

Wheezing in Infancy: An Overview of Recent Literature

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Abstract

Purpose of Review Wheezing in infancy is a common presentation with many potential causes. In writing this review, we sought to summarize the newest recommendations and testing available for the more common etiologies of wheezing.

Recent Findings Regarding the diagnosis of asthma, the modified asthma predictive index has recently been established as a useful predictive tool. Non-breath held multidetector CT with 3D volume rendering airway images is also a newer helpful diagnostic tool for tracheomalacia due to ease of use and its 100% positive predictive value. We found vaccines have greatly reduced the prevalence of epiglottitis, while advances in surgery are improving outcomes in infants with vascular rings.

Summary Wheezing in infants is a common problem with an extensive differential diagnosis from relatively benign to life threatening. To prevent over-looking a diagnosis that potentially requires surgical correction or emergent care, we recommend a structured approach to the history and physical exam with targeted testing directed towards the most likely diagnoses as outlined in this review.

Keywords Wheezing · Infant · Asthma · Bronchiolitis · Tracheomalacia

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Introduction

Infants with wheezing present a diagnostic challenge to the pediatrician due to the high prevalence and paucity of tools available for objective testing in infants with persistent wheezing. Wheezing occurs due to obstruction of the lower respiratory tract, which may happen anywhere from the intrathoracic trachea down to the large bronchioles. The sound is generated by turbulent airflow in the large airways which collapse upon expiration. Young children are more susceptible to develop wheezing because their airways are small, requiring less obstruction to produce an audible wheeze. Their airways are also more compliant, therefore they collapse more easily on expiration, resulting in turbulent airflow [1].

At least one episode of wheezing occurs in about 37–56% of infants. Recurrent wheezing, defined as three or more episodes in a 6-month period, occurs in 8–16% of infants [2–5]. Some of the noted risk factors for wheezing in the infant include pneumonia, oral corticosteroid use, an upper respiratory tract infection, attending daycare, having a parent with asthma or allergies, mother working outside the home, male gender, lack of breastfeeding, and presence of mold in the home [2, 4]. A positive asthma predictive index, exposure to environmental smoke, and presence of atopy have also been associated with recurrent wheezing [6].

The differential diagnosis of wheezing is quite extensive, therefore a careful history and physical exam is warranted prior to beginning a work-up directed towards the most likely diagnoses (Table 1). We present below a discussion of the literature regarding characteristics, typical work-up, and treatment for the various conditions of infants with wheezing.

Table 1 Differential diagnosis of wheezing in infants

Differential diagnosis
Most common:
Asthma
Gastroesophageal reflux
Bronchiolitis
Obstructive sleep apnea
Foreign body aspiration
Less common:
Cardiac disease (heart failure/congenital heart disease)
Pneumonia
Tracheobronchomalacia
Rare:
Cystic fibrosis
Vascular ring
Immunodeficiency
Ciliary dyskinesia
Congenital bronchial atresia
Epiglottitis

Gastroesophageal Reflux

A history of coughing after feeding associated with physician-diagnosed wheezing in the infant is strongly suggestive of gastroesophageal reflux (GER). The 2016 American Thoracic Society Clinical Practice Guidelines recommend 24-h pH monitoring in infants with persistent wheezing despite bronchodilator and anti-inflammatory therapy because 67–100% will be found to have GER and improve with treatment, preventing the need for further testing (conditional recommendation, very low quality evidence) [7•]. Likewise, patients of all ages with asthma may have incomplete resolution of symptoms with asthma therapy due to co-morbid GER; therefore, there should always be high suspicion for the presence of additional GER in infants with persistent wheezing despite asthma therapy. Typical treatment of GER includes initiation of lifestyle modifications, followed by a limited course of proton pump inhibitor in infants who do not improve with lifestyle modifications alone.

Epiglottitis

With the advent of the *Haemophilus influenzae* b vaccine, there has been a shift in the epidemiology of epiglottitis from the pediatric population to the adult population. A 2010 study of 4587 cases of epiglottitis over an 8-year period found the median age of patients with epiglottitis in the USA to be 45 [8]. Nonetheless, an infant with wheezing associated with stridor and drooling in the absence of cough strongly suggests the

diagnosis of epiglottitis. Many conditions can present with stridor, but the presence of drooling has been reported to be 79% sensitive and 94% specific for epiglottitis, making it an essential clue to accurate diagnosis [9]. Other signs that suggest a diagnosis of epiglottitis are a preference to sit, dysphagia, and refusal to swallow.

