Grand Rounds Review

Wheezing Exacerbations in Early Childhood: Evaluation, Treatment, and Recent Advances Relevant to the Genesis of Asthma

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Children who begin wheezing during early childhood are frequently seen by health care providers in primary care, in hospitals, and in emergency departments, and by allergists and pulmonologists. When a young child, such as the 2 year-old patient presented here, is evaluated for wheezing, a frequent challenge for clinicians is to determine whether the symptoms represent transient, viral-induced wheezing or whether sufficient risk factors are present to suspect that the child may experience recurrent wheezing and develop asthma. Most factors that influence prognosis are not mutually exclusive, are interrelated (ie, cofactors), and often represent gene-environment interactions. Many of these risk factors have been, and continue to be, investigated in prospective studies to decipher their relative importance with the goal of developing new therapies and interventions in the future. The etiologies of wheezing in young children, diagnostic methods, treatment, prognostic factors, and potential targets for prevention of the development of asthma are discussed.   © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:537-43)

CASE

A 2-year-old white boy presented to the emergency department (ED) in December 2013 with increased work of breathing. His mother reported that he had a 3-day history of cough and congestion, with intermittent fever. Tonight, she noticed that he was "breathing harder than usual." Results of a physical examination showed that he was afebrile and tachypneic, at 40 breaths per minute, with oxygen saturation of 98% on room air. He had significant nasal congestion and diffuse wheezing throughout all lung fields, with subcostal retractions. His medical history is significant for premature birth (32 weeks estimated gestational age), atopic dermatitis, and bronchiolitis that required hospitalization but not intubation during the spring of his first year of life. In the neonatal period, he did not require oxygen supplementation beyond 2 weeks of age. He was not breastfed. The family history was significant for maternal atopic asthma and for a 4-year-old sibling in preschool with an acute respiratory illness at home. The patient was not in day care, and there was no household exposure to domestic pets or tobacco smoke.

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Abbreviations used
  API- Asthma Predictive Index
  EGA- Estimated gestational age
  RV- Human rhinovirus
  ICS- Inhaled corticosteroids
mAPI- Modified Asthma Predictive Index
  RSV- Respiratory syncytial virus

ETIOLOGIES, EVALUATION, AND TREATMENT OF EARLY CHILDHOOD WHEEZING

Wheezing during the infant and toddler years is a common problem, estimated to affect 1 of 3 children at least once during the first 3 years of life.[1] The differential diagnosis of acute wheezing is protean, and information available to the clinician about the evaluation, treatment, and prognosis of infants and toddlers with wheezing exacerbations is somewhat controversial. Not enough is known about the distinction between asthma and episodic viral wheezing in young infants because many infants and toddlers who wheeze do not develop chronic and/or recurrent symptoms. However, 4- to 6-year-old children with wheezing during acute viral infections are often atopic and can have airway inflammation and reversible airflow limitation in addition to asthma-type signs and symptoms, including cough, difficulty breathing, wheezing, and tachypnea.[2]

Etiologies

Respiratory viral infections are the most common etiologies of acute wheeze in children and are identified in up to 90% of children younger than age 3 years who are hospitalized with wheezing.[3,4] During mid winter months in the Northern hemisphere, common pathogens associated with preschool wheezing include respiratory syncytial virus (RSV), human metapneumovirus, and influenza virus, especially in infants younger than 6 months of age who are wheezing[4,5]; whereas, atypical bacteria *Mycobacteria pneumoniae* and *Chlamydia pneumonia* occur more often in school-age children and adolescents.[6,7] During the first 6 months, however, up to 24% of infants with lower respiratory tract illness can test positive for *Chlamydia trachomatis*.[8] During other months of the year, notably spring and fall, human rhinovirus (RV) is the most prevalent virus detected and continues to be the most common viral pathogen linked to asthma among older children and adults. A newly described group of RVs called RV-C may be prevalent during mid winter months as well.[9]

