## Review Article

# Managing wheeze in preschool children: How difficult can it be?

Shaikh M. Iqbal

Department of Pediatrics, College of Medicine, King Saud University, Riyadh, Saudi Arabia

## ABSTRACT

Wheeze is a common symptom in infants and preschool children. Up to 30% of children wheeze at least once before the age of 3 years and 2% of those have it severe enough to warrant hospital admission. Not only parents but also physicians have difficulty in recognizing wheeze. Wrong diagnosis of the underlying condition leads to inappropriate and unnecessary management and patient morbidity. Asthma is the commonest underlying condition in children with wheeze, but the differential diagnosis is quite broad and a systematic approach including a good clinical history, thorough physical examination and appropriate investigations are essential to reach the accurate diagnosis.

**Keywords**:

Wheeze; Infants; Preschool children; Asthma.

## INTRODUCTION

Up to 30% of children have at least one wheezing episode before the age of 3 years and 48-50% of children wheeze before 6 years of age [1,2]. Up to 2% of all infants suffer from wheezing severe enough to warrant hospitalization [3,4].

Wheeze is traditionally defined as a high-pitched sound with a musical quality resulting from turbulence through narrowed tubes as a sign/symptom of broncho-spastic bronchial airways, and any other reason leading to narrowing of intrathoracic airways and expiratory flow limitation, e.g. anatomical abnormalities of the airways, cystic fibrosis and bronchomalacia [5]. Wheeze can be heard with and without the use of a stethoscope and is assumed to be associated generally with a diagnosis of asthma. Though wheeze is common in a large proportion of infants and young children presenting to the health practitioner with respiratory illness, its recognition is sometimes not easy as described before. It, nevertheless, is an important symptom and sign that needs to be identified accurately and thankfully children do not usually present to the clinician with wheeze alone and the associated symptoms and signs are important in reaching the right diagnosis and eventual successful management of the underlying condition.

Whilst wheeze is a common symptom and sign, not only do the parents have difficulties in recognizing it, but low consistency has also been reported between parent-reported and physician diagnosed wheeze [6,7]. Less than half of parents reported wheeze in children with severe asthma exacerbation who

**How to cite this article:**
Iqbal SM. Managing wheeze in preschool children: How difficult can it be? Sudan J Paediatr 2012;12(2):17-26.

required hospitalization and/or systemic steroids [8]. Physicians may be more accurate in recognizing wheeze especially by auscultation than parental report; however it is well known that there is a significant inter-observer variation and errors not only between physicians but also between specialists and studies have documented these observations [9-11].

## WHEEZING AND ASTHMA PHENOTYPES

The commonest cause of wheezing in preschool children is asthma. A recent study, however, argues that physician diagnosed wheeze should not be a prerequisite for diagnosis of asthma in children under 3 and use of quantitative global assessment of burden of asthma symptoms might be better at predicting asthma [12]. Great and invaluable amount of information has now been gathered about childhood wheezing and asthma phenotypes from large independent birth cohort studies [13-15]. The earliest reported birth cohort [13] divided the children into 4 phenotypes; those 1) who never wheezed (51%), 2) who had transient early wheeze (20%), 3) who developed late wheeze (15%) and 4) persistent wheezers (14%). The latter 2

cohort studies [14,15] have shown that the majority of children (61 to 75%) have never wheezed or have infrequent wheeze. Up to 23-34% of children start to wheeze very early in life by six months of age. Only 4.7 to 7.5% have a later onset of wheeze. Of those who start to wheeze early, a subgroup (16.5%) of them stop wheezing by 3.5 years (transient early) and some take about 7.5 years to subside (prolonged early - 3.1%) [14]. About 3.5-6% of children have persistent wheezing right from an early age. Children with intermediate onset phenotype (2.5%) start to develop wheezing episodes around 18 months of age and those with late onset phenotype (4.9%) do the same around 3.5 years of age.

These large cohort studies have provided information based on retrospective analysis and we can use it to speculate the future pattern that the wheezy infants and preschool children are probably going to follow, however the identification of the wheezing phenotype itself is not useful for immediate clinical management. To identify future asthmatics in young children who present with wheezing we can use the asthma predictive index (API) [Table 1], which was developed using

Table 1 – Asthma Predictive Index (API)*

| |
|---|
| Major findings |
| Medical diagnosis of eczema in the first 3 years of life |
| Parent diagnosed with asthma |
| Minor findings |
| Medical diagnosis of allergic rhinitis in the first 3 years of life |
| Wheezing episodes unrelated to colds in the first 3 years of life |
| Eosinophilia in peripheral blood of 4% or more |
| API Positives |
| Child with > 3 episodes of wheezing or obstructive bronchitis/year during the first 3 years, |
| AND |
| 1 major finding and 2 minor findings. |
| API Positive: 77% sure → infant will have asthma at school age |
| API Negative: 68% sure → infants will cease to have wheezing events at school age |
| Infants with positive API: 7 times greater risk of asthma at school age than those with a negative API (odds ratio,7.1; 95% confidence interval,3.5-14.1) |

*Adapted with permission from Castro-Rodriguez et al [16].

