

# Inhaled Corticosteroids Should Be Used in Infants and Preschoolers with Recurrent Wheezing

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The infant or child presenting to the physician's office with persistent or recurrent wheezing during the first 2 years of life poses, often times, a diagnostic dilemma, and a therapeutic challenge. Until very recently, no guidelines were present to help the clinician navigate the very limited treatment options. The diagnosis of asthma in the very young is primarily difficult because of the lack of consistency of what is called asthma, and the failure to recognize the different phenotypes of asthma at different ages. Many classification and phenotypic descriptions have been proposed, but they continue to cause more confusion to already confused parents and perplexed physicians. Although these studies have provided much insight into the natural history of wheezy disorders, they have failed to affect clinical management to a large extent. Controversy persists as to when and why and how long inhaled corticosteroids (ICS) should be used in wheezy infants. Based on the current knowledge in this age group, ICS seems to be indicated in infants with multi-triggers wheeze, and in infants with a positive asthma predictive index. This article reviews the different phenotypic presentations of wheezy infant, the role and indications of ICS in this situation, and, finally, suggests a treatment plan based on the apparent cause of wheezing.

## Introduction

THE INFANT WITH persistent or recurrent wheezing during the first 2 years of life poses a diagnostic dilemma, which can be a source of anxiety to both physicians and parents. The prevalence of recurrent wheezing in infants during the first year of life is high, with a mean prevalence of 21.4% in Latin America, and 15.0% in Europe,<sup>1</sup> making it one of the most common conditions encountered in pediatric practices around the globe. Further, a significant proportion of infants with recurrent wheezing progress to a more severe condition that results in high use of health resources utilization such as emergency department visits and/or hospitalizations.<sup>1</sup> The reasons for the frequency of wheezing in this young age group are multifactorial and are beyond the scope of this review, relating to an immature immune system; frequent exposure to viral infections; prenatal, perinatal, and postnatal factors; genetic, epigenetic and environmental interactions; and, finally, unfavorable physiology and anatomy of the developing lung.

Diagnosing the wheezy infant can be a complex and a challenging task even for the most experienced physician. What makes this task even more complicated is that wheezing can mean different things to different people. A survey of respiratory sounds in infants found that 64% of parents who described their child's noisy breathing as wheezing changed their opinions after reviewing a video

that described different lung sounds.<sup>2</sup> Therefore, epidemiologic studies based on recall history may be leading to overdiagnosis and could be fraught with inaccuracies.

## Defining the Problem

The differential diagnosis of wheezing in infancy is very broad and encompasses many respiratory conditions, which had been reviewed extensively elsewhere.<sup>3</sup> Excluding diagnoses other than asthma and gathering information that supports a diagnosis of asthma are probably the most important but also the most difficult issues to address in this age group.<sup>4</sup> What makes this problem acute is that wheezy infants who develop asthma coexist with a larger group of infants with transient wheezing, which disappear during preschool or school years. Distinguishing these 2 phenotypes on the basis of their clinical presentation can be problematic. A spirited ongoing debate as to the place of inhaled corticosteroids (ICS) treatment in wheezy infants depending on their phenotypic presentation continues to stimulate the pediatric respiratory community.

## Phenotypes of Infant/Toddler Wheeze

In the last 2 decades, a wealth of epidemiologic studies, championed by the Tucson group, have been generated by retrospective analysis of large cohorts of wheezy infants,

which have been followed prospectively.<sup>5,6</sup> These studies described 3 patterns of wheezing based on presentation of symptoms. Early transient wheeze, nonatopic persistent wheeze, and atopic persistent wheeze. An important lesson from the Tucson Children's Respiratory Study is that wheezy infants who develop asthma coexist with a larger group of infants with transient wheezing that disappear during preschool or school years, but distinguishing these 2 phenotypes, in the clinical setting, on the basis of their presentation can be problematic and unhelpful for the practicing clinician.

