

# Your Partner in Good Health



Dr. Jason J. Fullmer, MD, Austin Children's Chest Associates



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## IN THIS ISSUE

Shedding Light on  
Childhood Wheezing A2

Continuing  
Medical Education A5

Network Locator Map A7

# An Approach to Wheezing in Infants and Preschoolers

## *Using Epidemiology to Shed Light on a Difficult Diagnosis and Aid in More Effective Therapy*

By Jason J. Fullmer, MD, Pediatric Pulmonologist, Austin Children's Chest Associates

"Does my child have asthma?" . . . When confronted with this question by a parent of an infant or preschool child, pediatricians often struggle to find an adequate answer. Asthma is difficult to diagnosis in young children as many childhood illnesses are associated with cough or wheeze. Wheezing, typically associated with lower respiratory tract infections, is common in the first 3 years of life, with a prevalence of 32%, 17% and 12% in the first, second and third years of life respectively in one prospective study. Certainly all of these

children do not have asthma, which typically affects about 5.5% of the U.S. population. Furthermore, at least 50% of children that wheeze at this age will have at least one recurrent episode of wheezing within the next few months, further complicating the diagnostic dilemma.

Asthma is a disease of chronic airway inflammation, manifested by episodic airway obstruction that is at least partially reversible. In older children and adults, the gold standard for diagnosing asthma is the demonstration of reversible airway obstruction using pulmonary function testing. Children under the age of 5 typically do not have the coordination necessary to perform this maneuver. Therefore the clinician must investigate and exclude other causes of episodic wheeze and cough, and make his or her best educated guess to make a diagnosis of asthma in this age group.

Several large, prospective, longitudinal studies initiated during pregnancy or shortly after birth have now followed children past school age, and have significantly advanced

our understanding of the epidemiology of wheezing illnesses occurring during the first years of life. There is now clear evidence indicating that wheezing in early life is a heterogeneous condition in which recurrent episodes of airway obstruction are the final common pathway for the expression of different underlying mechanisms, and ultimately, for different diseases. These epidemiological studies have helped to identify three common recurrent wheezing phenotypes—transient early wheezers, non-atopic persistent wheezers and atopic persistent wheezers. These phenotypes will be discussed in detail later.

### **Typical vs. Atypical Wheezing**

Before classifying a child as a recurrent wheezer and attempting to fit him into a clinical phenotype, it is important to exclude conditions that may present as wheezing or cough, but require vastly different therapy. It is often useful to break these diagnoses into groups, based on age of presentation (**Table 1**). A thorough review of the medical history and physical exam can help to differentiate typical wheezing (associated with an asthma phenotype) from an atypical cause of wheezing (**Tables 2A and 2B**). Consideration should be given to:

**Timing**—Typical wheezing, whether associated with viral infections or with asthma, usually does not start until after 2 months of age. Wheezing or noisy breathing from birth is suggestive of bronchopulmonary dysplasia or congenital airway anomalies. Conversely, the sudden onset of wheezing in a toddler should raise the suspicion of a foreign body. As a general rule, very early or very late onset of wheezing should raise suspicion that the problem is atypical.

**Pattern**—The typical

**Table 1**

### **Conditions Other Than Asthma Associated with Wheezing**

#### **0-3 Months**

- Bronchopulmonary Dysplasia
- Congenital Anomalies of the Larynx (*Laryngomalacia, Vocal Cord Paralysis, Subglottic Stenosis, Cyst, Hemangioma*)
- Congenital Anomalies of the Trachea (*Tracheomalacia, Bronchomalacia, Vascular compression, Tracheoesophageal Fistula*)

#### **3-12 Months**

- Croup
- Gastroesophageal Reflux Disease/Aspiration
- Cystic Fibrosis
- Cardiac Asthma

#### **1-6 Years**

- Foreign Body Aspiration
- Primary Ciliary Dyskinesia
- Bronchiolitis Obliterans
- Congenital Lung/Airway Anomaly (*Bronchomalacia, CCAM*)