Tucson cohort data and included risk factors such as frequent wheezing, parental history of asthma, and signs of personal atopy [16]. There is also a modified API (mAPI) criteria which specified the frequency of wheezing as >3 exacerbations of wheezing in the past 12 months, with at least 1 physician-confirmed exacerbation. Additionally, the mAPI also specified allergic sensitization to 1≥ aeroallergen among the major criteria and replaced allergic rhinitis as a minor criterion with allergic sensitization to milk, egg or peanuts [17].

The European Respiratory Society (ERS) Task Force proposed simplifying the wheezy children into those with episodic wheeze (viral triggered) or those with multiple-trigger wheeze [18]. Episodic wheeze was defined as separate wheezy episodes in association to viral infection, with the child being well in between episodes. The children with multiple-trigger wheeze do so in response to other triggers in addition to being symptomatic during viral infections.

# MANAGING THE ACUTE WHEEZING EPISODE

It might be difficult to differentiate infants who have bronchiolitis and those who have the first wheezy episode secondary to a viral infection if using a North American definition [19] of bronchiolitis as opposed to the United Kingdom definition [20].

Supportive treatment is usually all that is needed for the management of acute viral bronchiolitis. A subgroup of the infants with personal or family history of atopy may respond to inhaled bronchodilators and a trial may be justified for them cautiously as they may develop a paradoxical response. Some infants with bronchiolitis may also benefit from nebulised racemic epinephrine or nebulised hypertonic saline [21]. For preschool children with an acute wheezy episode, short acting inhaled 2ß agonists should be used for symptomatic treatment. Ipratropium bromide can be considered in patients with severe wheeze in addition to the short acting 2ß agonists. One can consider giving a short 3-day course of oral corticosteroids to these children with severe episode enough to warrant hospital admission [18]. For preschool children with multiple-trigger wheeze, maintenance therapy of inhaled corticosteroids at equivalent daily dose of up to 400 mg/ day beclomethasone should be initiated [18]. If responded to treatment, they should be weaned to the lowest dose to achieve adequate control and treatment discontinuation should be considered after several months. If children become symptomatic on cessation of the maintenance therapy, it should be restarted. If the diagnosis is unclear, especially in children less than 2 years of age, a trial of inhaled corticosteroids can be tried and those children, who do not respond to the treatment despite adequate compliance, should be referred to pediatric pulmonologist.

# DIFFERENTIAL DIAGNOSIS

The differential diagnosis for wheezing in preschool children is quite broad and an open mind and high degree of suspicion is required to ascertain the cause. All children who present with recurrent wheeze do not have asthma and some with asthma may have a co-morbidity, which makes their management difficult, and others may have an asthma mimicking condition. A good and comprehensive clinical history from the parents, a thorough physical examination, and appropriate diagnostic investigations are needed to arrive at a diagnosis and initiate appropriate treatment. In taking a history one should ask about age of onset, the pattern of wheezing, and its association with feeding, cough, coryza, diurnal variation and seasonality. A list of differential diagnosis is given (Table 2).

Table 2 - Differential diagnosis of wheezing in infants and preschool children

| |
|---|
| Acute viral bronchiolitis |
| Viral infections causing episodic wheeze |
| Asthma |
| Aspiration lung disease (due to recurrent primary aspiration or GERD and secondary aspiration) |
| Bronchopulmonary dysplasia |
| Inhaled foreign body |
| Cystic fibrosis |
| Primary ciliary dyskinesia |
| Immunodeficiency and recurrent chest infections |
| Bronchomalacia |
| Congenital vascular anomalies |

## Aspiration lung disease

Recurrent aspiration (RA) either primary or secondary to Gastro-oesophageal reflux disease (GERD) on its own can cause significant morbidity or it could be a co-morbid condition in infants and preschool children complicating asthma. They may present in infancy with vomiting, choking and/or coughing during feeds. There are some infants who offer no clue in the history and may have silent aspiration. Investigations to diagnose children with primary aspiration and those with GERD and RA include video-fluoroscopic swallow study, barium swallow, an upper gastrointestinal radiographic examination with barium and overnight pH study. Investigators looking at the prevalence of GERD with respiratory symptoms in a study report that 40- 60%% of children with wheeze had GERD [22,23].