To help define the risk factors for asthma in later years, an asthma predictive index was developed after following almost a thousand children through 13 years of age.<sup>7</sup> A stringent index requires frequent wheezing in the first 3 years of life plus 1 of 2 major criteria (atopic dermatitis in the child, parental diagnosis of asthma) or 2 of 3 minor criteria (diagnosis of allergic rhinitis in the child, eosinophilia [eosinophils  $\geq 4\%$  of the total white blood cells], wheezing apart from colds). A loose index for the prediction of asthma requires any wheezing during the first 3 years of life plus 1 of 2 major criteria or 2 of 3 minor criteria.<sup>7</sup> A positive stringent index was associated with asthma at school age in 76% of cases, whereas a negative stringent index was associated with an absence of asthma at school age in 97% of children. These data lend a strong argument for the use of asthma predictive index as a reference in young infants and children presenting with recurrent wheezing, and indeed it was adopted by the National Asthma Education and Prevention Program guidelines in 2007.<sup>8</sup> This index was further refined in 2004 to specify the frequency of wheezing as more than 3 exacerbations of wheezing in the past 12 months, with at least 1 physician-confirmed exacerbation. Additionally, this modified asthma predictive index includes allergic sensitization to  $\geq 1$  aeroallergen among the major criteria and replaces allergic rhinitis as a minor criterion with allergic sensitization to milk, egg, or peanuts.<sup>9</sup>

More recently, phenotyping of preschool wheeze has been developed by analyzing data collected more frequently than by the Tucson group, using sophisticated mathematical modeling.<sup>10,11</sup> It was adopted by the European Respiratory Society (ERS) task force, which proposed that the terms transient, late-onset, and persistent wheeze should probably be limited to population-based cohort studies and should not be used clinically.<sup>11</sup> They further proposed that wheeze should be described in terms of its temporal pattern and classified as episodic (viral) or multiple-trigger wheeze. For this reason, a different approach was selected to describe patterns and precipitants of symptoms: episodic wheezing is thought to be present only in association with viral upper respiratory tract infections; and multi-trigger wheezing, in which symptoms are present with and between viral infections. In this model, episodic wheeze most commonly declines over time, disappearing by the age of 6 years, but can continue as episodic wheeze into school age, change into multiple-trigger wheeze or disappear at an older age.<sup>11</sup> Sonnappa et al.<sup>12</sup> recently showed that these 2 subsets of wheezy infants differ primarily in their lung function. Infants with multiple-trigger wheeze had lower lung function, with conductive airways ventilation inhomogeneity than infants with viral-triggered wheeze. Whether this finding indicates that the episodic/multiple-trigger classification does distinguish 2 functionally different phenotypes has been recently challenged.<sup>13</sup> It has been postulated that lower airway

function may simply classify children according to disease severity, and not identify a differential disease mechanism, present before the symptoms occurred. In support of this contention are the results of another study<sup>14</sup> suggesting that the proposed episodic/multiple trigger classification is not stable over time, and children frequently change from one type of clinically defined wheeze to the other even in the course of only 1 year. Indeed, in the course of 1 year, the stability of this phenotypic classification remained the same in only 45.9% of children and altered in 54.1% of children.<sup>14</sup> Given these new challenging findings, the asthma predictive indices offer the advantage that they are quite stable over time and have been consistently shown to be acceptable predictors of subsequent development of persistent asthma symptoms.<sup>13</sup> However, even though these large-scale, long-term observational studies have provided much insight into the natural history of wheezy disorders, they have failed to affect clinical management to a large extent. This is thought to be due mainly to the inclusion of children with asthma with other wheezy disorders, and the methodology of relying on parental reports of wheezing without corroborating clinical assessment. Indeed, these studies suggest strong indicators for developing asthma and are very helpful in population-based studies, but they do not provide specificity and positive predictive values to be clinically relevant. Unfortunately, prospective studies including repeated measurements of lung mechanics and other serial objective assessment of conditions that cause wheezing during infancy and childhood in these cohorts of children are almost entirely lacking.