**Table 2A - History**

| Typical Wheeze   | Atypical Wheeze   |
|--|---|
| <ul style="list-style-type: none"> <li>• Early onset, but not present at birth</li> <li>• Symptom free intervals</li> <li>• Episodic attacks</li> <li>• Possible personal atopy</li> <li>• Possible family atopy</li> <li>• Possible viral infection</li> <li>• May respond to asthma therapy</li> <li>• Unrelated to feeding</li> </ul> | <ul style="list-style-type: none"> <li>• Any age. Very early or very late should cause concern</li> <li>• Symptom free intervals less common</li> <li>• May be continuous</li> <li>• Unrelated to atopy</li> <li>• Unrelated to family atopy</li> <li>• Unrelated to viral infection</li> <li>• Unlikely to respond to asthma therapy</li> <li>• Possibly related to feeding</li> </ul> |

**Table 2B - Physical Exam**

| Typical Wheeze  | Atypical Wheeze  |
|---|--|
| <ul style="list-style-type: none"> <li>• Normal development</li> <li>• No chest deformity</li> <li>• No clubbing</li> <li>• No marked upper respiratory tract disease</li> <li>• Wheezing or decreased breath sounds generalized</li> <li>• Normal neurologic exam</li> <li>• Musical, polyphonic wheeze</li> </ul> | <ul style="list-style-type: none"> <li>• May have failure to thrive</li> <li>• May have chest deformity</li> <li>• May have clubbing</li> <li>• May have difficult to treat sinusitis or otitis media</li> <li>• Wheezing or decreased breath sounds localized</li> <li>• May have neurologic abnormalities</li> <li>• May have monophonic wheeze</li> </ul> |

wheezing pattern consists of short exacerbations of wheeze or cough, followed by long symptom-free intervals. A history of continuous or near continuous wheeze for weeks suggests a much greater likelihood of a serious problem such as a congenital anomaly, Cystic Fibrosis or a foreign body.

**Personal or Family History of Atopic Diseases**—As allergic diseases are very common in the community, a family history should only be regarded as positive if parents or siblings of the patient are affected. Personal atopy, such as infantile eczema, is about twice as common and maternal asthma is more than twice as common in infants with persistent wheezing that go on to develop asthma.

**Physical Examination**—Failure to thrive is not associated with typical wheezing phenotypes and may indicate a more serious pulmonary or cardiac disorder. The typical wheeze is generalized, polyphonic and often musical in

character. Monophonic or localized wheezing should raise concern for an alternative diagnosis. Other physical exam findings suggesting an atypical wheeze include digital clubbing, neurological abnormalities, chest wall deformities and an abnormal cardiovascular examination.

**Recurrent Wheezer Phenotype**

Once alternative diagnoses have been considered and ruled out, one can attempt to place the “typical infant wheezer” into a recurrent wheezer phenotype. It is important to

understand that there may be overlap between groups, as it is not always possible to identify absolute thresholds for complex risk factors, and thus no marker perfectly distinguishes between the different phenotypes

described below. **Table 3** summarizes the characteristics of the three phenotypes.

**Transient Early Wheezing**— This group accounts for 60% of infant wheezers less than 3 years of age. Symptoms usually develop in the first year of life, and typically resolve by age 3. There is usually no strong family or personal history of atopic diseases. Wheezing episodes occur almost exclusively with viral respiratory infections, and can be quite severe. Risk factors for this group include an association with maternal smoking during pregnancy, male sex and daycare attendance. Studies of infant lung function show that members of this phenotype do not have increased airway hyperresponsiveness, but start life with diminished maximal expiratory flows, suggesting their airways have a smaller inner diameter. This hypothesis is supported as these infants' symptoms resolve as they (and their airways) grow.

[CONTINUED ON PAGE A4](#)

**Table 3 - Recurrent Wheezing Phenotypes**

|  | Transient Early Wheezing  | Nonatopic Wheezing   | Atopic Wheezing (Asthma)                                      |
|--|---|--|---|
| • % of wheezing infants <3 yrs.                                      | • 60%   | • 20%  | • 20%   |
| • Age  | • 2 mo. to 3-6 yr   | • 2 mo. to 10-13 yr  | • Late infancy through adulthood                              |
| • Possible underlying cause  | • Small airways   | • Genetic and acquired alteration in regulation of airway tone | • Genetic predisposition to atopy with environmental triggers |
| • Association with family history of asthma or atopy                 | • No strong association   | • No strong association  | • Strong association  |
| • Association with atopic dermatitis or allergic rhinitis in patient | • No  | • No   | • Yes   |
| • Wheezing apart from colds  | • No  | • No   | • Yes   |
| • Elevated IgE or eosinophilia > 4%                                  | • No  | • No   | • Yes   |
| • Response to inhaled corticosteroids                                | • No objective data   | • No objective data  | • Typically good response                                     |
| • Risk Factors   | • Maternal smoking during pregnancy, daycare attendance, male sex | • RSV lower airway infection <1 year, prematurity              | • Personal or family history of atopy                         |