A recent study has shown that about 50% of infants and young children with recurrent wheezing and no gastrointestinal symptoms have silent GERD [24]. Up to 86% of patients with GERD in another study did not have gastrointestinal symptoms [23]. Up to 64% of infants with wheeze were shown to have GERD, 60% of whom were able to come off inhaled steroid therapy within 3 months of starting anti-reflux therapy in another study [25]. Even in older children there is an association between GERD and wheezing [26,27]. However, the evidence to support GERD treatment to improve asthma control is variable [28-30].

We have seen children with recurrent wheeze to have severe GERD and RA and had already developed obliterative bronchiolitis and bronchiectasis by the time they reached the pulmonology team (Figure 1). Screening for GERD and RA is important to initiate early antireflux medication or even gastrostomy and fundoplication in selected cases. The results of initiating treatment may help in children coming off inhaled steroids completely.

## Foreign body inhalation

Inhaled foreign body (IFB) is common in children under 3 years of age [31]. Most of the IFB are food items, with peanuts being the most common [32]. IFB should be suspected in any child who presents with a sudden onset of cough and focal wheeze following a history of choking. Most of the IFB in children are not radio-opaque; however they may be associated with hyperinflation, atelectasis, or consolidation. Up to 50% of the children have normal Chest X-rays [33]. Chest radiographs (posteroanterior and lateral views) and bronchoscopy later may be necessary for diagnosing and removing the FB. A computerized tomography (CT) scan is usually not required for diagnosing the IFB.

The history of choking is not always essential and we have even seen an infant who presented to our facility
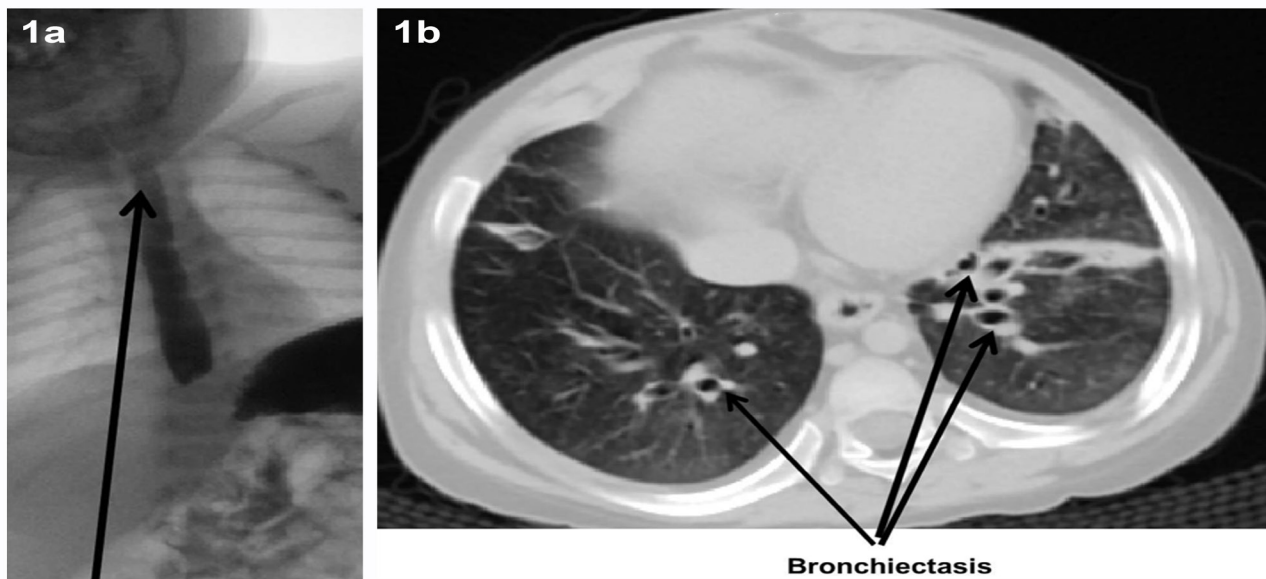
Figure 1- a) Barium study showing severe gastro-esophageal reflux disease (GERD). Contrast reaching upper third of oesophagus.     b): Recurrent aspiration pneumonias resulting in bilateral bronchiectasis (arrows).

