in children under 2 years.

BRONCHODILATORS FOR THE MANAGEMENT OF THE ACUTE WHEEZY EPISODE

Salbutamol

Despite a paucity of evidence, salbutamol is commonly prescribed for wheezing episodes in young children. The pharmacology and pharmacokinetics of salbutamol have been relatively well documented in older children and adults.³⁰ In older children with asthma, inhaled salbutamol acts rapidly with effects seen within a few minutes having maximal effectiveness 10–15 min after administration. The half-life of salbutamol in adults is between 2 and 4 h and it has been proposed that this is similar during childhood.^{w1} Salbutamol is a partial agonist, which reaches its maximal bronchodilating effects at relatively low doses.^{w2} The results from clinical studies are best described as 'mixed'. Although some studies show a beneficial effect of short-acting β_2 -receptor agonists on lung function and clinical parameters,^{w2–w4} some show negligible effects^{w5–w8} and others demonstrate a worsening of symptoms and/or lung function parameters.^{w9–w12} A Cochrane review conducted in 2002 concluded that there is no clear evidence to support the use of β_2 -receptor agonists for recurrent wheeze in children under 2 years.^{w13} This review included eight trials and compared the effect of β_2 -agonist against placebo in 229 patients less than 2 years of age in four different settings. Importantly, salbutamol did not have an impact on requirement for hospital admission or length of hospital stay. The evidence, or rather lack of it, is even more compelling for infants with bronchiolitis. A Cochrane review analysed 28 trials with 1912 children with bronchiolitis who were given either bronchodilators or placebo and found no significant improvement in measures of oxygenation, rate of hospitalisation or duration of hospitalisation.^{w14}

Ipratropium bromide

The use of anticholinergics to treat infant wheeze also remains controversial. Anticholinergics seem to be biologically active and have effects on symptoms which parents can perceive in the home setting.^{w15} However, these data need to be interpreted with caution. In this small study involving just 23 infants, parents reported subjective superiority to nebulised water (OR 0.15, 95% CI 0.04 to 0.64), which was not replicated in diary symptom cards (OR 0.60, 95% CI 0.19 to 1.88). The assumption that nebulised water is biologically inert is in itself questionable. The inhalation of hypotonic solutions may well adversely influence both pulmonary haemodynamics and airway function. The most recent Cochrane review on this area was conducted in 2005 and included this study and five others. Data were included from a total of 321 infants in three different settings.^{w16} There were no significant differences in the length of hospital stay between ipratropium bromide and placebo; or between ipratropium bromide and β_2 -agonist compared with β_2 -agonist alone. Although combined ipratropium bromide and β_2 -agonist when compared with β_2 -agonist alone showed reduced need for physician determined 'additional therapy' at 45 min, there were no differences in hospitalisation, respiratory rate or oxygen saturations in emergency department. In fact, the only evidence that anticholinergics have any beneficial clinically relevant measurable effects in the hospital setting comes from a single study.^{w17} The quality of this study is rather low (Jadad score 2). While the authors demonstrated an improvement in clinical severity score in children receiving fenoterol and ipratropium in combination compared with nebulised saline at 24 h (OR 0.06, 95% CI 0.01% to 0.23%), they were unable to show other benefits such as a reduction in hospital stay. Moreover, children in this study who received ipratropium and fenoterol showed a non-significant unexplained increase in hospital stay compared with those who received fenoterol alone (mean difference 0.80 days, 95% CI –0.02% to 1.62%). The authors of the Cochrane review very reasonably conclude that a widespread indiscriminate use of anticholinergic agents in the treatment of wheeze cannot be supported in children under the age of 2 years.^{w16} Despite this, the authors' experience is that the use of ipratropium bromide remains pervasive in clinical practice within the UK. Certainly, we would agree with Everard *et al*^{w16} in calling for more carefully conducted research in this area.

Epinephrine

Epinephrine (adrenaline) is a non-selective β -agonist with a short half-life and a rapid onset of action. Its lack of selectivity may be of use in the treatment of viral bronchiolitis. While the Cochrane review by Gadomski and Brower demonstrated that bronchodilators other than epinephrine are relatively ineffective in

the treatment of acute bronchiolitis,^{w14} but the same is not true of epinephrine. Epinephrine has an additional theoretical benefit because it contains α -adrenergic properties in addition to the β -adrenergic effect. It has been proposed that this additional α adrenergic effect may reduce mucosal oedema and therefore improve clinical status during bronchiolitis.^{w17} A 2011 Cochrane review of epinephrine in the treatment of viral bronchiolitis in acute care settings identified 19 studies involving 2256 children. When comparing epinephrine with placebo, no differences were found for length of hospital stay, but there was evidence suggesting that epinephrine is effective for reducing hospital admissions (risk ratio 0.67; 95% CI 0.50% to 0.89%).^{w18} When used in combination with dexamethasone, these effects are even more impressive. Results from one large, high-quality trial suggest that combined treatment with systemic glucocorticoids (dexamethasone) and epinephrine may significantly reduce admissions.^{w19} However, there is insufficient evidence to support the use of epinephrine for the treatment of bronchiolitis among children already admitted to the hospital. There are no good-quality studies comparing effects of salbutamol, ipratropium and epinephrine in children less than 2 years with wheeze. A study to assess medication for wheeze in 1–5-year-old children in the community (4227 children) showed overtreatment of mild and episodic viral wheeze and chronic cough.^{w20} Personal experience of the authors suggests that there is an overuse of inhalers, particularly ipratropium, in preschool children.