**CONTINUED FROM PAGE A3**

**Non-atopic Wheezing**—This group accounts for 20% of recurrent wheezing episodes in the first 3 years of life. These children have symptoms that develop during the first year of life and are typically associated with viral lower respiratory tract infections. Symptoms abate with time and typically resolve between 6 and 13 years. Risk factors include a history of respiratory syncytial virus lower respiratory tract infection at less than 1 year of age and prematurity. Lung function in the children with this phenotype typically shows decreased lung function with airway hyperresponsiveness. The underlying mechanism in this case is thought to be an alteration in the regulation of airway tone, making children more likely to wheeze during viral infections.

**Atopic Wheezing (Asthma)**—This group accounts for the final 20% of infants with recurrent wheezing in the first 3 years of life. Unfortunately the future asthmatics cannot be distinguished clinically from other wheezing children during the first years of life. There are clues that can help the clinician to identify these children though. Symptoms often start later than the other recurrent wheezing phenotypes, often in the 2nd or 3rd year of life. Wheezing often occurs apart from colds. When compared to other groups, atopic wheezers are four times more likely to have a family history of asthma and two to three times more likely to have a history of atopic dermatitis. Atopic wheezers have, as a group, higher prevalence of eosinophilia (>4% white blood cells). Taken together these features can give the clinician clues to a possible history of future asthma. The importance of identifying these patients is illustrated by lung

function testing. Studies have shown that infants with an atopic wheezing phenotype have relatively normal lung function at birth, but if untreated, have progressively decreasing lung function and increased airway hyperresponsiveness.

**Treatment**

Management guidelines have been developed in an attempt to improve and standardize asthma treatment in adults and children. Unfortunately, due to the heterogeneity of conditions causing wheezing in infants and preschool children, these guidelines do not apply well to this age group. Martinez and Godfrey have proposed an algorithm based on the age and background of the child, the frequency of attacks and response to therapy to help manage these children. They recommend the initiation of low-dose inhaled corticosteroids for any patient with 2 or more wheezing episodes and an atopic background, or 3 and more wheezing episodes and a non-atopic background. Therapy is subsequently increased or decreased based on clinical response. True atopic asthmatics will typically respond well to conventional, anti-inflammatory asthma therapy. To date there is not sufficient evidence to assess the response of other wheezing phenotypes to this therapy. If a patient fails to respond to medical therapy, it is important to pay special attention to correct drug delivery, as nebulizers, dry powder inhalers and metered dose inhalers are frequently used incorrectly if the family

has not been given adequate education and instruction. Finally, referral to a specialist in pediatric pulmonary medicine may be necessary to rule out alternative diagnoses and evaluate therapy. This is especially true if an infant experiences a life-threatening episode, doubt exists concerning the diagnosis, failure to thrive is observed, medium- to high-dose inhaled corticosteroids are needed, more than two courses a year of an oral corticosteroid are needed or if adherence problems are identified.

**Prognosis**

Epidemiologic studies do provide some answers to the prognosis of children that wheeze. An infant with recurrent wheezing episodes at less than 2 years of age has a 60% chance of outgrowing his symptoms between 3 and 6 years, and will most likely not develop persistent asthma (unless there is a personal or family history of atopy). Children with wheezing symptoms between 2 and 6 years of age have a 50% chance that the wheezing is viral induced, again, especially if there is no atopic personal or family history, and will likely outgrow their symptoms. Children older than 6 years of age who continue to have wheezing episodes are likely to have atopic asthma. Despite this more than 50% of these patients will see their asthma clinically improve or resolve by adulthood.

**Recommended Reading**

1. *Martinez FD, Godfrey S. Wheezing Disorders in the Preschool Child. New York, Martin Dunitz. 2003.*

For more information on asthma, contact Steve Conti with the SETON Healthcare Network's Asthma Outreach Program at (512) 324-3320. To access patient referral forms online, visit [www.childrenshospital.com/asthma](http://www.childrenshospital.com/asthma).