Evaluation of a child with wheezing illness relies on a careful history and physical examination. The clinician should consider the differential diagnoses and differentiate wheezing from rhonchi generated from the upper and large lower airways. Acute wheezing in the young child may be infectious (often with associated fever or upper respiratory symptoms) or may be related to foreign body aspiration (sometimes with abrupt onset, choking episode, unilateral wheezing, unequal breath sounds, or typical radiographic findings). Noninfectious etiologies of chronic or recurrent wheezing in the infant and toddler age groups may include structural abnormalities (which usually do not respond to bronchodilator therapy and may include cardiovascular disease, anomalies of the tracheobronchial tree, mediastinal masses) or functional causes (including aspiration syndromes, eg, gastroesophageal reflux, which may present with vomiting; hoarseness; symptoms while supine or after feedings; or "recurrent croup"). Other conditions that may present

TABLE I. Host and environmental factors that may influence the genesis of asthma during childhood

Host factors that increase asthma risk	Reference no.
Male sex	23, 26
Premature birth (<28 wk EGA)	27, 28
Low lung function	26, 30
Delayed maturation of Th1 antiviral immunity	31
Decreased antiviral innate immunity	32, 33
Familial or personal atopy	See Table II (26, 34-36, 75, 76)
Environmental factors	
Increase risk of asthma	
Wheezing caused by viruses (especially RSV and rhinovirus)	40-43
Exposure to dust mite allergen at home during infancy	55
Neonatal pharyngeal colonization with respiratory bacterial pathogens* and virus and/or bacteria interactions	44
Courses of antibiotics	45, 46
Environmental tobacco smoke exposure	58
Urban air pollution (eg, diesel fuel particles)	59
Acetaminophen in early childhood	53
Decrease risk of asthma	
Day care attendance and exposure to older siblings	38, 39
Bacterial colonization of the gut, airway, and skin	44, 47, 49, 52
Exposure to dogs in early life	56, 57

EGA, Estimated gestational age.
*For example, *S pneumonia, H influenzae, M catarrhalis* (from Ref 44).

with recurrent wheeze include immune deficiency, cystic fibrosis, and other host-related diagnoses. In general, localized wheezing, recurrent pneumonia, feeding difficulties, and a lack of response to bronchodilator therapy suggest a nonviral etiology of wheezing.

Important information to guide therapy for acute infectious wheeze and to assess the risk of developing asthma includes a history of prior wheeze, frequency of recurrent wheezing, recurrent or chronic cough, cough with exercise, severe wheeze that requires hospitalization and/or an emergency department visit, nocturnal symptoms (marker of diffuse airway inflammation and/or obstruction), wheezing caused by documented viral respiratory infections, and response of previous episodes to short-acting β-2-agonist treatments and oral corticosteroids. Also important are the birth history (gestational age, delivery mode), feeding history (breastfed), family history of atopy and asthma, personal history of atopic dermatitis or food allergies, and environmental exposures known to increase or decrease the risk for symptom severity and persistence of wheezing (Table I).

