CME review article

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Evaluation of infants and children with refractory lower respiratory tract symptoms

Bradley E. Chipps, MD*

Objective: To define the diagnostic possibilities for young children who present with recurrent wheeze.

Data Sources: Review of medical literature and 30 years of practice experience.

Study Selection: Relevant medical literature.

Results: When evaluating an infant or child presenting with recurrent respiratory symptoms, several diagnoses must be considered. The workup should include assessment of the risk factors for asthma and careful investigation into the specific symptoms. Recurrent or persistent wheezing and/or coughing often result in a diagnosis of asthma with therapeutic trials of asthma treatment. When the therapy is ineffective, other diagnoses should be considered, including gastroesophageal reflux, protracted bacterial bronchitis, tracheobronchomalacia, and cystic fibrosis. Appropriate testing should be performed in these pediatric patients.

Conclusion: In young children with recurrent lower airway symptoms who have a negative modified Asthma Predictive Index result, the described diagnostic possibilities should be considered.

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INTRODUCTION

Recurrent or persistent respiratory symptoms often prompt consideration of a diagnosis of asthma. Wheezing occurs in one third of infants and more than half of preschool children and often results in therapeutic trials of asthma treatment, such as bronchodilators and inhaled corticosteroids.[1] Caregivers also frequently report cough, and though it is a nonspecific symptom, chronic or recurrent cough is often treated as asthma.

REPORT OF A CASE

A 14-month-old boy presented with a history of recurrent chest rattle and cough. He had 2 emergency department visits for increased respiratory symptoms, which were treated with prednisone, azithromycin, and inhaled albuterol (by pressurized metered-dose inhaler) with minimal benefit. There have been multiple formula changes, with no indication of food allergy and negative radioallergosorbent test results for currently ingested foods. The patient continues to gain weight but spits up repeatedly. He had no history of eczema, and the rest of the systems review produced negative results. The father had mild seasonal allergic rhinitis; the mother had no history of allergic rhinitis or asthma.

DISCUSSION

Initial Evaluation of the Child or Infant With Recurrent Respiratory Symptoms

When evaluating an infant or child presenting with recurrent respiratory symptoms, a consideration of the risk factors for asthma and a thorough inquiry into the nature of the symptoms are important. According to the modified Asthma Predictive Index (mAPI), the presence of 1 of the major criteria

Affiliations: * Capital Allergy and Respiratory Center, Sacramento, California.

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Table 1. The Modified Asthma Predictive Index[2]

Major criteria	Minor criteria
Parental history of asthma	Allergic sensitization to egg, milk, or peanut
Physician-diagnosed atopic dermatitis	Wheezing apart from colds
Allergic sensitization to ≥1 aeroallergens	Blood eosinophilia (eosinophil count, ≥4%)

or 2 minor criteria given in Table 1 indicates a high likelihood that the infant or child will develop persistent asthma.[1–3]

When addressing wheezing in infants, it is preferred that the wheeze is documented by a physician because parents vary widely in their understanding and definition of wheeze.[3] In addition, it is important to clarify whether the patient wheezes only during periods of upper respiratory tract infection (URI) or also when feeling well. The characteristics of the cough are also important. Unlike cough in adults, most management guidelines for children include the quality (eg, dry, wet, brassy, staccato) and duration of cough as a determinant for diagnosis and treatment recommendations.[4] A cough associated with active asthma is dry, usually responds to bronchodilator and controller therapy, and is commonly associated with activities such as exercise, laughing, or tickling. Cough with wheeze apart from URIs is consistent with a diagnosis of asthma, and persistent nocturnal cough in the wheezing child or infant may be associated with more severe disease.[3]

Physical examination of the 14-month-old patient revealed the following:

- Head: moderate nasal congestion with "snorty" respirations
- Heart: regular sinus rhythm
- Chest: rhonchi, no retractions, and a slight decrease in turbulent airflow after inhaled β-agonist treatment
- Extremities: negative

The mAPI for this patient was negative, suggesting a low risk for developing asthma.

Reduced lung function as a characteristic feature of asthma does not become apparent until the school years in part because of the inability of the young child to perform lung function tests. Some hospitals and allergy/pulmonology clinicians can perform lung function testing on children younger than 5 years using recently developed techniques; however, most health care professionals do not perform spirometry on patients in this age group. This makes diagnosing asthma in the young child or infant with wheeze a challenge. A multicenter allergy study of more than 1,300 children reported an association between sensitization to perennial allergens (such as house dust mite and animal dander) in the first 3 years of life and development of asthma symptoms, including loss of lung function during the school years, at 7 years of age (Figure 1).[1] Other indicators in infants for the early development of atopic disease and possible asthma include high titers of hen's egg and cow's milk IgE antibodies.[5] Likewise, asthma is rarely the diagnosis when children present with chronic cough in the absence of wheeze.

