

THE ROLE OF BRONCHOSCOPY IN WHEEZING PRESCHOOL CHILDREN

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ABSTRACT

Lower airway tract illnesses with wheeze are common in the preschool child and occur in approximately one-third of all children. Most children with preschool wheeze do not need further investigation, but referral is needed in the following cases: if the child does not respond to treatment, if the diagnosis is in doubt, if there are other comorbid conditions present and if the wheezing is audible without a stethoscope. When the wheeze is harsh, low pitched and monophonic, large airway obstruction must be considered. The role of bronchoscopy in pre-school wheezing includes evaluating the airways for any structural and anatomical abnormalities. Thirty per cent of children investigated by airway survey will benefit from bronchoscopy. In 40–60% of children with recurrent or persistent wheeze an organism is isolated from the bronchoalveolar lavage specimen. The reported complication rate in these studies was very low.

A selective group of preschool wheezing children who are not responding to treatment have symptoms of large airway obstruction; symptoms suggestive of gastro-oesophageal reflux or unilateral chest signs may benefit from flexible bronchoscopy to diagnose the cause of their wheezing.

Keywords: bronchoscopy; preschool wheeze; large airway obstruction; bronchoalveolar lavage

INTRODUCTION

Lower airway tract illnesses with wheeze are common in the preschool child and occur in approximately one-third of all children. These children can be divided into two groups based on their symptoms and can follow the pattern of episodic viral or multiple trigger wheeze.¹ These phenotypes can change over time in an individual child.^{2,3}

Bush et al divided childhood wheezing into four groups:

1. Normal child
2. Serious conditions which it is essential to diagnose or refer
3. Minor conditions that may exacerbate or mimic wheezing, for example gastro-oesophageal reflux (GER)
4. True wheezing syndromes, including episodic viral wheeze and multiple trigger wheeze.⁴

The history and physical examination are used to categorise children and to decide whether further investigations are necessary. Although preschool wheezing is common, there is a paucity of evidence to guide clinicians in selecting diagnostic tests.

Most children with preschool wheeze do not need further investigation, but referral is needed in the following cases:

- if the child does not respond to treatment;
- if the diagnosis is in doubt;

- if there are other comorbid conditions present, and
- if the wheezing is audible without a stethoscope.

Serious conditions must be considered when the following are present: symptoms from the first day of life; a child with wheezing who is not thriving; chronic wet cough; sudden onset of symptoms; continuous, unremitting symptoms; systemic illness; digital clubbing; severe chest deformity; stridor; fixed wheeze, or asymmetric signs on auscultation.

When the wheeze is harsh, low pitched and monophonic, large airway obstruction must be considered. This wheeze is prominent centrally and the lungs are generally not hyperinflated as in small-airway obstruction. Subcostal retraction is also more common in small-airway obstruction. Table I shows the causes of large-airway pathology.

BRONCHOSCOPY

Killian introduced bronchoscopy into clinical practice in 1897.⁵ Bronchoscopy is an important diagnostic tool in the management of respiratory tract diseases in children. In addition to allowing direct visualisation of the respiratory passages, it allows for endobronchial treatment of airway lesions and the collection of samples for histopathological, microbiological and cytological investigations.⁶

TABLE 1: CAUSES OF LARGE-AIRWAY PATHOLOGY

Acquired causes:

- Pulmonary tuberculosis
- Mediastinal masses
- Foreign-body aspiration
- Post-intubation injuries

Other causes:

- tumours
- Cryptococcus
- Intraluminal tumours
- bronchial adenoma

Congenital causes:

- Bronchogenic cyst
- Duplication cyst
- Vascular malformations
- Tracheal stenosis
- Tracheobronchomalacia

Bronchoscopy is not only used in the removal of foreign bodies but helps with diagnosing congenital lung abnormalities and acquired lung pathology; it also plays a role in the investigation of children with recurrent and/or opportunistic respiratory infections.

Godfrey et al published a study on the utility of flexible bronchoscopy in children, examining 200 consecutive procedures.⁹ In this study, the main indications were wheezing (26%), recurrent pneumonia (21%) and atelectasis (12.5%).⁷ Similarly, in another study, 536 fibre-optic bronchoscopies were performed on children (<14 years), where the commonest indications were persistent atelectasis (31%), stridor (25%), tuberculosis (12%), suspected foreign-body inhalation (11%) and persistent wheezing (10%).⁸

In a multicentre European study, the primary diagnosis prior to bronchoscopy was recurrent or persistent pneumonia (17%), followed by wheezing unresponsive to treatment (15.5%), persistent atelectasis (14%) and stridor (13%).⁹

ROLE OF BRONCHOSCOPY IN PRESCHOOL WHEEZING

Routine investigations for children with wheezing who are not responding to treatment include a blood test such as IgE and RAST, IgG, IgM, IgA as well as IgG subclasses. A sweat test and genetic testing for cystic fibrosis could be considered. Gastro-oesophageal reflux needs to be excluded with the use of contrast studies and pH monitoring. Nasal ciliary brushings can be used to exclude primary ciliary dyskinesia (PCD).