### **Risk Factors for Chronic Persistent Adult Asthma May Be Determined in Early Childhood**

Fernando Martinez eloquently suggested few years ago that "The fast growing lung of the preschool child may be particularly susceptible to the effects of chronic inflammation associated with persistent asthma. Therefore, to be successful, strategies for the prevention of deterioration of lung function in patients with asthma will also need to be focused on very young children, in whom the disease process is just beginning."<sup>15</sup> Many studies have debated the onset of airway inflammation in childhood asthma, and the early need of aggressive intervention. In an unselected birth cohort studied in late childhood, >1 in 4 children had wheezing that persisted from childhood to adulthood or that relapsed after remission. The factors predicting persistence or relapse were sensitization to house dust mites, airway hyperresponsiveness, female sex, smoking, and early age at onset.<sup>16</sup>

While this debate continues as to when airway inflammation occurs in the developing lung, more evidence is forthcoming that pathologic changes in infantile wheezing are strikingly similar to the adult pathology and are present very early in life. Indeed, to evaluate evidence of airway inflammation, endobronchial biopsies from wheezy preschool children (aged 3 months to 5 years), and age-matched control subjects were obtained. Reticular basement membrane thickness was significantly higher, and eosinophilic inflammation was significantly greater in the wheezy infants than in the control subjects ( $P < 0.05$  for both measurements).<sup>17</sup>

As the clinical characterization of disease presentation and consequently its progression has so far been proven

difficult, more studies are attempting to refine our understanding of surrogate inflammatory markers such as exhaled nitric oxide (FeNO) presence in infantile wheezing. In this regard, wheezy young children <4 years of age with a stringent index for the prediction of asthma at school age were found to have elevated levels of FeNO compared with children with recurrent wheeze and a loose index for the prediction of asthma, and children with recurrent cough.<sup>18</sup> Further, a moderate dose of inhaled fluticasone dipropionate was found to be effective in reducing the levels of FeNO compared with placebo, even in the absence of significant changes in lung function and symptoms.<sup>19</sup>

In addition, new studies have challenged the common belief that wheezing in nonatopic infants may represent a different subset of pathology, as epidemiologic studies have long suggested that it is resolved by adolescence.<sup>20</sup> Unexpectedly, Turato et al.<sup>21</sup> found that all pathological features typical of asthma were similar in atopic and nonatopic children with multi-trigger wheeze responsive to bronchodilators. Both nonatopic and atopic children 2 to 10 years of age had increased epithelial loss, thickened basement membrane, and increased neo-vascular formation and eosinophils on endobronchial biopsies. These results suggest that when multi-trigger wheezing responsive to bronchodilators is present, it is associated with pathological features of asthma even in nonatopic children.<sup>21</sup>

### How Do We Treat Wheezing Infants?

The treatment and evaluation of wheezy infants can be a complex process. Anti-inflammatory asthma medications can be helpful in wheezy infants and toddlers who have evidence of airway reactivity and airway inflammation. Stating that ICS should be used in wheezy infants in general is similar to asserting that antibiotics should be used for infants with fever!

Until recently, the treatment of wheezy infants has been mainly based on anecdote and clinical experience. The National Asthma Education and Prevention Program have added an algorithm for the treatment of wheezing associated with asthma in infants and children in their 2007 revision.<sup>8</sup> Low dose ICS are now recommended as the preferred initial treatment for infants and children who have >3 episodes of wheezing per year lasting more than 1 day, and the presence of a major factor such as parental history of asthma or eczema, or 2 minor factors, such as eosinophilia, wheezing without colds, or allergic rhinitis. Studies have shown that when preschool children with wheeze are selected on the basis of the asthma predictive index, they seem to respond to ICSs as a group.<sup>22,23</sup>

Treatment is also recommended for infants requiring symptomatic treatment with a short acting beta agonist for more than twice weekly, and/or the occurrence of severe exacerbations <6 weeks apart.<sup>8</sup> This new algorithm also judiciously suggested that if no clear benefit is observed in 4 to 6 weeks, to consider adjusting therapy or alternative diagnoses, meaning that not all wheeze is asthma. Similarly, the ERS task force suggests ICS as an initial therapy for multiple triggers wheeze, and montelukast (MK) for episodic wheeze, but due to the overlap of phenotypes the ERS recommend that ICS and MK can be used on a trial basis in any situation, but should be discontinued if no clear benefit is obtained.<sup>11</sup>