Diagnostic evaluation

A chest radiography may be helpful in the acute setting for a young child with fever or persistent wheezing, or with concerns about anatomic etiologies or foreign body. Elevated blood eosinophils (obtained before starting systemic steroids in the acute care setting) in a young child may indicate atopy and be a risk
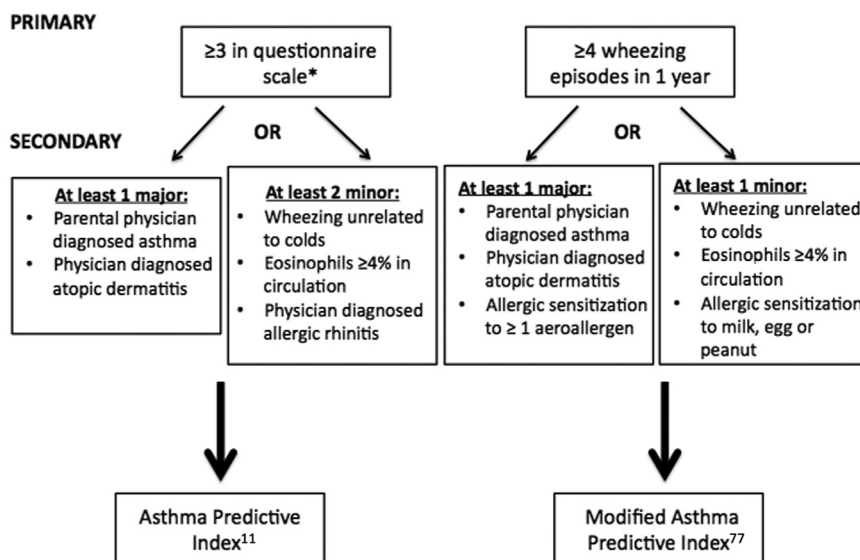
FIGURE 1. The Asthma Predictive Index (API) compared with the modified Asthma Predictive Index (mAPI): the API requires a blood eosinophil count to judge eosinophilia as part of the risk factor score and, therefore, is more stringent than the mAPI. The API, however, may be more useful in research studies that focus on the ontogeny of asthma or in the clinical evaluation of young children who experience moderate-to-severe or persistent wheezing exacerbations. *Scale ranging from 1 (very rarely) to 5 (on most days).

factor for recurrent wheezing,[10] in keeping with the indices used to determine Asthma Predictive Index scores (Figure 1).[11-15] Testing for viruses and bacteria is generally not performed in the clinical setting. Rapid influenza testing is available and can help guide antiviral use; although the sensitivity of the test is low, the specificity is typically ≥90%.[16,17] Rapid testing for RSV is available, but results do not always influence treatment. Real-time RT-PCR is available for RV, human metapneumovirus, RSV, influenza, parainfluenza, coronavirus, and others; however, availability varies among institutions, and the tests may be costly and not influence treatment.

Treatment

Recent literature has revealed controversy regarding the use of systemic corticosteroids for likely virus-induced wheeze.[18] A Cochrane Review determined that glucocorticoids had no effect on hospitalization or length of stay of children with bronchiolitis.[19] However, children with an atopic phenotype, those with blood eosinophilia, and those with recurrent wheeze may respond better to systemic and inhaled corticosteroids. Further studies that differentiate treatment of first-time wheezing, recurrent wheezing, wheezing that requires hospital care, children with atopic predisposition, or other predisposing conditions are needed. A trial of bronchodilators is warranted to determine efficacy; however, in first-time wheezing induced by a virus, there may be little benefit. Other therapies under consideration for acute wheeze include inhaled hypertonic saline solution and inhaled epinephrine.[20,21]

The therapeutic options for recurrent wheeze or asthma are different from those for acute first-time wheezing. The goal of long-term management of recurrent wheeze or asthma is to reduce symptoms, use of short-acting β-agonists, and risk for future severe exacerbations and hospitalizations.[22] Management depends on wheezing phenotypes and prognostic factors. In general, the first-

line controller therapy continues to be inhaled corticosteroids (ICS). Often, this treatment is started as a therapeutic trial of patients with recurrent wheeze for whom the diagnosis is consistent with airflow obstruction and/or reversibility. Studies are ongoing regarding intermittent administration of high-dose ICS on onset of upper respiratory symptoms in young children with known recurrent wheeze or asthma. Results of 1 trial found improved outcomes of difficulty breathing and interference with activity of children at higher risk for asthma, and results of another study found that daily, low-dose budesonide did not have a greater impact on reducing asthma exacerbations when compared with intermittent high-dose budesonide.[20,23] Intermittent treatment may be considered for the child with primarily viral-associated wheezing. Children who have frequent symptoms not only associated with upper respiratory infections should be considered differently and may benefit from continuous therapy. In addition to considering the efficacy of ICS treatment, the adverse effects of high-dose ICS (eg, growth suppression) should be considered. Oral leukotriene antagonists also are commonly used in young children who wheeze. Initial daily therapy may reduce episode frequency in children with intermittent wheezing during viral infections, but this requires further investigation.[21] The concept of stepping up short-term therapy is another option, which includes increasing rescue and controller medications at the onset of a viral infection or with exposure to a known trigger and then decreasing back to baseline after the exposure ceases or the infection resolves.[24] The efficacy of this approach also warrants further study.