A scan using high-resolution chest computed tomography (HRCT) is indicated if bronchiolitis obliterans or other structural abnormalities are considered.

The role of bronchoscopy in preschool wheezing includes evaluating the airways for any structural and anatomical abnormalities. This includes the upper and the lower airways. It is also important to always evaluate the upper airways with flexible nasoendoscopy and laryngoscopy and not just a flexible bronchoscopy through a laryngeal mask airway. Large airways can be either structurally or functionally abnormal or can present a combination of abnormalities. Tracheomalacia



Figure 1: Bronchoscopy image of double aortic arch with anterior compression of the trachea from the right and posterior compression

and bronchomalacia can be missed if the child is not breathing spontaneously. Vascular abnormalities are more commonly found than airway stenosis. These abnormalities can include double aortic arch, innominate artery compression, left pulmonary artery sling or left main bronchus (LMB) compression by a patent ductus arteriosus remnant.¹⁰ The pattern of compression seen on bronchoscopy can be a guide to the type of vascular compression present.

The trachea will be compressed both anteriorly and posteriorly by a double aortic arch and only anteriorly in the case of the innominate artery (see Figure 1). A left pulmonary artery sling causes compression of the distal trachea and the carina. Airways can also be compressed by congenital and acquired cardiac conditions and it is mostly the LMB that is vulnerable.

The two important congenital causes of airway obstruction are bronchogenic cyst and airway narrowing due to compression or stenosis (see Figures 2 and 3). Both cause wheezing that is indistinguishable on clinical grounds but diagnostic at bronchoscopy. Bronchogenic cysts can occur at different anatomical locations, with those located in the subcarinal and paratracheal region more commonly causing airway compression. Tracheobronchial anomalies can present with stridor, wheeze, cough, recurrent pneumonia or recurrent and persistent atelectasis. Airway abnormalities can present in association with other conditions such as genetic syndromes, congenital heart defects and vascular abnormalities. Tracheal stenosis is a rare but life-threatening congenital malformation. Tracheomalacia is more common and may be associated with vascular rings or trachea-oesophageal fistula.¹¹

Only a few articles have been published on the value of bronchoscopy in persistent wheezing in children. In one such

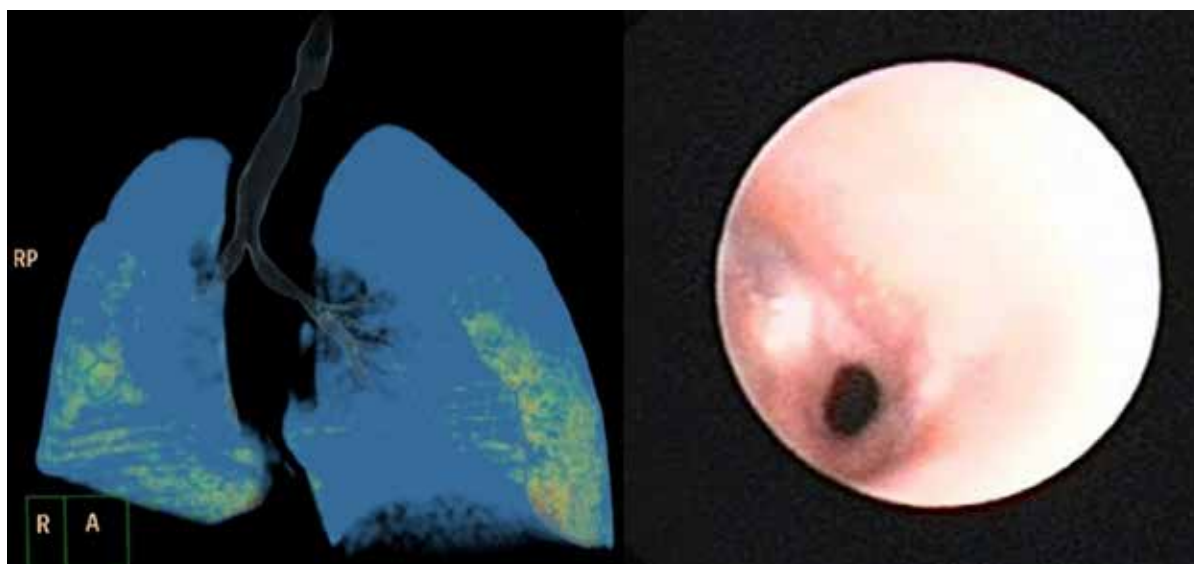


Figure 2a: Chest CT-scan reconstruction: narrow segment of trachea and hypoplastic right lung