Sinusitis may cause respiratory symptoms, but diagnosis is difficult in young children and infants. Symptoms suggestive of sinusitis in this age group include nasal congestion and pus draining into the pharynx. Confirmation by imaging usually requires sedation. A trial of antibiotics for at least 2 weeks is a reasonable consideration. Alternately, if symptoms suggest sinusitis, referral to an otolaryngologist for evaluation is suggested.

Differential Diagnosis of Recurrent, Refractory Wheeze in Children and Infants

Although the case presented herein is fairly straightforward, it illustrates some of the challenges faced by the physician in diagnosing recurrent wheeze, with or without cough, that is nonresponsive to conventional therapies in young patients. These children pose a diagnostic challenge. Diagnoses other than asthma that should be considered are given in Table 2, and some are described herein.

Laryngomalacia and Primary Tracheobronchomalacia

Laryngeomalacia and/or primary tracheobronchomalacia result from an inherent weakness in the structural integrity of the cartilaginous rings, allowing wall collapse and airway obstruction. These developmental defects are in young children and usually resolve by the age of 2 years as the airway grows in length and diameter, but more persistent disease can occur.[5] Laryngeomalacia is characterized by inspiratory stridor. Tracheobronchomalacia is characterized by expiratory airway collapse, is exacerbated by increased respiratory effort such as crying and coughing, and, in contrast to asthma, improves during sleep. Mild cases may only be symptomatic

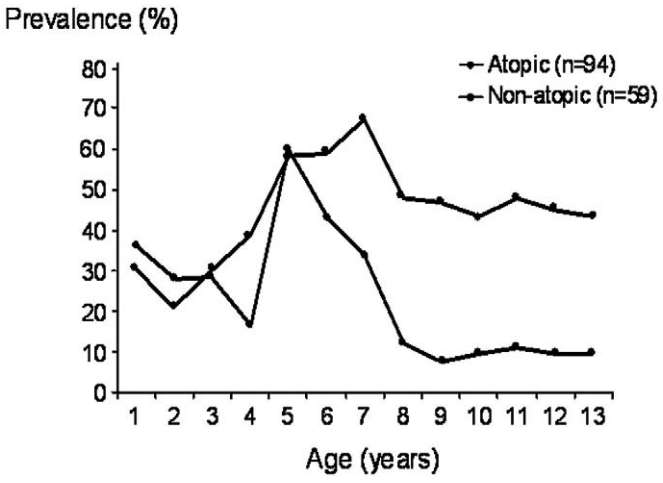

Figure 1. Perennial allergen sensitization early in life and development of asthma during the school-age years in 153 children: a birth cohort study.[1] The low numbers shown may contribute to a type 2 error.

Table 2. The Differential Diagnosis of Recurrent, Refractory Wheeze[a]

Upper airway noise
Asthma
Tracheobronchomalacia
Foreign body aspiration
Mechanical airway obstruction
Persistent bacterial bronchitis
Gastroesophageal reflux/aspiration syndromes
Cystic fibrosis

[a] There currently remains no clear diagnostic definition of protracted bacterial bronchitis, and more study is warranted to characterize this syndrome.

while crying or during periods of URIs; more severe cases will be persistently symptomatic. On physical examination, a harsh, low-pitched, monophonic wheeze is appreciated. Tracheobronchomalacia will fail to respond to bronchodilators or inhaled corticosteroids.[6] The diagnosis of primary tracheobronchomalacia can be made clinically, but bronchoscopy can aid in diagnosis and in the evaluation of severity. Bronchoscopy will show dynamic collapse of affected bronchi on expiration.[6] Tracheobronchomalacia may occur with concomitant laryngeomalacia, resulting in both inspiratory and expiratory stridor.

