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.

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.3 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

Laryngomalacia 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 Laryngomalacia 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.

Table 1. The Modified Asthma Predictive Index2

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
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<tbody>
<tr>
<td>Parental history of asthma</td>
<td>Allergic sensitization to egg, milk, or peanut</td>
</tr>
<tr>
<td>Physician-diagnosed atopic dermatitis</td>
<td>Wheezing apart from colds</td>
</tr>
<tr>
<td>Allergic sensitization to ≥1 aeroallergens</td>
<td>Blood eosinophilia (eosinophil count, ≥4%)</td>
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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.
Foreign body aspiration is common and resulted in 4,600 deaths. Foreign body aspiration 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. It usually affects children younger than 5 years and has been recognized more by pediatric pulmonologists to whom these children are referred. 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.

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%). 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.

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

### Table 2. The Differential Diagnosis of Recurrent, Refractory Wheezeh

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
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<tr>
<td>Upper airway noise</td>
<td>Discomfort during crying or during periods of URI; more severe cases may be persistently symptomatic. On physical examination, a harsh, low-pitched, monophonic wheeze is appreciated. Traacheobronchomalacia will fail to respond to bronchodilators or inhaled corticosteroids. 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.</td>
</tr>
<tr>
<td>Asthma</td>
<td>Diagnosed and often misdiagnosed as asthma. 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. It usually affects children younger than 5 years and has been recognized more by pediatric pulmonologists to whom these children are referred. 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.</td>
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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 colleagues15 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.

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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REFERENCES


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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.

Participants: This program is designed for physicians who are involved in providing patient care and who wish to advance their current knowledge in the field of allergy/asthma/immunology.

Credits: ACAAI designates each Annals CME Review Article for a maximum of 2 category 1 credits toward the AMA Physician’s Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity. The American College of Allergy, Asthma and Immunology is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

CME Examination


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.