The recent National Heart, Lung, and Blood Institute guidelines[22] recommend that practitioners see children with asthma at least every 6 months to review medications, risk, and level of control, with the goal of minimal therapy to control symptoms. The guidelines also stipulate that the use of preventive therapy only during seasons known to be problematic for a child is an acceptable option for some patients, as is a

medication break during the summer when viral infections are less frequent. This may be most beneficial and appropriate for children with mild to mild-persistent symptoms. However, there is some concern, especially with young children who have experienced moderate-to-severe symptoms, for discontinuing controller therapy during the months just before the peak season for asthma hospitalizations.[25] A vital component of therapy is asthma education for families, including instruction on proper device and spacer techniques, and a current action plan that describes appropriate medication indications and usage.

PROGNOSIS

In a prospective study, from Tucson, Arizona, of childhood wheezing, 60% of children who began wheezing before 3 years of age had transient conditions and did not develop asthma.[26] The remaining 40% continued to wheeze when re-evaluated at age 6 years. Identifying which infants and toddlers are predisposed to recurrent wheezing during the school-age years has been the focus of many prospective studies. A list, based on these studies, of host and environmental risk factors (known and putative) that may promote or diminish the chances for developing asthma during childhood is presented in Table I.

Among the host factors listed, the sex of the child has been well studied. There are more boys who wheeze as infants, and roughly two-thirds of school-age children with asthma are boys.[23] After puberty, a shift occurs, with more girls than boys affected. It is unclear whether the risk factors for predicting the development of asthma during the school-age years also apply to the onset of asthma in girls after puberty. Babies born prematurely, even without chronic lung disease, have an increased risk for recurrent wheezing during infancy and childhood.[27,28] Low lung function also is a risk factor for early childhood wheezing. It can persist beyond infancy in those children born prematurely and also is characteristic of infants who are small for gestational age (eg, babies born to mothers who smoke during pregnancy).[26,29,30] A Th2 bias, delays in maturation of Th1 antiviral immunity, and altered innate and mucosal immunity are risk factors that are likely associated with the atopic phenotype and may become manifest through gene-environment interactions.[31-33]

Results of prospective studies have highlighted the increased risk for developing asthma among infants who have atopic dermatitis and/or food allergy.[34,35] Family history, especially parental (particularly maternal) asthma, is well known to increase the risk for asthma during childhood.[26,36] In 2 previous studies, children who wheezed during the first 3 years of life and still had exacerbations at age 6 years had higher levels of serum total IgE during the first year of life.[26,36] As children grow older, up to 50% of toddlers (ages 2-3 years) and 80%-90% of school-age children seen for wheezing in the emergency department had allergen-specific IgE antibodies in their serum, and most of the school-age children with wheezing had high titers of serum IgE to dust mite.[37-39] Taken together, the detection of atopy during early childhood may be one of the strongest host risk factors for the development of persistent wheezing and asthma (Table II). The Asthma Predictive Index and modified Asthma Predictive Index scores incorporate variables ascertained at ages 2 to 3 years that can be useful for predicting which preschool-age children with wheezing have a increased risk for subsequent wheezing and the development of asthma[11-15] after 6 years of age (Figure 1).

TABLE II. Atopic risk factors associated with the development of asthma

Atopic factors	Reference no.
Family history (especially maternal and/or paternal asthma)	26, 36
Atopic dermatitis	34
Food allergy	35
Elevated total serum IgE during infancy	26, 36
Sensitization (IgE antibody) to aeroallergens of infants and toddlers (2 and 3 years old)*	75, 76

*May precede episodes of viral-induced wheeze (from Ref 46).