with history consistent with acute viral bronchiolitis. On being consulted for an unusually prolonged course of illness, we found mild hyperinflation of the right middle and lower lobes on chest radiograph and an IFB was removed by rigid bronchoscopy after its presence was confirmed by CT scan and virtual bronchoscopy. The IFB was found to be a small piece of chicken bone (Figure 2).
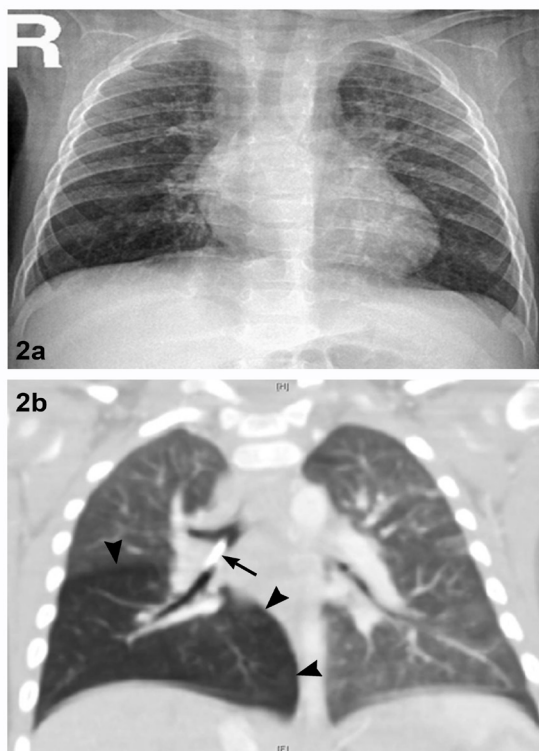


Figure 2- a) Chest X-ray shows hyperinflation of the right middle and lower lobes.     b) Coronal section CT scan of infant's chest showing (darker area) hyperinflation of right middle and lower lobes (arrowheads) with hyperdense (bright white) foreign body in the bronchus intermedius (arrow).

## Cystic fibrosis (CF)

CF is the most common autosomal recessive disorder in Caucasians. It also occurs in Hispanics, African-Americans, but is less prevalent in Asian and Arab populations. It results secondary to mutations in the CFTR (transmembrane conductance regulator) gene which codes for a protein that functions as a cyclic adenosine monophosphate (cAMP) regulated chloride channel. CFTR gene mutations result in abnormalities of chloride transport across epithelial cells on mucosal surfaces. This results in decreased chloride secretion and increased sodium and water reabsorption across epithelial cells [34]. The volume and height of the epithelial lining fluid is reduced causing decreased hydration of mucous, which promotes infection and inflammation as the mucociliary clearance becomes impaired. A large proportion children with cystic fibrosis will be picked up on newborn screening and the majority will be diagnosed before age of three. The key to prevent permanent damage to the lung is to intervene early with treatment plans and to achieve this if the diagnosis is picked up on screening before the child is symptomatic [35].  One has to suspect CF if a child presents later with history of recurrent cough, wheeze and failure to thrive along with foul smelling greasy stools. If there are additional signs of digital clubbing (usually in older children), then one

has to screen with a sweat chloride test and also send for genetic mutations that may be common in that part of the world. If the diagnosis is delayed, the children can present with irreversible damage to the lungs (bronchiectasis) [Figure 3] and progress to end stage lung disease requiring lung or a combined heart –lung transplant. The other complications are CF related liver disease and CF related diabetes.  Once diagnosed, the children need regular follow up by a multidisciplinary team which includes a pediatric pulmonologist, gastroenterologist, endocrinologist, specialist nurses, dietician, pharmacist, psychologist and social worker. There is exciting new development in treatment strategy in trying to increase the expression or improve the function of the mutated CFTR protein with pharmacological agents in patients with specific mutations [36]. Other novel treatment options are continually being explored and developed to improve the overall care and increase the lifespan of the patients.

## Primary ciliary dyskinesia (PCD)

Primary ciliary dyskinesia (PCD) or immotile cilia syndrome (ICS) is an autosomal recessive condition in which abnormal ciliary ultra structure and function result in the lack of effective ciliary motility, causing impaired mucociliary clearance. This leads to recurrent or persistent respiratory infections, sinusitis,
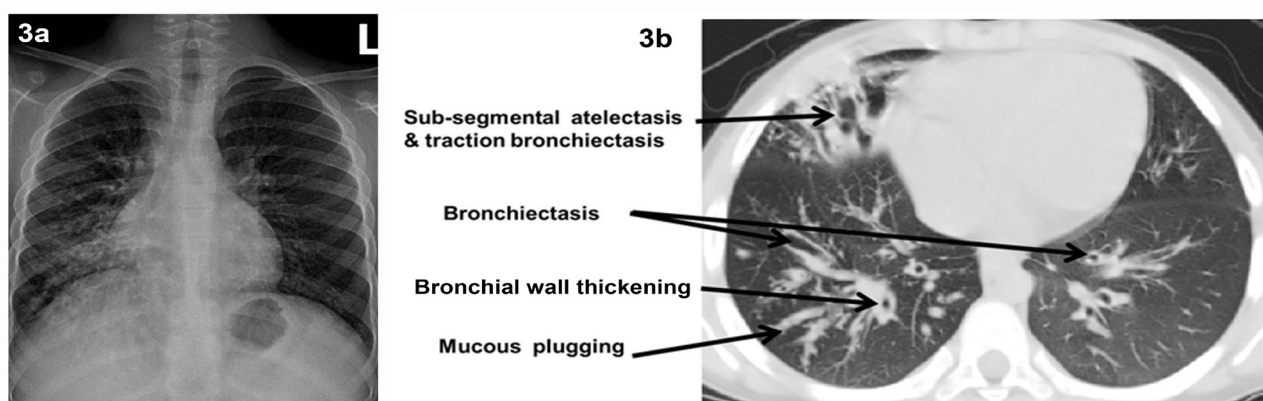