Mechanical Airway Obstruction

Mechanical airway obstruction, including vascular rings, such as right-sided or double aortic arch and anomalous innominate artery, and vascular slings, such as pulmonary artery sling, is a potential underlying cause of secondary tracheobronchomalacia.[6] Vascular rings and slings are due to the aberrant formation of mediastinal vessels, resulting in compression and narrowing of the trachea and/or esophagus. Clinical findings usually begin early in the first year of life and may include noisy breathing (usually since birth), dyspnea, wheeze or stridor, dysphagia, choking, hoarse cry, increased respiratory secretions, and aspiration. The severity of symptoms depends on the nature and degree of the anomaly, and symptoms may worsen with exertion due to vascular engorgement with activity. Other causes of mechanical obstruction include congenital diaphragmatic hernia, trachea-esophageal fistulas, congenital lobar emphysema, congenital cystic adenomatoid malformation, and pulmonary sequestration. Compression of the airway can be demonstrated with bronchoscopy, and a barium swallow can be used to visualize compression of the esophagus. However, neither procedure can be used to diagnose the type of anomaly present. Similarly, esophagrams are nonspecific and may show normal findings despite the presence of an anomaly that does not compress the esophagus. A magnetic resonance image of the chest or angiography is required to confirm the diagnosis and identify the anomaly.

Foreign Body Aspiration

Foreign body aspiration is common and resulted in 4,600 deaths in the United States in 2005.[7] The highest incidence is in patients younger than 3 years, in whom food is the most common aspirated object.[7] Foreign body aspiration may result in the acute onset of wheeze and/or cough but may also result in indolent symptoms. Wheezing is often unilateral or localized but may be difficult to discern in the young child. The diagnosis is confirmed by bronchoscopy and removal of the foreign body.[7]

Protracted Bacterial Bronchitis

Protracted or persistent bacterial bronchitis (PBB) is underdiagnosed and often misdiagnosed as asthma.[8–10] PBB is a pediatric condition characterized by the presence of an isolated moist or wet cough lasting more than 4 weeks in the absence of other specific causes and that resolves with antibiotic treatment.[8–10] It usually affects children younger than 5 years and has been recognized more by pediatric pulmonologists to whom these children are referred.[8] In a medical record review of 81 such cases, the most common reasons for referral were persistence of cough and difficult to treat asthma; 59% had symptoms for more than 1 year.[9]

Marchant and colleagues evaluated children presenting with at least 3 weeks of cough (89% had wet cough) and found that the most common diagnosis was PBB (43%).[10] Normal resolution occurred in 22%; asthma was diagnosed in only 4% of patients. Wheeze decreased slightly after inhaled treatment, which may reflect the difficulty of treating a patient in this age group or may reflect the severity of the disease.[10]

There currently remains no clear diagnostic definition of protracted bacterial bronchitis, and more study is warranted to characterize this syndrome. However, recent data indicate that it is associated with an intense neutrophilic airway inflammation.[11] A definitive diagnosis can be made by bronchoscopy with bronchoalveolar lavage and culture. In infants and children the most common organisms implicated in PBB are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Reliance on throat culture should be dissuaded because of the low specificity. Some investigators have suggested that a trial of antibiotics may be used to avoid bronchoscopy.[8–10] However, this approach is controversial and may not result in a definitive diagnosis. Unsuccessful trials with antibiotics should be cause for further evaluation and referral.

Gastroesophageal Reflux

Gastroesophageal reflux (GER) is common in infants and children, and aspiration with swallowing in the absence of GER may also cause respiratory symptoms in infants.[12] Although a high percentage of children with respiratory symptoms are reported to have GER detectable by abnormal esophageal pH, symptoms may be subtle, especially in young children.[13] Some patients may present with excessive burping or emesis, coughing after meals, and nocturnal cough or wheeze, and discomfort indicated by crying and/or arching of the back may be the only symptom in infants.[13] A positive response to empiric therapy with thickened feedings and an acid suppression regimen may be used to support a presumed diagnosis of GER.[10,14,15] A study of infants diagnosed as having GER and treated with similar conservative (nonpharmacologic) measures in a primary care setting found substan-

Table 3. Criteria for Diagnosing Cystic Fibrosis (CF) in Children and Infants[18–20]

1 of:	PLUS 1 of:
≥1 Typical phenotypic feature of CF	Elevated sweat chloride level >60 mEq/L (>30 mEq/L of Cl^- in children <2 years) on 2 occasions
Sibling with CF	2 Identified *CFTR* mutations
Positive newborn screening test result	Abnormal nasal potential difference

CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductor regulator; Cl, chloride.

tial symptom improvement in 78%.[16] The diagnoses of GER and asthma are not mutually exclusive, particularly in older children.[13,17] As many as half of children with asthma and abnormal esophageal pH show few or no obvious symptoms of GER (eg, heartburn, regurgitation).[13] In patients with comorbid asthma, effective treatment of GER may result in improved asthma symptoms and decreased need for asthma medications. More controlled clinical trials are warranted to determine the significance of GER as a contributor to respiratory symptoms in children.[17]