### Evidence Supporting the Role of ICS for Infant/Toddler Wheeze

In a recent meta-analysis on the efficacy of ICS in preschoolers with recurrent wheezing or asthma for at least 6 months before study entry, spanning many years and including thousands of subjects, Castro-Rodriguez et al.<sup>24</sup> found that patients who received ICS had significantly less wheezing/asthma exacerbations than those on placebo (18.0% versus 32.1%). Further, positive response to ICS was higher in those with a diagnosis of asthma than wheeze but was independent of age (infants versus preschoolers) and the atopic condition. In addition, children treated with ICS had significantly fewer withdrawals caused by wheezing/asthma exacerbations, less albuterol use, and more clinical and functional improvement than those on placebo.<sup>24</sup>

Other potential roles for ICS in addition to achieving symptoms control are to reduce disease severity. Indeed, in preschool children with intermittent moderate to severe wheezing and a positive modified asthma predictive index, continuous use of ICSs for 2 years led to significant improvements in disease burden, including reduction in symptoms and diminished oral corticosteroid use.<sup>23</sup> This was accompanied, however, by a statistically significant but transient reduction in linear growth velocity.<sup>23</sup> Another study found that episodic use of an ICS or a leukotriene receptor antagonist can decrease symptom burden, during acute respiratory tract infections in these children, particularly those with positive asthma predictive index.<sup>25</sup> Going beyond the asthma predictive index, the authors examined patient characteristics that were associated with positive response to ICS.<sup>26</sup> They found greater improvement with ICS in infants who experienced more symptomatic days at baseline, among boys, white subjects, and participants with an emergency department visit or hospitalization within the year before the study enrollment.<sup>26</sup> In other words, subjects with more severe disease had a better response to ICS. High-dose inhaled steroids have also been tried at the beginning of an upper respiratory viral infection and continued for 10 days.<sup>27</sup> This preemptive modality of treatment with high-dose fluticasone as compared with placebo reduced the use of rescue oral corticosteroids, but led to a smaller gain in height and weight in the actively treated preschool children, making this approach rather undesirable.<sup>27</sup>

What complicates things further is that environmental and genetic factors may directly influence or modify the response to treatment with corticosteroids among young children with wheezing. Persistent allergens in the immediate dwelling, environmental tobacco smokes both *in utero* and at home, polymorphisms in the corticosteroid pathways, and innate immune response with type I helper T cells reaction can all mitigate corticosteroids response. Further, multiple pathology leading to infantile wheezing can coexist; for example, airway reactivity, superimposed on recurrent viral infection, or moderate gastro-esophageal reflux can all be present in one individual, making the response to ICS rather mute, and the work-up more intricate. There is little research evidence to guide the choice of investigations that are mainly left to the clinical judgment of the treating physician.

Despite the fact that ICS seems to improve control of symptoms, they have not been capable to prevent the decline in lung function and the development of irreversible obstruction and airway remodeling. The study by Guilbert

et al.<sup>23</sup> provides contrasting evidence that treatment with ICS in early life does not alter the natural history of asthma as effects did not carry over after the drug was stopped during the third study year. It is unknown whether continuous use of the same ICS would have had any substantial benefit on airway remodeling, or perhaps the use of an ICS that can penetrate deep into the small airways, a site of significant inflammation in asthma, could have resulted in a different outcome. Nonetheless, equally important were the comments by Gold and Fuhlbrigge, on this study that in recognition of the fact that the diagnosis of asthma is difficult in the very young, a diagnostic trial of inhaled bronchodilators and anti-inflammatory medications may be helpful, with careful monitoring of the response to therapy.<sup>28</sup>

