Preschool-Aged Wheezing

NICO W. VEHSE, MD

ABSTRACT

Wheezing is a common physical finding in the pediatric age group 0-4 years and can have multiple diverse causes. Infectious causes are the most common culprit and lead to bronchiolitis or preschool asthma. The identification and understanding of these causes is fundamental in the appropriate treatment of our patients. The differentiation and underlying pathologies of these 2 conditions can be confusing and complicated. A systemic review of these conditions attempts to alleviate some of this confusion and tries to provide some clinical guidance for the treatment of these patients.

KEYWORDS: wheezing, bronchiolitis, asthma, airway inflammation

INTRODUCTION

Infants and children younger than 6 years of age have frequent healthcare needs related to respiratory symptoms. The primary reason for seeking help is related to respiratory viral infections, as some children may present with lower airway obstruction and severe symptoms.[1] These symptoms may be difficult to treat due to multiple mechanisms causing lower airway obstruction in children ages newborn to preschool years. Airway malformations have been excluded as it necessitates a separate discussion.

Bronchiolitis

The first time an infant presents with wheezing – defined as a high-pitched expiratory chest auscultation sound – can be challenging. The differential diagnoses are extensive and objective data are very limited. The most common reason for these symptoms is bronchiolitis, but the use of the diagnostic term is variable. Some providers consider any patient with wheezing and an age younger than 2 years as bronchiolitis, whereas other providers may diagnose only infants younger than 6 months of age presenting with a first-time occurrence of wheezing. On review of the published research on bronchiolitis since 2005, most authors defined bronchiolitis by ICD-9 code, clinical diagnosis or included only first episodes of wheezing in various age ranges. Some authors included recurrent wheezing patients and some did not give any clear definition of bronchiolitis at all.

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The use of a positive respiratory syncytial virus (RSV) test was also used as part of the definitions. Therefore, bronchiolitis patients are a very diverse population in research and clinical practice.

Bronchiolitis is defined by the American Academy of Pediatrics (AAP) as: "a disorder most commonly caused in infants by viral lower respiratory tract infection (LRTI); it is the most common LRTI in this age group and is characterized by acute inflammation, edema and necrosis of epithelial cells lining small airways, increased mucus production, and bronchospasm."[2] Bronchiolitis is initiated by an upper respiratory viral infection and numerous viruses cause bronchiolitis in infants, with RSV being the most common. Bronchiolitis is a self-limiting disease with 12 days as the median duration of illness for children <24 months, although 20% of children have a continuation of respiratory symptoms after 21 days. Hospital admission or emergency department assessment for respiratory and nutritional support is sometimes necessary.

Unfortunately the term bronchospasm polluted the definition of bronchiolitis and almost all studies assessing the treatment of bronchiolitis. In cases where patients suffer from bronchospasms due to reversible lower airway obstruction, the inhalation of short-acting-beta-agonist (SABA) bronchodilators will relieve these spasms, and therefore this type of bronchospasm should not be regarded as bronchiolitis. Assessing response to therapy is challenging in the absence of infant spirometry; nonetheless, respiratory scoring systems such as the one used at Hasbro Children's Hospital provide the best practical clinical assessment tool. A response to inhaled SABA on more than one occasion is very unlikely a false positive test and indicates reversible lower airway obstruction and not bronchiolitis. Thus, the respiratory scoring system can help exclude infants with reversible lower airway obstruction from the bronchiolitis population. This tool might help guide providers in clinical practice to more appropriate therapies.

REVERSIBLE LOWER AIRWAY OBSTRUCTION

Another very common reason for first-time wheezing in young infants and toddlers is reversible lower airway obstruction during respiratory viral infections.[3] This can only be diagnosed by albuterol trials and clinical impression, as mentioned above. It is challenging to decide which infant might benefit from such a trial and no clear guidelines exist on how this trial should be performed. A trial of albuterol – three consecutive albuterol doses (2.5 mg/3ml) via nebulizer or four separate doses of 100 µg with a metered-dose inhaler (MDI) and a valved-holding chamber (VHC) – may be indicated.[4] A good candidate for such a trial, but not exclusively, might be an infant with a family history of allergy, atopy, asthma or exposure to tobacco smoke. Many physicians are reluctant to diagnose an infant with recurrent and reversible airway obstructions as asthma and many other names are used to express the child's diagnosis, i.e. reactive airways disease, twitchy airways and others. This reluctance stems from the uncertainty regarding the chronicity of the child's respiratory condition.

Reactive airways disease, asthma, viral wheezing and all other used terms for these patients describe the same physiology of reversible lower airway obstruction from smooth, small-airway muscle spasticity. The etiology of these reversible airway obstructions is very diverse in the discussed age group and increasing diversity continues to be elucidated.[5] As a result, long-term management of exacerbation prevention becomes complicated and requires very individualized approaches. All these children should be treated with inhaled SABA for symptom relief and the MDI with VHC-delivered method is the most effective and safest way to deliver inhaled medications to the lower small airways.

The prognosis for infants through preschool-aged children presenting with respiratory viral infections and reversible lower airway obstruction remains unknown. The best epidemiological study to date is the Tucson Children's Respiratory Study.[6] This was a prospective cohort study identifying three distinct groups of children with different natural history of diseases: transient-early wheezers, late-onset wheezers and persistent wheezers. Patients with allergic sensitization had a later onset of symptoms and were most likely to continue with chronic asthma symptoms. Ongoing analyses of the data lead to the development of an "Asthma prediction index" for children with reversible lower airway obstruction during respiratory viral infections. Children with a first-degree relative suffering from asthma, atopy or allergies will have a 75% chance of having asthma symptoms past the age of 6 years. The same holds true for infants and toddlers with atopy or allergies themselves. It is important to remain mindful that nobody can prospectively decide if the patient in question is part of this 75% population or the 25% who will have resolution of symptoms.