Figure 2b: Bronchoscopy images demonstrating tracheal stenosis

study of 113 children (median age 14 months) with persistent wheezing, pathological findings were found in 48% of cases. This included tracheobronchomalacia ($n = 38$), foreign-body aspiration ($n = 14$) and vascular compression ($n = 2$).¹²

Gu et al reported on 156 children with refractory wheezing and found that 21.8% of them had airway malformations, which included tracheomalacia, airway stenosis and tracheal bronchus. The rate of malformations was higher in children less than 12 months of age (31%). A bronchoalveolar lavage (BAL) performed in these children showed that neutrophil-mediated airway inflammation was characteristic in those with refractory wheezing. From BAL specimens a virus was identified in 13.9% ($n = 17$) and bacterial organisms in 59.6% ($n = 93$). In the BAL, *Mycoplasma pneumoniae* were found in 51.6% ($n = 63$). Other bacteria isolated included *Haemophilus influenza* ($n = 12$) and *Streptococcus pneumonia* ($n = 12$).¹³

Boesch et al recently reported on children with persistent or recurrent wheezing. The potential anatomical cause for wheezing was identified in 45.7% of patients and inflammatory changes were identified in 49.5% of procedures. Tracheobronchomalacia was the most commonly identified anatomical lesion.¹⁴

Both Marguet et al and Le Bourgeois have previously reported high levels of neutrophils in the BAL of wheezing children. These may be related owing to the high level of interleukin 8 secretion in these patients.^{15,16}

Saglani et al have reported on the use of investigation of young children with severe recurrent wheeze and if there is any clinical benefit in doing so: 37 out of 47 children had abnormal bronchoscopy findings. Their findings included structural abnormalities ($n = 13$), excessive mucus ($n = 20$) and macroscopic inflammation ($n = 10$). Bacteria were cultured from BAL specimens in 27% of cases. In addition, an endobronchial



Figure 3: CT scan images of bronchogenic cyst in the neck causing tracheal compression

biopsy was done which showed that 44% had eosinophilic changes and 28% had a thickened reticular basement membrane.¹⁷

The American Thoracic Society (ATS) recently published their clinical practice guidelines on the diagnostic evaluation of infants with recurrent or persistent wheezing. They evaluated the following questions: Should infants with persistent wheezing despite treatment with bronchodilators, inhaled corticosteroids or systemic corticosteroids undergo airway survey via flexible bronchoscopy and should a BAL be done?¹⁸ Regarding both of these questions, very low-quality evidence was found. In the case of bronchoscopy, case series only were identified. Collectively, 1 364 patients were identified and 452 (33%) were found to have anatomical abnormalities that led to wheezing. This included tracheomalacia, bronchomalacia, vascular rings and airway compression by a vascular structure. No serious complications of bronchoscopy were recorded, except for transient hypoxemia in 5–10% of cases.¹⁸

Most children with wheezing caused by tracheomalacia, bronchomalacia or tracheobronchomalacia are managed conservatively, especially if the symptoms are mild and the airway malacia is the only abnormality present. Most of these children improve with time. Only children with life-threatening symptoms, recurrent pneumonia or severe failure to thrive require an intervention that includes constant positive airway pressure or airway surgery. In most of these cases the surgery will be aortopexy, which relieves most wheezing resulting from tracheomalacia, but is less effective in cases with tracheobronchomalacia. About 80–100% of patients with vascular rings or vascular compression of the airways improve with surgery. Most wheezing caused by vascular rings and vascular airway compression is unlikely to self-resolve and needs surgical correction.¹⁸

In conclusion, approximately 30% of children being investigated by airway survey will benefit from bronchoscopy. This would be through surgery or indirectly by avoiding unnecessary tests and treatment. Also, very importantly, parents can be reassured about the lesion and the most likely outcome.

Data are available from 20 studies on performing a BAL in wheezing children. In 40–60% of children with recurrent or persistent wheeze an organism is isolated from the BAL specimen. The reported complication rate in these studies was very low. Furthermore, children with a positive BAL culture received a prolonged course of antibiotics, and in one study 48% of children receiving antibiotics the cough resolved compared to only 16% of those who did not receive an antibiotic.¹⁸ It is estimated that 20–30% of children with persistent wheezing who have a bronchoscopy and BAL performed were found to have a lower respiratory tract infection, which improved following a course of antibiotics.¹⁸

BRONCHOSCOPY IN WHEEZING PRESCHOOL CHILDREN IN DEVELOPING COUNTRIES

In countries with high incidence of TB and HIV, these must also be considered as causes of wheezing that is not responding to treatment. TB can present in young children with airway

obstruction as a result of enlarged lymph nodes compressing the large airways. The bronchus intermedius, left main bronchus and trachea are the most common airways at risk of being externally compressed, or the airway can be narrowed by a combination of external compression and ulceration into the airways.¹⁹ The role of bronchoscopy is twofold in these cases: it enables the airway to be accessed directly and diagnostic samples can be obtained for culture and/or GeneXpert.²⁰

In HIV-infected children with airway obstruction, *Cryptococcus* lymph-node enlargement, viral papillomata, Kaposi's sarcoma and other opportunistic infections must be considered. Bronchoscopy may be diagnostic and diagnostic biopsies can be collected.