If suspected, epiglottitis should be addressed emergently by securing a stable airway via intubation or possible tracheotomy, if clinically warranted, because the disease can progress rapidly. Initial evaluation usually consists of a lateral neck radiography, classically known for the “thumb sign,” though this is not a sensitive diagnostic tool [10]. Direct visualization of the epiglottis with flexible laryngoscopy can be used to make the diagnosis with more confidence. Furthermore, a CT scan of the neck with contrast aids in ruling out a phlegmon or abscess. Once a stable airway is established and diagnosis is confirmed, antibiotics should be administered to target the most likely organisms, typically with a second- or third-generation cephalosporin and possibly an anti-staphylococcal agent [11].

Tracheobronchomalacia

Tracheomalacia is a condition in which weakening of the trachea’s cartilage results in collapse of the airway, and can originate as a congenital or acquired abnormality. The majority of tracheomalacia cases are intrathoracic resulting in collapse of the airway on expiration. Extrathoracic, or cervical, tracheomalacia is less common and presents as collapse of the airway on inspiration [12]. The condition is known as tracheobronchomalacia when the mainstem bronchi are also involved. Collapse of the airway can be due to an intrinsic defect within the cartilaginous wall of the trachea, external compression by cardiovascular structures, or iatrogenic causes such as prolonged positive pressure ventilation. The compression of the airway often causes expiratory wheezing which can be indistinguishable from asthma on auscultation.

When wheezing is associated with positional changes, there may be tracheomalacia, heart failure, or anomalies of the great vessels, warranting angiography, bronchoscopy, computed tomography (CT), magnetic resonance imaging (MRI), and/or echocardiography to identify the etiology and rule out mimicking diagnoses. For diagnosis, specifically of tracheobronchomalacia, either paired inspiratory-dynamic expiratory chest CT or functional bronchoscopy may be employed [13]. Both of these diagnostic techniques typically require general sedation and intubation, which is not feasible in all cases. A newer form of imaging, known as non-breath held multidetector CT (MDCT) with 3D volume rendering airway images, has been found to have 100% positive predictive value for identification of tracheomalacia and requires

only mild sedation. With less than 75% sensitivity, however, the 3D MDCT should not be used as a screening test [14].

Most infants with mild to moderate tracheomalacia do not require intervention because their symptoms are typically mild and resolve by age 2 [12]. For infants with more severe disease who require intervention, standard forms of treatment include CPAP, aortopexy, and internal stenting, with tracheostomy reserved for refractory cases [15]. Advances in medical knowledge continue to identify effective treatment modalities for infants with moderate to severe disease, such as external stenting and tracheopexy, in an attempt to improve outcomes in these infants [16–18].

Foreign Body Aspiration

Choking followed immediately by coughing is the most common presentation of a foreign body aspiration, and the right mainstem bronchus is the most common location for lodging of the item [19]. Unilateral wheezing, dyspnea, cyanosis, and chronic/recurrent pneumonia are further clinical manifestations that warrant suspicion of foreign body aspiration. Frontal and lateral chest and neck radiographs are typically obtained initially due to ease of access, though the majority of foreign bodies are radiolucent. Multidetector CT and MRI have been more recently established as excellent imaging modalities for the detection of an aspirated foreign body, while bronchoscopy remains the procedure of choice for definitive diagnosis and treatment [19].

Asthma

One of the most common causes of recurrent wheeze in the infant is asthma, a disease classically known for both smooth muscle hyper-reactivity and inflammation of the bronchioles. Aspects of the history that suggest asthma include cough, dyspnea, and/or wheezing triggered by environmental allergens, laughing, crying, or presence of these symptoms during sleep in the absence of infection [20••]. Frequent viral upper respiratory infections and recurrent episodic illnesses along with a history of wheezing have also been described as historical clues to the presence of asthma [21].

Because infants cannot perform pulmonary function testing, and raised volume rapid thoracoabdominal compression use is limited due to the need to sedate the infant and need for technician expertise, most clinicians generally rely upon clinical predictive tools to help in making the diagnosis [22]. The asthma predictive index (API) remains one of our best clinical predictors for the development of asthma in infants, based on the National Asthma Education and Prevention Program (NAEPP) guidelines [23]. The original API was first developed in 2000 based on a study conducted within the

longitudinal Tucson Children's Respiratory Study of 1246 infants who were assessed for presence of atopy up to age 3, and then followed for development of asthma up to age 13. While the stringent form of the index carries a relatively low sensitivity for prediction of asthma (15% prediction up to age 13), the specificity for asthma is very high at 97% [24].