### Work-Up for Wheezy Infants

Wheezy infants constitute a heterogeneous group of patients. A complex and detailed work-up is usually necessary to arrive at the correct diagnosis. Prescribing therapy targeted at the cause of wheezing is the most common approach in managing these patients. A simple approach would be first to exclude other diagnoses based on “warning flags,” that is, symptoms of cystic fibrosis, reflux, aspiration, and underlying diseases such as severe neurodevelopment handicap, and then a therapeutic trial of asthma treatment, such as bronchodilators, ICS, and MK. When wheezy symptoms are refractory to conventional asthma therapy, then judicious use of diagnostic tests and individualized approach are required. An accurate diagnosis depends on a detailed medical history that includes possible risk factors for developing asthma, and a temporal description of the wheezing, a thorough physical examination, and an understanding of the numerous differential diagnoses. Investigations for the wheezy infants are justified when symptoms are present from birth, and/or the airway obstruction is abnormally severe, the recovery is very slow or incomplete resulting in prolonged or repeated hospital admission in the first few years of life, and the wheezy episodes continue in the absence of viral infections.<sup>11</sup> A provocative, somewhat invasive study based on a fixed protocol of investigations including a chest computed tomography scan, blood tests, nasal ciliary brushings, fiberoptic bronchoscopy, bronchoalveolar lavage, endobronchial biopsy, and passage of an oesophageal pH probe found that infants and young children with severe recurrent wheeze, who remain symptomatic despite a trial of inhaled steroids, yield positive diagnosis in three-quarters of cases.<sup>4</sup> Of these, 39% were atopic, two-thirds had evidence of gastro-oesophageal reflux, and 37 out of 47 had an abnormal bronchoscopy.<sup>4</sup>

We have proposed an individualized diagnostic approach to the causes of infantile wheezing<sup>29,30</sup> based on infant pulmonary function testing. This noninvasive test is FDA approved in infants as young as 4 months of age. Infant pulmonary function studies can help differentiate between central airflow (intrathoracic, extrathoracic, or fixed) and peripheral airflow obstruction. The infant with either intrathoracic, extrathoracic, or fixed airflow obstruction on the flow-volume loop may benefit from flexible fiberoptic bronchoscopy. The infant with either an intrathoracic or fixed airway obstruction should undergo an esophagogram to evaluate the anatomy for extrinsic tracheal compression. The infant with peripheral airflow obstruction and a good

response to bronchodilators may have infantile asthma, whereas the infant with peripheral airflow obstruction and no response to bronchodilators should be evaluated further for possible gastroesophageal reflux disease, and for other causes, which are associated with wheezing symptoms. We found a positive response to bronchodilators to be a distinguishing variable in wheezy infants with peripheral airway obstruction. Infants exposed to maternal smoking and infants with gastroesophageal reflux disease were more likely to have no response to bronchodilators than infants with a family history of asthma.<sup>31</sup>

### Conclusion

The burden of persistent infantile wheezing reflects in part the failure of earlier segmented research strategies. Hans Bisgaard in a recent review<sup>32</sup> eloquently stated the problems and the suggested solutions very clearly. He suggests that new research alliances and novel analytic approaches are needed to achieve more than just interesting observations of statistically significant associations. He points to the difficulty of achieving meaningful risk factors analysis due to the imprecision of asthma phenotypes, together with the broad disease's heterogeneity and the age-dependent presentation. Long-term, longitudinal studies, in his opinion, require cohorts starting before birth with longitudinal deep phenotyping, and repeated objective assessments to differentiate the age-dependent disease processes, and identify intermediary phenotypes and early predictors of disease progression.<sup>32</sup> Future efforts, in his opinion, should also be spent on identification of factors that allow for both primary and secondary strategies for asthma prevention.

The well-known dictum “all that wheezes is not asthma”<sup>33</sup> should always be in the mind of physicians treating wheezy infants and toddlers. Risk factors should not be overlooked, and all infants with wheezing should not be treated in similar fashion, but treatment plans should be based on the underlying cause of wheezing. Until we have a better understanding of the asthma phenotypes in the very young, and biomarkers predictive of treatment response, we should continue diligent use of diagnostic tests for proper diagnosis, and careful use of appropriate asthma guidelines for better treatment.

ICS continue to play a major role in the treatment of infantile wheezing as detailed in the previous sections. ICS have 3 potential roles in this regard: treating symptoms, potentially hastening the resolution of the disease and decreasing disease burden, and potentially preventing airway remodeling. Based on our current knowledge as detailed previously, it is fair to state that ICS do the first 2 of these relatively well in the right patient, but their effects on the third are unknown.

### Author Disclosure Statement

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