Many studies have evaluated the effects of viral respiratory tract infections on the development of asthma. RSV was initially reported to increase the risk for persistent wheeze and possibly the development of allergy and asthma in children up to 13 years of age.[40,41] Results of other studies indicate that this risk may be limited to those infants whose RSV-induced wheezing was severe enough to require hospitalization.[42] Recent studies of children with an atopic parent found that the risk for persistent wheeze at age 6 years was even stronger after rhinovirus-induced wheezing than RSV-induced wheezing during the first 3 years of life.[43] Subsequent studies from the same cohort indicated that sensitization to inhaled allergens is likely to precede the initial episode of wheeze with virus, thus raising the possibility that allergic mechanisms may play a role in the etiology of virus-induced wheeze that leads to asthma.[37] In contrast, results of studies of infants in day care or those exposed to older children at home indicate that more-frequent viral infections may have a protective effect on the genesis of asthma.[38] It should be noted, however, that publications regarding day care environment reinforce that further research is needed.[39]

The role of bacterial pathogens in the airway and bacteria-virus interactions have been highlighted recently.[44] Neonatal colonization of the hypopharynx with *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Haemophilus influenzae* or a combination of these but not colonization with *Staphylococcus aureus*, was observed to increase the risk for recurrent wheeze and asthma.[44] It is not known if the wheezing host is predisposed to this colonization as well as to asthma or if bacterial infections are in the causal pathway to asthma. Studies that involve interventions with antibiotics may be important to understand this interaction, although the adverse effects of administering antibiotics on gut flora also has been considered a risk factor for the development of asthma.[45,46] Still controversial or understudied is the administration of antibiotics to mothers during pregnancy and the effects of administering intravenous antibiotics to babies born prematurely during the neonatal period.

In keeping with the hygiene hypothesis, the microbiome (ie, usually understood to be the genome of collective microorganisms that inhabit a specific site) has emerged as a major area of investigation with potential therapeutic opportunities.[47] The influence of early bacterial colonization of the airway, gut, and skin on the development of the immune system and atopic disorders has received considerable attention.[48,49] The possibility that these differences may be linked to a higher risk for developing asthma among babies born by caesarean section is of interest[50] but still unclear because of the adjustments required for prematurity.[51] Children who grow up in a rural farming

community and who experience different microbial and endotoxin exposures have a significantly lower risk for developing asthma than children brought up in urban environments.[52]

At the moment, the effects of other environmental exposures on the development of asthma remain controversial with respect to planning interventions, including the use of acetaminophen to treat fevers of young children, early childhood vaccines, and exposure to parasitic infections.[53,54] Exposure to high levels of dust mite allergen in the home during infancy has been noted to increase the risk for developing asthma in childhood.[55] However, exposure to pets, especially dogs, during infancy decreases the chances for developing asthma into the teenage years, which challenges previous recommendations about removing pets from the homes of young children who are already sensitized.[56,57] Investigators have postulated that increased endotoxin exposure in homes may mediate this relationship.[56] Exposures to environmental tobacco smoke, fireplace and gas stove emissions, and urban air pollution (especially diesel fuel particles) are known to aggravate inflammation in the airway of a child with asthma, but their role in promoting the genesis of asthma is still unclear.[58,59]

PREVENTION

Despite our growing understanding of environmental, immunologic, and genetic factors associated with the risk for developing asthma, no intervention has reliably prevented asthma onset in children at risk. Numerous studies have targeted prevention of allergic sensitization as a means to prevent asthma. Allergen avoidance was tested in a randomized, prospective, controlled study in which maternal and infant pairs avoided the main food allergens, but avoidance did not reduce aeroallergen sensitization, respiratory allergy, or asthma among the offspring from birth to 4 years of age.[60] Likewise, if dust mite avoidance measures are added to food allergen avoidance by maternal and infant pairs, there also is no significant decrease in rates of asthma of the offspring.[61] Of children with allergic rhinitis who are already sensitized to few aeroallergens, allergen immunotherapy may reduce development of new sensitizations and may prevent asthma onset, but these results need further confirmation in larger trials.[62]