Figure 3 – a) Chest X- ray of a child with cystic fibrosis showing nodular and parabronchial bronchiectatic changes in the right middle and right lower lobes.      b) High resolution CT chest of a child with cystic fibrosis showing generalized bronchiectatic changes with bronchial wall thickening mostly involving the right middle lobe and associated with subsegmental atelectasis and areas of mucous plugging.

otitis media and male infertility. In 50% of the patients, ICS is associated with situs inversus (Figure 4). The true incidence is not clearly known but the estimated incidence varies from 1:4000 to 1:22000 worldwide [37]. It might account for up to 13% of all patients with bronchiectasis, being relatively more common in

North African than in European patients [38]. About 12 genetic mutations are currently identified from Saudi Arabia.  In our institute 13 patients were found to have *RSPH*9 p.Lys268del [39].

Neonatal respiratory symptoms vary from clear rhinorrhoea and tachypnoea, with or without the need
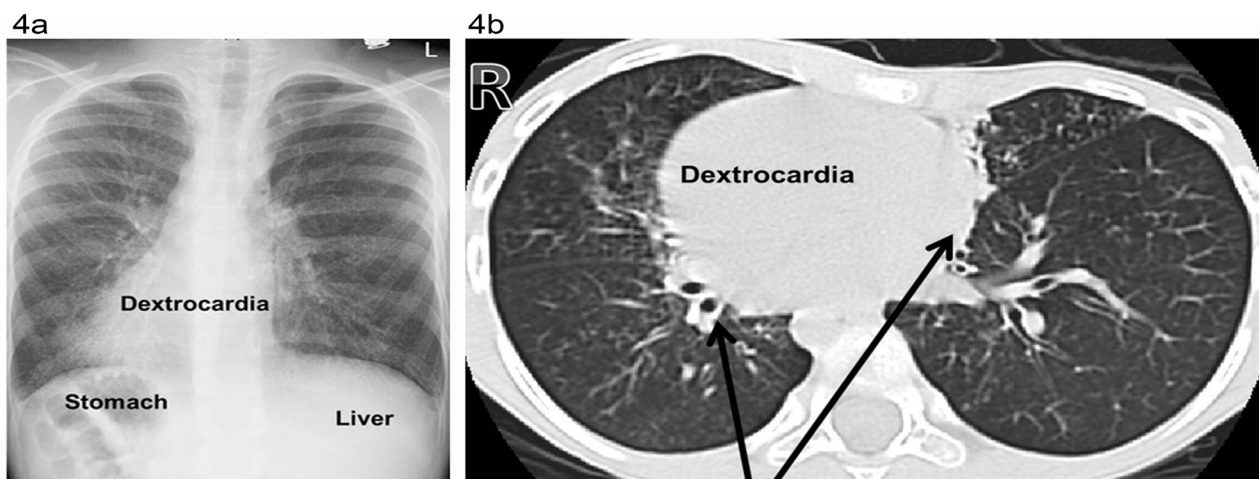


Figure   4 – a) Chest X-ray of a child with primary ciliary dyskinesia (PCD) showing total situs inversus and unclear right heart border with tram track shadows  extending to the peripheries suggestive of right middle lobe bronchiectasis.      b) High resolution CT scan of a child with PCD  showing dextrocardia along with juxtacardiac fibro-etelectasis in the lingula and right middle lobe with traction bronchiectasis (arrows).

for supplemental oxygen therapy, in about 75% of babies born at full-term [40,41].

The older children have chronic productive or wet-sounding cough, with or without recurrent atelectasis or pneumonia. Atypical asthma that is nonresponsive to treatment, especially if associated with a wet-sounding cough, should raise a suspicion of PCD. The diagnosis requires the presence of the characteristic clinical phenotype and either specific ultra-structural ciliary defects, identified by transmission electron microscopy, or evidence of abnormal ciliary function. The management of these children involves regular follow up and treatment strategies to improve mucociliary clearance and treat bacterial infections to prevent permanent lung damage like bronchiectasis (Figure 4b).