LONG-TERM MANAGEMENT AND OUTCOME OF WHEEZE

Approximately 25% of the children with persistent asthma had started to wheeze by 6 months and 75% had wheezing by 3 years in long-term studies.^{w21–w23} Rhinovirus and respiratory syncytial virus have been linked to an increased risk of wheezing over time.^{w24–w26} In those children with severe early wheeze, half of the hospitalised children under 2 years were symptom free by 5 years and 70% by 10 years. Probably, due to tendency of relapse in adolescent years, this had decreased to 57% by 17–20 years.^{w27–w29} These studies also showed that female sex, passive smoking during infancy and early sensitisations to allergens were risk factors for symptoms continuing into adulthood. Young children with severe wheeze have a higher risk of developing asthma later in life particularly if they are also atopic. Parental education regarding avoidance of household smoking and known allergens have shown to be effective in long-term management of wheeze.^{w30}

DRUG DELIVERY DEVICES

The selection before prescribing an aerosol device for a child can be confusing due to the availability of many different types.^{w31} As a general principle,

pressurised metered-dose inhaler (pMDI) plus spacer and nebulisers are the two commonly used devices in wheeze. MDI without spacers are difficult to use in preschool children because of the difficulty in coordinating the device with inspiration. While a few children under 3 years of age can manage MDI plus spacer, most of them will require a face mask.^{w32} A systematic study in children less than 5 years of age with acute wheeze or asthma showed that the delivery of inhaled β_2 -agonists by pMDI without spacer was more effective, recovery was quicker and hospital admission was reduced by 60% when compared with nebulizer.^{w33} Parental education in maintaining the equipment and administering the medication is important. The new unwashed and unprimed plastic spacers are electrostatically charged leading to reduced drug delivery but this can be easily overcome by washing the spacer with detergent and allowing to drip dry. The authors have experienced situations where the wheezy children do not tolerate either of these methods and nurses and parents struggle to deliver the medication. In some of these children, we have used a nebuliser to deliver the medication while monitoring their response closely.

DISCUSSION

Let us start our summary by returning to the clinical case (Amy) and our own clinical experiences. The authors have seen dozens of children like Amy admitted to hospital over the last 12 months. Our own experience suggests that a significant minority (if not the majority) will have had clinical trials of bronchodilators despite a lack of clinical evidence for such trials of treatment. Indeed, it is common to be faced with a situation where parents report that these treatments have been effective, but there is little objective evidence supporting this. Ironically, those treatments that are most likely to be effective in the emergency room, such as nebulised epinephrine, are rarely used in routine clinical practice. These clinical scenarios place us directly upon the horns of a dilemma. It is difficult to deny treatments, which parents believe are effective without appearing hard-headed and inflexible. Indeed, parents may request extended stays in hospital or indeed re-admission to continue nebulised treatments that are of limited clinical value. The evidence base where it exists suggests that bronchodilators are of limited value in young children. However, this is not because of a lack of airway smooth muscle that is present early in fetal development. Rather, bronchodilators may paradoxically increase airway obstruction in infancy because under normal circumstances, tonic contraction of smooth muscle holds open the small airways.^{w10} Administration of bronchodilators which relaxes smooth muscle may lead to increased airway collapse. Thus, we cannot recommend routine use of bronchodilators in any wheezy infant. Careful reassurance may be all that is required. However, if a trial of

salbutamol is initiated, we would advise that careful, objective re-evaluation of a child 10–15 min after administration is mandatory, and routine use of bronchodilators should only be continued if and only if objective benefit can be shown. We certainly should discourage routine use of any bronchodilators and only continue use in the case of infants where objective evidence of benefit can be demonstrated.

Case 1

A 6-month-old boy is brought to see the paediatric ST1 because parents are concerned that he has developed loud noisy breathing after having fever and runny nose for 3 days. He was born at term and is fully immunised. He has not needed antibiotics since birth. There is no family history of atopy. On examination, he appears to be coryzal, well hydrated with mild tachypnoea and oxygen saturations of 96%. He has moderate recession and has bilateral expiratory wheeze on auscultation. He is happy and playing in the waiting area. What is the most appropriate course of action with this patient?

Comments—This child has developed wheeze probably secondary to viral upper respiratory tract infection. His wheeze is likely to improve once his viral infection resolves. So his parents were reassured and sent home.

Case 2

A 20-month-old girl was brought to the emergency department by ambulance from the out of hours (OOH) services. She has been having fever and cough for 2 days, which worsened earlier today. Parents noted that she was working hard and wheezing. They had tried salbutamol inhaler four puffs every 4 h with no improvement. At OOH, she was given a salbutamol nebuliser and sent by ambulance as her oxygen saturations were 90% in air. She has been admitted previously with similar history and needed paediatric high dependency unit admission and regular nebulisers. She has eczema and is allergic to eggs. There is a family history of asthma and hay fever. On examination, she has fever (38.2°C), is tachypnoeic and tachycardic and her saturations are 98% in 5 l/min by a face mask. She has widespread wheeze bilaterally on auscultation and has severe recession. What is the most appropriate course of action with this patient?

Comments—This child needs treatment initially with a 2.5 mg salbutamol nebuliser driven by 6 l/min oxygen and should have continuous monitoring. If there is limited response, then ipratropium bromide may be added to the treatment regimen. An underlying lower respiratory tract infection needs to be considered and antibiotics to be commenced if required. Oral amoxicillin should be used if community-acquired pneumonia is diagnosed on clinical or radiological grounds. Once stabilised, she will need to be admitted

for observation and weaning of bronchodilators. She is likely to need follow-up in outpatients.

Collaborators Dr Jyothi Srinivas.

Contributors Both authors contributed equally to this manuscript and act as guarantors for its content.

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