Cystic Fibrosis

Cystic fibrosis (CF) usually presents with chronic pulmonary disease, manifested by persistent colonization and infection with typical CF pathogens, chronic cough and sputum production, persistent chest radiograph abnormalities, wheezing and air trapping, nasal polyps, and digital clubbing.[18,19] Gastrointestinal and nutritional abnormalities, including failure to thrive, generally accompany the respiratory symptoms, but milder variations exist. CF should be considered in patients who have respiratory symptoms with a negative mAPI result and who do not respond to treatment. A diagnosis of CF can be established using the parameters described in Table 3.[18–20]

There is an increased risk of complications when patients are diagnosed by symptoms alone (median age at diagnosis, 14.5 months) rather than newborn screening (median age at diagnosis, 0.5 month).[18,19] Therefore, as a result of newborn screening, an increasing number of diagnoses of CF are now made in early infancy.[19]

Is There a Role for Detailed Invasive Investigations in Children and Infants With Recalcitrant, Recurrent Wheeze?

A study by Saglani and colleagues[15] evaluated the clinical benefit of using detailed, invasive investigations in diagnosing severe recurrent wheeze in young children (between 3 months and 5 years of age) (Table 4). A total of 47 children, with an average age of 26 months, underwent investigation. The investigations yielded abnormal results in three quarters of patients.[15] Forty-one percent were diagnosed as having asthma, 23% as having primarily GER, and 13% as having predominantly infection (significant bacterial growth and neutrophilia in bronchoalveolar lavage fluid). In 11 of 47, a definite diagnosis could not be made.[15] Notably, in every diagnostic category, the average patient age was 28 months, except in the infection category, in which the average age was 9.5 months. The authors concluded that investigations, including bronchoscopy, can be performed safely and may yield clinically relevant information, especially with regard to structural airway abnormalities, bacterial infection, and GER.[15] However, an evaluation of the clinical significance of these results in terms of outcomes requires additional prospective intervention trials.

Table 4. Summary of a Series of Investigations Used to Evaluate Children With Severe, Recurrent Wheeze[15]

Time	Examinations
Before admission	Chest x-ray examination, pulse oximetry, sweat chloride measurement, complete blood cell count, skin tests, B-cell function (if indicated)
Day 1	Investigations with patients under general anesthesia: high-resolution computed tomographic chest scan, fiberoptic bronchoscopy with bronchoalveolar lavage and endobronchial biopsies, placement of esophageal pH probe
Day 2	Review and discharge

CONCLUSION

When evaluating an infant or child presenting with recurrent wheeze and/or cough that is refractory to standard asthma therapies, a number of other diagnoses must be considered, including GER, PBB, tracheobronchomalacia, and CF. The workup of such patients may include chest x-ray examination, pulse oximetry, evaluation of atopic status, sweat test, bronchoscopy with bronchoalveolar lavage and culture, high-resolution chest computed tomography, and pH probe. A protocol is given in Table 4.

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Requests for reprints should be addressed to:
Bradley E. Chipps, MD
Capital Allergy and Respiratory Disease Center
5609 J St
Suite C
Sacramento, CA 95819
E-mail: bchipps@capitalallergy.com

Objectives: After reading this article, participants should be able to demonstrate an increased understanding of their knowledge of allergy/asthma/immunology clinical treatment and how this new information can be applied to their own practices.

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CME Examination

1–5, Chipps BE. 2009;104:279–283.

CME Test Questions

1. What is the most reliable predictor of persistence of wheezing?
   a. recurrent respiratory infection
   b. clinical response to short-acting β-agonist
   c. early sensitization and exposure to environmental allergens
   d. male sex
   e. development of seasonal allergic rhinitis
2. Workup of young patients with persistent wheezing should include all but which of the following?
   a. chest x-ray examination
   b. sweat chloride
   c. trial of high dose oral steroid for 2 weeks
   d. oxygen saturation
   e. bronchoscopy
3. What is the most common cause of persistent cough in young children?
   a. asthma
   b. recurrent sinusitis
   c. recurrent bacterial bronchitis
   d. aspiration syndrome
   e. recurrent pneumonia
4. Confirmation of a cystic fibrosis diagnosis includes all of these except:
   a. positive newborn screening test result
   b. elevated sweat chloride level on 2 occasions
   c. identification of 2 cystic fibrosis mutations
   d. culture of respiratory secretions positive for *Pseudomonas*
   e. sibling with cystic fibrosis
5. Foreign body aspiration is most commonly
   a. found in the left lung
   b. found in children younger than 3 years
   c. associated with severe challenging events
   d. diagnosed by chest x-ray examination
   e. treated by observation only

Answers found on page 298.