## Bronchiolitis obliterans

Bronchiolitis obliterans (OB) is a rare irreversible obstructive lung disease that occurs in children after severe viral infection of the lower respiratory tract, resulting in bronchiolar narrowing and obliteration by inflammation and fibrosis [42]. It should be suspected if symptoms of cough, wheeze, dyspnoea and exercise intolerance are disproportionately severe to chest X-ray findings. Although adenovirus is a commonly implicated infectious agent in a non-transplant pediatric population, other viruses like influenza can cause it. OB is characterized by tachypnoea, increased antero-posterior chest diameter, crackles, wheezing, which along with the radiographic features may wax and wane for weeks or months, with recurrent episodes of atelectasis, pneumonia, and wheezing [43].

The diagnosis of bronchiolitis obliterans can be made with confidence in patients with consistent clinical presentation and evidence of fixed airways obstruction by pulmonary function testing and high resolution CT (HRCT) scan of lung (Figure 5), without resorting for lung biopsy.

Management includes general supportive measures which include avoidance of inhaled irritants like smoke, airway-clearance techniques, adequate nutritional intake, annual influenza vaccination, and supplemental oxygen for hypoxemic patients.

## Bronchopulmonary dysplasia

Bronchopulmonary dysplasia (BPD) is a chronic lung disease that affects babies born prematurely and have needed mechanical ventilation and oxygen therapy for acute respiratory distress. The increased survival of very immature infants due to improved antenatal and neonatal care has led to increased BPD incidence. The rates of wheezing, or bronchial hyper-responsiveness, are generally reported to be higher
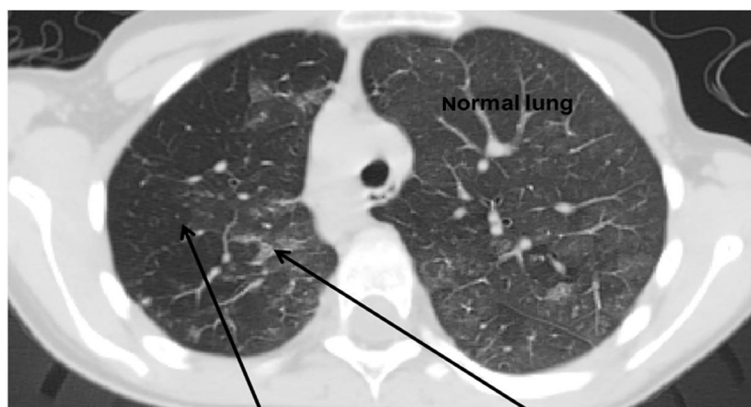


Figure 5 - Bronchiolitis obliterans: Expiratory high resolution CT scan of the chest showing areas of hyperinflated lung (arrow) and patchy ground glass haziness (arrow) also described as geographical or mosaic pattern of the lung.

in BPD survivors [44-46]. Lung function including respiratory resistance and compliance, are impaired during the early phases but subsequently improve, due to airway growth and development of new alveoli [47]. Pulmonary function abnormalities are characterized as mild to moderate airflow obstruction with air trapping. The management of children in the first 2-3 years of life involves ensuring adequate nutrition and monitoring growth. Supplemental oxygen may be necessary to reduce the respiratory workload and maintain oxygen saturations more than 95% to reduce frequent hospitalizations and help prevent possible development of pulmonary hypertension. Palivizumab, a monoclonal antibody against respiratory synctitial virus, has reduced the hospitalization rates by 39% and is recommended in high-risk population by many health authorities

worldwide. Some of these children with BPD may have small airways obstruction and decreased exercise tolerance along with higher incidence of asthma and may need inhaled bronchodilators and corticosteroids.

## Other causes

Structural airway abnormality like tracheo-bronchomalacia, either isolated/congenital, or secondary to vascular lesions may lead to persistent wheezing and poor exercise tolerance which does not respond to bronchodilation. Flexible bronchoscopy, barium study and CT angiography may be needed to diagnose and manage these children. Surgical options like resection of the abnormal vascular ring/sling or aortopexy may be needed depending on the finding on investigations.

Children with or with out immunodeficiency may

develop persistent bacterial bronchitis (PBB). One study identified that 60% of children with PBB were symptomatic before 2 years of age with wheeze and shortness of breath and also reported that 30% of children with asthma also had PBB [48]. Children with PBB usually present with moist cough and associated wheeze and seem to get better after courses of oral or parentral antibiotics. A prolonged course of 2-6 weeks broad spectrum empirical antibiotic choice to treat the commonest bacteria that cause PBB (*Streptococcus pneumoniae, Moraxella catarrhalis, Haemophilus influenzae*) may be enough. However, identifying the bacteria and the antibiotic sensitivities by obtaining bronchoalveolar lavage samples during bronchoscopy may be a more accurate way of managing these patients.