The best evidence-based management for children with atopy and recurrent reversible lower airway obstruction is delineated in the 2007 NHLBI asthma guidelines[7] used in the United States or the PRACTALL Asthma European Consensus.[8] These children can be confidently diagnosed with asthma around age 5 years when they can produce repeatable and reliable spirometry results. Prior to this, the provider has to rely on subjective impression of symptom relief from inhaled SABA. This population will be well cared for by their pediatrician or family practitioner by using the 2007 NHLBI guidelines, but might require specialist care if more than mild to moderate asthma control medications are needed.

Non-atopic children with acute, intermittent airway inflammation and recurrent, reversible lower airway obstruction will have respiratory symptoms during the respiratory viral season.[9] Their exacerbations seem limited to episodes of respiratory viral infections and the season is traditionally from September through April. September and April are also the 2 months of the year with increased hospital admission for children with reversible lower airway symptoms.[10] Therefore, therapy and guidance needs to be focused on this time period.

LOWER AIRWAY INFLAMMATION

Children without chronic lower airway inflammation seem to have very questionable benefits from daily, inhaled corticosteroids (ICS) alone. This can be explained by their acute intermittent lower airway inflammation during respiratory viral infections and the difference in their inflammatory cell profile. The cell profile during acute exacerbations is very different from those of mild, well-controlled asthmatics who derive great benefit from low-dose ICS on a daily basis. Neutrophils, not eosinophils or lymphocytes, are the major culprits during acute symptoms. Basic research has revealed that neutrophils and eosinophils respond very differently to low-dose corticosteroids. Eosinophils become readily apoptopic when exposed to low-dose corticosteroids and are readily taken up by macrophages in the airways. This uptake by macrophages is the essential step towards resolution of inflammation.[11] Apoptosis is less likely in neutrophils due to many environmental factors, including IL-8, G-CSF, local tissue hypoxia, low-dose corticosteroids and low extracellular pH.[12, 13] Unfortunately, all these conditions are prevalent during lower airway obstruction.[14] The prolonged activation of neutrophils results in release of their toxic substances into the airways, causing further acute and chronic inflammation. It is unknown why some children have a tendency to respond to this inflammatory process by developing bronchospasm and prolonged inflammation. Fortunately, treating these children with high-dose pulse systemic corticosteroids (2mg/kg/day) seems to provide acute relief and resolution of the neutrophil-induced airway inflammation.

No evidence exists for effective symptom control of children with intermittent, acute, viral-induced neutrophilic lower airway inflammation and reversible airway obstruction. Many personalized and empirically-derived treatments have been used in the past, but none of these

are evidence-based therapies. Some providers might use intermittent high-dose inhaled steroids, others might hold daily medications and use intermittent systemic steroids plus inhaled SABA. Others use both a moderate-dose ICS and a leukotriene-receptor antagonist (LTRA) during the critical period or for the high-risk patient.

It has been my practice to use the latter plus the addition of a very aggressive inhaled SABA schedule during upper respiratory infections. The rationale is to suppress the acute inflammation with ICS and to block the leukotriene-mediated pathway responsible for lower-airway neutrophil recruitment with LTRAs. In vitro studies have also demonstrated that the combination of corticosteroids and long-acting beta-receptor agonists might be beneficial in decreasing inflammatory markers during viral infections.[15] It is unclear whether the regimens or the frequent close follow-ups are responsible for the provider's perception of efficacy of therapy. More likely, it is a combination of multiple factors.

Few novel anti-inflammatory medications have reached the market since the invention of ICS. LTRAs are one example; however, they are not effective when used as single agents to manage lower airway inflammation. ICS attenuates eosinophilic airway inflammation in asthma and remodeling of airway structures. LTRAs block leukotriene-mediated pathways of asthma. Despite the variety of medications available today, there is still no single safe therapy to manage neutrophilic inflammation in pediatric airways. The discovery of such a therapy would have far reaching impact on the treatment of cystic fibrosis, bronchopulmonary dysplasia, acute asthma exacerbations and viral-induced respiratory symptoms.

CONCLUSION

My practice in caring for the newborn through preschool population with recurrent respiratory problems is based on the physiology, immunology and chemistry of each individual patient. It has come to my realization that asthma is a poor diagnosis and more of a symptom description occurring during a respiratory syndrome. Unfortunately, none of the mentioned conditions have a cure. Preventative treatments are very limited and only symptom-relieving therapies are available for managing acute symptom exacerbations.

Patients younger than 6 years of age will continue to produce the highest healthcare cost and require frequent healthcare utilization until we are able to identify objectively the underlying mechanisms and control the causes of their respiratory symptoms safely and consistently. For now, we are best served by maintaining a keen clinical eye, providing good patient education and limiting environmental exposures through better infection and allergen avoidance. We should use our diagnostic terms wisely to avoid confounding the true underlying physiology, biochemistry, and biological factors causing our patients' suffering and to also help guide us to appropriate effective therapies for relieving their symptoms.

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Author

Nico W. Vehse, MD, is assistant professor of pediatrics, Division of Pediatric Pulmonology, Department of Pediatrics at The Warren Alpert Medical School of Brown University, and is affiliated with Hasbro Children's Hospital.

Disclosures

The author has no financial disclosures to report.

Correspondence

Nico W. Vehse, MD
Hasbro Children's Hospital
Department of Pediatrics
593 Eddy Street
Providence RI 02903
401-444-6540
Fax 401-444-6543
nvehse@lifespan.org