A modified asthma predictive index (mAPI) was used in 2004 as inclusion criteria for the Preventing Early Asthma in Kids clinical trial which compared the efficacy of inhaled corticosteroids to placebo in 2–3-year olds at high risk for asthma [25]. The mAPI had not been critically assessed as a predictive tool until 2013, at which time a post-hoc analysis of the Childhood Origins of ASThma (COAST) study was performed. The analysis concluded subjects with four episodes of wheezing who met at least one major or two minor criteria for the mAPI from infancy to 3 years old had a 72% post-test probability for asthma in unselected populations and 90% post-test probability in high-risk populations [26]. The mAPI is a more inclusive and objective predictive index as it includes positive IgE to aeroallergens and foods as criteria which were not included in the initial API (Table 2).

Unfortunately, there are few objective measures to assess for the presence of asthma in an infant. Fractional excretion of nitric oxide (FeNO) is currently used as a biomarker for airway inflammation in adults and children with limited evaluation of its clinical utility in the wheezing infant. A small 2013 post-hoc analysis of 32 infants, age 6–24 months, with recurrent wheezing was able to demonstrate correlation between persistent wheezing at age 3 and elevation in single-breath fractional excretion of nitric oxide [27]. While further studies are warranted before this becomes a general recommendation in an infant population, the Global Initiative for Asthma (GINA) guidelines do currently suggest elevated FeNO as a predictor for asthma in children age 1–5 [20••].

Aside from the history, clinical predictive tools, and FeNO , presence of asthma may be assessed by a 2–3-month trial for response to short-acting beta2-agonists and low-dose inhaled

Table 2 Modified Asthma Predictive Index criteria

Modified Asthma Predictive Index [26]

Major criteria^a:

- Parental physician-diagnosed asthma
- Physician-diagnosed atopic dermatitis
- Allergic sensitization to at least one aeroallergen

Minor criteria^a:

- Wheezing unrelated to colds
- Eosinophils 4% in circulation
- Allergic sensitization to milk, egg, or peanuts

mAPI criteria for use in patients ≤ 3 years old with ≥ 4 wheezing episodes per year

^a At least 1 major OR 2 minor criteria are required

corticosteroids (Evidence D) [20••]. A trial of systemic corticosteroids is also warranted in more severe cases. The diagnosis of asthma is more likely if the wheezing greatly improves with the use of therapy and worsens when therapy is discontinued. If there is no improvement with a trial of beta2-agonist, low-dose inhaled corticosteroids, and systemic steroids, then further work-up should be pursued, to consider other diagnoses in the differential, as outlined below.

Bronchiolitis

Bronchiolitis is the inflammation of the bronchioles secondary to infection. A seasonal pattern of wheezing occurring November–April, associated with low-grade fever and rhinorrhea, suggests bronchiolitis, which remains solely a clinical diagnosis [21]. Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis, and can be detected by culture or reverse-transcriptase polymerase chain reaction (RT-PCR) of nasal and/or throat swabs, though detection of the virus is not necessary for diagnosis [28]. Chest radiography yields inconsistent, non-specific findings thus is also not essential for diagnosis, though it can be helpful in ruling out other etiologies such as pneumonia [29, 30].

A recent proof-of-concept trial has demonstrated that the use of azithromycin for RSV bronchiolitis can significantly decrease the number of days with respiratory symptoms as well as prolong the time to next wheezing episode [31•]. This study was performed on the basis that azithromycin attenuated neutrophilic airway inflammation as demonstrated in a murine model. Further studies are warranted before administration of azithromycin for bronchiolitis becomes standard practice. Therefore, presently the mainstay of therapy continues to be supportive care.

Interestingly, a recent gene-sequencing study has identified variants in ADRB2 (the gene encoding the beta-2-adrenergic receptor), FLG (the gene encoding filaggrin), and NCAM1 (Neural Cell Adhesion Molecule 1) as risk factors for the development of asthma after RSV bronchiolitis in European Americans, and variants in NOS1 (Nitric Oxide Synthase 1) as a risk factor in African Americans [32]. Genetic testing is currently a cost-prohibitive practice, but may one day become a useful tool in early identification of asthmatics who present with bronchiolitis in infancy.