## CONCLUSION

While wheeze is a common symptom with which the preschool children present, accurate identification from thorough clinical history, physical examination and appropriate investigations is essential to reach the right diagnosis and manage the underlying condition.

## ACKNOWLEDGEMENT

## REFERENCES

1. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life: the group health medical associates. N Engl J Med 1995; 332: 133–138.
2. Bisgaard H, Szefler S. Prevalence of asthma-like symptoms in young children. Pediatr Pulmonol 2007; 42: 723–728.
3. Boyce TG, Mellen BG, Mitchel EF,Jr, Wright PF, Griffin MR. Rates of hospitalization for respiratory syncytial virus infection among children in medicaid. J Pediatr 2000; 137:865-870.
4. Koehoorn M, Karr CJ, Demers PA, Lencar C, Tamburic L, Brauer M. Descriptive epidemiological features of bronchiolitis in a population-based cohort. Pediatrics 2008; 122:1196-1203.
5. Elphick HE, Sherlock P, Foxall G, Simpson EJ, Shiell NA, Primhak RA, et al. Survey of respiratory sounds in infants. Arch Dis Child 2001; 84:35-9.
6. Bisgaard H, Bønnelykke K. Long-term studies of the natural history of asthma in childhood. J Allergy Clin Immunol 2010; 126:187-97.
7. Cane RS, Ranganathan SC, McKenzie SA. What do parents of wheezy children understand by ''wheeze''? Arch Dis Child 2000; 82:327-32.
8. Bisgaard H, Swern AS, Knorr B. To wheeze or not to wheeze: that is not the question-the sequel. J Allergy Clin Immunol 2012 Feb 23.
9. Lowe L, Murray CS, Martin L, Deas J, Cashin E, Poletti G, et al. Reported versus confirmed wheeze and lung function in early life. Arch Dis Child 2004; 89:540-3.
10. Pasterkamp H, Wiebicke W, Fenton R. Subjective assessment vs computer analysis of wheezing in asthma. Chest 1987; 91:376-81.
11. Bisgaard H, Bønnelykke K. Long-term studies of the natural history of asthma in childhood. J Allergy Clin Immunol 2010; 126:187-97.
12. Nanna Skytt, Klaus Bønnelykke, and Hans Bisgaard. To wheeze or not to wheeze: That is not the question. J Allergy Clin Immunol 2012; 130:403-7.
13. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med 1995; 332:133–8.
14. J Henderson, R Granell, J Heron, A Sherriff, A Simpson, A Woodcock, et al Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood Thorax 2008;63:974–980.
15. Brunekreef B, Smit J, de Jongste J, Neijens H, Gerritsen J, Postma D, et al. The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study: design and first results. Pediatr Allergy Immunol 2002; 13:55-60.
16. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. Am J Respir Crit Care Med 2000;162: 1403-6.

17. Guilbert TW, Morgan WJ, Krawiec M, Lemanske RF Jr, Sorkness C, Szefler SJ et al. The Prevention of Early Asthma in Kids study: design, rationale and methods for the Childhood Asthma and Research Network. Control Clin Trials. 2004; 25:286-310.

18. Brand PL, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A, et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence -based approach. Eur Respir J 2008; 32:1096–1110.

19. American Academy of Pediatrics. Diagnosis and management of bronchiolitis. Pediatrics 2006;118:1774–93.

20. Scottish Intercollegiate Guidelines Network. Bronchiolitis in children. A national clinical guideline. Report No 91. SIGN, 2006.

21. Iqbal SM. Management of acute viral bronchiolitis in children: evidence beyond guidelines? Sudan Journal of Paediatrics 2012: 12(1):40-48.

22. Cinquetti M, Micelli S., Voltolina, C. and Zoppi G. The Pattern of Gastroesophageal Reflux in Asthmatic Children. Journal of Asthma 2002; 39:(2) 135-142.

23. Jain A, Patwari AK, Bajaj P, Kashyap R, Anand VK. Association of gatroesophageal reflux disease in young children with persistent respiratory symptoms. J Trop Pediatr 2002; 48: 39–42.

24. Kang SK, Kim JK, Ahn SH, Oh JE, Kim JH, Lim DH, et al.   Relationship between Silent Gastroesophageal Reflux and Food Sensitization in Infants and Young Children with Recurrent Wheezing.   J Korean Med Sci. 2010 Mar;25(3):425-428.

25. Sheikh S, Stephen T, Howell L, Eid N. Gastroesophageal reflux in infants with wheezing. Pediatr Pulmonol 1999; 28:181–186.