Studies focused on viral-induced wheezing and development of asthma have led to the hypothesis that prevention of such infections might abrogate asthma onset.[63] Such prevention could be achieved by means of vaccination, modulation of innate or adaptive immune systems, or by antimicrobial therapy. Palivizumab (a humanized mAb anti-RSV) prophylaxis given to preterm infants (33-35 weeks of gestational age) during their first RSV season decreased recurrence of wheezing up to 3 years of age.[64-67] These studies indicate that reducing RSV-associated lower respiratory tract infections can reduce wheezing episodes in the first years of life, but more studies with longer follow-up are needed to determine whether it also prevents asthma onset.

It is hypothesized that microbiome exposure may be the mechanism by which the risk of asthma development is reduced by exposure to dog in early life among children without a family history of asthma[68] and by exposure to farm animals and consumption of unpasteurized milk in central European infants.[69] Researchers hypothesize that digestive tract microbiome from animals may colonize the gut and respiratory tract of infants and account for these effects. However, recent meta-analyses concluded that probiotic administration in prenatal and/or early

life has so far reduced the risk of atopic sensitization and total IgE levels but may not reduce the risk of asthma or wheezing. Additional studies that used more diverse microbial products are ongoing.[70,71]

Exposure to passive smoke in early life doubles the risk of asthma onset, but parental smoking cessation interventions have not been efficacious enough to be tested in prevention trials.[72] Other well-designed studies have been performed to determine whether daily or intermittent treatment with ICS might delay the progression from episodic to persistent wheezing and asthma. These studies, however, failed to demonstrate a disease-modifying effect.[73] In keeping with this, the Prevention of Early Asthma in Kids clinical trial evaluated preschool children at high risk for asthma, including atopic risk factors, but failed to show a primary asthma prevention benefit after prolonged (2 years) treatment with ICS was discontinued, even though their asthma symptoms were better controlled while on therapy.[13]

Based on studies to date, the most promising strategies for primary prevention of asthma have been early allergen immunotherapy to prevent advancing allergic sensitization and antiviral treatment to prevent severe RSV lower respiratory infections. Other interventions, such as early life exposures to dog and/or farm animals, consumption of unpasteurized milk, or parental smoking cessation, are still controversial. The possibility that therapeutic intervention with omalizumab given early in childhood to infants at risk to prevent allergic sensitization and/or asthma has been noted as a reasonable hypothesis worth future study and consideration.[74]

CONCLUSION

The 2-year-old boy in our case had multiple risk factors for recurrent wheezing and/or asthma, including male sex, prematurity, history of severe bronchiolitis, atopic dermatitis, and maternal atopic asthma. However, his exposure to an older sibling who was in day care may be protective. The patient's current episode of wheezing was most likely of viral etiology. A trial of a short-acting β-agonist would be warranted, in addition to fluid and oxygen supplementation if needed. In a first episode of wheezing, results of current studies indicate that oral steroids may not be beneficial; but, with our patient's atopic background and history of severe wheeze, a short steroid burst could be considered with follow-up to monitor the response. If he continues to have recurrent episodes of wheezing, then either daily or intermittent inhaled steroids could also be considered. He was not a candidate for RSV prophylaxis with palivizumab because he was not younger than 6 months of age at the onset of the RSV season. Because of his atopic dermatitis, a peripheral blood eosinophil count, evaluation by an allergist for aeroallergen skin prick testing, and possibly serum IgE measurement are indicated to assess the risk for asthma development as well as to decrease exposure to symptom triggers. Much remains to be understood about wheezing in the preschool-age child, biomarkers of future asthma development, and primary prevention of asthma. Growing knowledge, it is hoped, will soon lead to new preventive and therapeutic measures.

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