Congenital Bronchial Atresia

Congenital bronchial atresia represents a rare malformation of the bronchial tubes which is usually asymptomatic, though recurrent pulmonary infections can occur. Multiple infections in the same pulmonary lobe associated with localized wheezing raise suspicion for congenital bronchial atresia. When

suspected, further evaluation includes a CT scan of the chest, which is the most sensitive means for diagnosis [33]. Although identification of a blind-ending bronchus on bronchoscopy is less sensitive, it is pathognomic for the malformity. In the setting of recurrent infection, evaluation for the presence of immunodeficiency should be undertaken simultaneously as part of the work-up. If congenital bronchial atresia is diagnosed as the cause of multiple pulmonary infections, the affected region of lung should be resected to prevent further infections.

Cystic Fibrosis, Immunodeficiency, and Ciliary Dyskinesia

An infant with wheezing, multiple respiratory tract infections, and failure to thrive should be evaluated for cystic fibrosis, and simultaneously ruled out for immunodeficiency and ciliary dyskinesia. About 25% of cystic fibrosis patients diagnosed before age 2 present with wheezing as part of their symptom profile [34]. A 2014 study evaluating children with cystic fibrosis found that those with wheezing prior to age 3 had a significantly lower FEV1 at age 6 than those who never wheezed [35]. Testing of serum immunoglobulin levels, ciliary function, and sweat chloride testing is a reasonable start, with subsequent follow-up genetic testing for CFTR mutations if cystic fibrosis is strongly suspected. Acute pulmonary exacerbations in pediatric patients with cystic fibrosis are characterized by new crackles, increased cough, increased sputum, and weight decline. These exacerbations are typically treated with anti-pseudomonal antibiotics, chest physical therapy, and mucolytics [36].

Vascular Ring

When wheezing is exacerbated by neck flexion and relieved by neck hyperextension, one must consider the diagnosis of vascular ring. Vascular rings represent a congenital anomaly, most commonly including a double aortic arch or right aortic arch with left ligamentum, in which the aortic arch compresses the esophagus and/or trachea [37]. Infants with vascular rings classically present with stridor and a bark-like cough, however they can also present with wheezing, recurrent upper respiratory tract infections, and/or dysphagia. Vascular rings may occur in association with genetic syndromes such as trisomy 21 and chromosome 22q11 deletion, though isolated vascular rings can occur in otherwise healthy infants as well [38, 39].

As with most other diagnoses of wheezing in the infant, the work-up should begin with a frontal and lateral chest radiograph, with abnormal findings followed up with CT scan of the chest and/or MRI [39]. Patients with dysphagia should also undergo a barium swallow for further evaluation,

followed up by CT and/or MRI if any abnormalities are found to further evaluate for vascular ring. Symptoms of vascular ring can overlap with those of tracheomalacia, especially because a vascular ring can cause the development of tracheomalacia, therefore bronchoscopy should be performed in suspected cases to rule out the co-existence of tracheomalacia. An echocardiogram should also be considered to rule out other types of congenital heart disease, which have been reported to be present in about 18% of patients with vascular ring [40]. Once the presence of vascular ring is confirmed in a symptomatic patient, treatment requires surgical repair.

Cardiac Disease

Wheezing presenting in association with tachypnea, diaphoresis, retractions, or grunting can represent heart failure in an infant, often due to congenital heart disease [41]. The presence of cardiac murmur, cardiomegaly, and/or cyanosis without respiratory distress are other indicators of possible cardiac disease [42]. With this presentation, EKG, chest radiography, echocardiography, angiography, or a combination of these diagnostic tests may be appropriate based on the predominant symptoms present. If cardiac disease is suspected, consulting a cardiologist would be the most appropriate next step for optimization of medical evaluation and therapy.

Conclusion

Wheezing in infants is a common problem with an extensive differential on a spectrum from relatively benign to life threatening. To prevent over-looking a diagnosis that potentially requires surgical correction, we recommend a structured approach to the history and physical exam with targeted testing directed towards the most likely diagnoses. Early recognition of conditions that can be rapidly fatal, such as epiglottitis and foreign body aspiration, is paramount. If these conditions are not clinically suspected, a trial of beta2 agonist, inhaled corticosteroids, and systemic steroids is typically first line with the addition of empiric therapy for GER if the wheezing improves but does not resolve. Finally, further evaluation should be pursued based on the infant's overall presentation with the understanding that work-up and management must be tailored to the individual and be based on the provider's best clinical judgment.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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