26. Gold BD. Asthma and gastroesophageal reflux disease in children: exploring the relationship. J Pediatr 2005; 146: Suppl. 3, S13–S20.

27. Hsu JY, Lien HC, Chang CS, Chen GH. Abnormal acid reflux in asthmatic patients in a region with low GERD prevalence. J Gastroenterol 2005; 40: 11–15.

28. Khoshoo V, Le T, Haydel RM Jr, Landry L, Nelson C. Role of gastroesophageal reflux in older children with persistent asthma CHEST. 2003; 123(4):1008-1013.

29. Leggett JJ, Johnston BT, Mills M, Gamble J, Heaney LG. Prevalence of gastroesophageal reflux in difficult asthma: relationship to asthma outcome. Chest 2005; 127: 1227–1231.

30. Weinberger M. Gastroesophageal reflux disease is not a significant cause of lung disease in children. Pediatr Pulmonol Suppl 2004; 26: 197–200.

31. Tan HKK, Brown K, McGill T, Kenna MA, Lund DP, Healy GB. Airway foreign bodies (FB): a 10 year review. Int J Pediatr Otorhinolaryngol 2000; 56:91–9.

32. Steen KH, Zimmerman T. Tracheobronchial aspiration of foreign bodies in children: a study of 94 cases. Laryngoscope 1990;100:525–30.

33. Zerella JT, Dimler M, McGill LC, Pippus KJ. Foreign body aspiration in children: value of radiography and complications of bronchoscopy. J Pediatr Surg 1998; 33:1651–4.

34. Boucher RC. Evidence for airway surface dehydration as the initiating event in CF airway disease. J Intern Med 2007; 261: 5–16.

35. Farrell PM, Lai HJ, Li Z, Kosorok MR, Laxova A, Green CG et al. Evidence on improved outcomes with early diagnosis of cystic fibrosis through neonatal screening: enough is enough!. J Pediatr 2005; 147(3): S30–S36.

36. Kerem E. Mutation specific therapy in CF. Paediatr Respir Rev 2006; 7(1): S166–S169

37. A Barbato, T. Frischer, C.E. Kuehni, D. Snijders, I. Azevedo, G. Baktai et al. Primary ciliary dyskinesia: a consensus statement on diagnostic and treatment approaches in children Eur Respir J 2009; 34: 1264–1276.

38. Verra F, Escudier E, Bignon J, Pinchon MC, Boucherat M, Bernaudin JF, et al. Inherited factors in diffuse bronchiectasis in the adult: a prospective study. Eur Respir J 1991; 4: 937–944.

39. AlSaadi MM, Gaunt TR, Boustred CR, Guthrie PAI, Liu X, Lenzi L, et al.  From a Single Whole Exome Read to Notions of Clinical Screening: Primary Ciliary Dyskinesia and RSPH9 p.Lys268del in the Arabian Peninsula. Annals of Human Genetics 2012; 76: 211–220.

40. Coren ME, Meeks M, Morrison I, Buchdahl RM, Bush A. Primary Ciliary dyskinesia: age at diagnosis and symptom history. Acta Paediatr 2002; 91: 667–669.

41. Noone PG, Leigh MW, Sannuti A, Minnix SL, Carson JL, Hazucha M et al. Primary Ciliary  dyskinesia: diagnostic and phenotypic features. Am J Respir  Crit Care Med 2004; 169(4): 459–467.

42. Kurland G, Michelson P. Bronchiolitis obliterans in children. Pediatr Pulmonol 2005; 39:193–208.

43. Siby P. Moonnumakal and Leland L. Fan. Bronchiolitis obliterans in children Current Opinion in Pediatrics 2008, 20:272–278.

44. Ng DK, Lau WY, Lee SL. Pulmonary sequelae in long-term survivors of bronchopulmonary dysplasia. Pediatr Int 2000; 42:603–7.

45. Palta M, Sadek-Badawi M, Sheehy M,  Albanese A, Weinstein M, McGuinness G, et al. Respiratory symptoms at age 8 years in a cohort of very low birth weight children. Am J Epidemiol 2001; 154:521–9.

46. Halvorsen T, Skadberg BT, Eide GE, Roksund O, Aksnes L, Oymar K. Characteristics of asthma and airway hyper-responsiveness after premature birth. Pediatr Allergy Immunol 2005;16:487–94

47. Doyle LW, Faber B, Callanan C, Freezer N, Ford GW, Davis NM. Bronchopulmonary dysplasia in very low birth weight subjects and lung function in late adolescence. Pediatrics 2006; 118:108–13.

48. Donnelly D, Critchlow A, Everard M L. Outcomes treated for persistent bacterial bronchitis. Thorax 2007; 6280–84.84.