FOREIGN-BODY ASPIRATION (FBA)

The diagnosis of a foreign body in a paediatric airway may be difficult, because this phenomenon most commonly occurs in infants and toddlers who are unable to communicate the circumstances leading to the aspiration event. The signs and symptoms may be non-specific. Barrios et al have reported that among all the clinical symptoms, the history of a choking crisis has the highest diagnostic sensitivity and specificity (97% and 63% respectively).²¹ Wheezing in the absence of known pulmonary disease should be considered indicative of FBA until proven otherwise, especially if the wheezing is unilateral.

GASTRO-OESOPHAGEAL REFLUX (GER) AND PRESCHOOL WHEEZING

Both bronchoscopy and BAL may be of value in evaluating the preschool child with wheezing and symptoms of GER. It is important to exclude upper airway pathology that can lead to aspiration. This includes vocal cord palsy and dysfunction, laryngomalacia and a laryngeal cleft. When a laryngeal cleft is suspected, both flexible and rigid bronchoscopy with palpation of the inter-arytenoid notch must be done as the diagnosis may be missed if only a flexible bronchoscopy is performed. Although rare, an H-type trachea-oesophageal fistula must also be excluded. Boesch et al identified a laryngeal cleft in 17% of cases with persistent or recurring wheezing.

GER may be associated with chronic or recurrent asthma-like symptoms secondary to bronchoconstriction reflexes and/or inhalation of gastric content. The lipid-laden macrophages index (LLMI proportion) of lipid-laden alveolar macrophages in a BAL sample has been used as an index to establish the degree of gastric aspiration. BAL cells are stained with oil-red and the amount of lipid per single macrophage is evaluated by a semi-quantitative method described by Colombo and Hallberg, giving a score of 0–4 to each cell, according to the amount of lipid in the cytoplasm.²² The final index is determined by evaluating 100 cells.²² The utility of the LLMI as a marker for GER in respiratory disease has been controversial, its use problematic for the following reasons:

- It is found in a variety of other pulmonary conditions.
- It is not the gold standard for recurrent aspiration.
- It does not differentiate whether aspiration is related to swallowing abnormalities or to GER.

In taking all the evidence into consideration, the LLMI is still used by clinicians as an adjunct investigation for children whose symptoms are suspicious for aspiration and therefore warrant bronchoscopy. Recently BAL pepsin was evaluated as a possible diagnostic test for GER.²³ It may be useful in cases where pH monitoring is inconclusive, but the symptoms are suggestive of GER.

USE OF ENDOBRONCHIAL BIOPSY IN PRESCHOOL CHILDREN WITH PERSISTENT WHEEZING

Markers of airway remodelling are epithelial injury, thickening of the reticular basement membrane, goblet cell and airway smooth muscle hypertrophy, hyperplasia and angiogenesis.^{24,25} Some studies have suggested that remodelling occurs early during the course of asthma owing to long-standing airway inflammation. Most studies on wheezing show conflicting results, but reveal a poor relationship between inflammation and remodelling in young children.^{26,27} Lezmi et al recently reported that in preschoolers with severe recurrent wheeze airway wall structure did not correlate with inflammatory cell counts and that atopy is associated with higher hypertrophy of the airway smooth muscle. Airway inflammation and remodelling may develop independently.²⁸ Currently, routine endobronchial biopsy has a limited role and remains a research tool.

CONCLUSION

A selective group of wheezing preschool children who are not responding to treatment and who have symptoms of large airway obstruction, symptoms suggestive of GER or unilateral chest signs may benefit from flexible bronchoscopy to diagnose the cause of their wheezing. Bronchoscopy in preschool children with persistent wheezing has a twofold role. It is important in helping to exclude anatomical abnormalities and may also help to identify pathogens, the type of inflammation present and whether aspiration is present. Overall, the risk of anaesthesia is justified in this population based on the high frequency of management changes that are exposed by the bronchoscopy findings. The changes in management range from medical management to surgical interventions, including the removal of foreign bodies. It is also important to be able to identify an alternative explanation for the wheezing that may result in the elimination of unnecessary medication. Future research is necessary that investigates the markers of more specific inflammation and environmental exposure.

DECLARATION OF CONFLICT OF INTEREST

The author declares not conflict of interest.

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