

Identifying and managing the infant and toddler at risk for asthma

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Recurrent wheezing is a common problem, with approximately 50% of children experiencing wheeze in the first year of life,¹ resulting in a substantial effect on the children, their families, and the health care system. However, the diagnosis of persistent asthma remains imperfect, with only 40% of these infants experiencing continued wheezing symptoms in later childhood¹ and with variation in expression of both symptoms and risk factors over time. The focus of this article is to provide evidence-based recommendations for identifying and managing infants and toddlers at risk for asthma.

IDENTIFICATION OF THE YOUNG CHILD AT RISK FOR ASTHMA

Often, the first wheezing episodes in young children are associated with viral illnesses. Both rhinovirus and respiratory syncytial virus have been linked to initial wheezing episodes and the risk of recurrent wheezing in early childhood. Furthermore, it has been observed that children who experience both early-onset allergic sensitization and respiratory tract illnesses that include wheezing have the highest risk of persistent asthma.² This suggests that both viral infections and allergic sensitization might damage the airway, leading to inflammation and hyperresponsiveness to external stimuli and continued wheezing.

Wheezing phenotypes describe the characteristics and risk factors associated with children who experience continued wheezing. In the Tucson Children's Respiratory Study 4 different wheezing phenotypes were identified in a large population-based birth cohort followed for lower respiratory tract infections based on the presence of wheezing symptoms during the first 3 years of life and again at age 6 years.¹ Children in the persistent wheezing (onset before age 3 years and still present at age 6 years) and late-onset wheezing (symptoms after 3 years of age) groups, who are

Abbreviations used

API: Asthma Predictive Index
ICS: Inhaled corticosteroid
LTRA: Leukotriene receptor antagonist
NAEPP: National Asthma Education and Prevention Program

at increased risk of allergic sensitization, might represent those children who are most likely to experience asthma-like symptoms that persist into adolescence and adult life. Young children might be difficult to place into accurate phenotypes given the change in risk factors over time. Thus, the persistent and late-onset wheezing phenotypes have also been described as multiple-trigger wheeze for children who wheeze when exposed to a variety of triggers rather than solely with viral infections to allow the clinician to better identify these children.³

Various predictive models or clinical indicators of risk have also been proposed to identify those children who will continue wheezing into late childhood. The Tucson investigators created a clinical Asthma Predictive Index (API) that defined the risk of asthma for children with recurrent wheezing (Table I).^{4,5} Using the API, a child having recurrent wheezing with 1 major criterion (parental history of asthma or a history of the child having atopic dermatitis) or 2 of 3 minor criteria (allergic rhinitis, wheezing apart from colds, and peripheral eosinophilia $\geq 4\%$) had a 4.3 to 9.8 times greater risk of having asthma during later school years. Active asthma was present in 76% of children with a positive API score, whereas asthma was not present in 95% of children with a negative score.

DIAGNOSIS OF ASTHMA IN THE YOUNG CHILD

The diagnosis of asthma should be considered in a young child with episodic reversible symptoms of airflow obstruction and airway hyperresponsiveness. There are several indicators that increase the probability of asthma in children, such as wheezing on examination, a history of cough that is worse at night, recurrent wheezing, and recurrent difficulty in breathing. The symptoms often worsen with activity, viral respiratory tract infections, exposure to allergens or irritants, changes in weather, or strong emotional responses. In addition to a positive API score, as outlined above, a history of atopic dermatitis, allergic sensitization, or response to asthma medications in the child or a family history of atopic disease also support the diagnosis of asthma.⁶ Other respiratory tract diseases and comorbidities that cause wheezing, such as aspiration, gastroesophageal reflux, airway anatomic abnormalities, airway foreign bodies, and cystic fibrosis, should also be considered in very young children.⁶

TREATMENT OF ASTHMA IN THE YOUNG CHILD

Recent evidence-based guidelines, such as the National Asthma Education and Prevention Program (NAEPP),⁶ take

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TABLE I. Modified API* versus original API⁴ (modified from Guilbert et al⁵)

1. A history of ≥ 4 wheezing episodes with at least 1 physician's diagnosis
2. In addition, the child must meet at least 1 of the following major conditions or ≥ 2 of the following minor conditions:

mAPI: Major criteria	Original API: Major criteria
● Parental history of asthma ● Physician-diagnosed atopic dermatitis ● Allergic sensitization to ≥ 1 aeroallergen	● Parental history of asthma ● Physician-diagnosed atopic dermatitis
mAPI: Minor criteria	Original API: Minor criteria
● Allergic sensitization to milk, egg, or peanuts ● Wheezing unrelated to colds ● Blood eosinophils $\geq 4\%$	● Physician-diagnosed allergic rhinitis ● Wheezing unrelated to colds ● Blood eosinophils $\geq 4\%$

mAPI, Modified API.

*Differences in indices are shown in boldface.

into account the current severity of the underlying disease and the present level of control. They also consider the current impairment that the child is experiencing and the risk of exacerbations. Their treatment recommendations were based on review of the key studies in preschool-aged children with a history of recurrent wheezing or asthma, as summarized in Table II.^{7-12,13-19} The NAEPP acknowledged that inhaled corticosteroid (ICS) therapy in preschool children with recurrent wheeze does not alter the natural course of the disease; however, they have recommended the use of daily controller therapy for recurrent wheezing to decrease the risk and impairment of the disease in this age group. This recommendation was based in part on the results of a previous study. Two hundred eighty-five toddlers with a positive modified API score (Table I) were started on a 2-year treatment with an ICS or placebo.⁷ During the treatment period, children treated daily with ICSs had a reduced symptom burden and improved lung function compared with those receiving placebo. This has also been supported by a recent meta-analysis.²⁰ Furthermore, more favorable responses to ICSs than placebo in these high-risk preschool children were more likely in those with an emergency department visit or hospitalization for asthma in the past year, boys, white subjects, or those who have aeroallergen sensitization.⁸

In addition to ICSs, leukotriene receptor antagonists (LTRAs) have been approved for use in this age group and recommended as an alternative therapy to ICSs by the NAEPP. The efficacy of LTRAs in intermittent viral wheezing episodes in preschool children was studied in 549 preschool children 24 to 60 months of age with intermittent asthma-like symptoms that compared montelukast with placebo.⁹ Montelukast was better than placebo in reducing the rate of and time to first exacerbation and supplementary ICS courses, but it did not reduce oral corticosteroid courses.

However, the NAEPP has also called for more clinical evidence to define the optimal treatment options for recurrent wheezing in preschool children.⁶ Acknowledging the limited data in this age group, the NAEPP recommends a stepwise progression of medications, such as medium-dose inhaled steroids, inhaled steroids in combination with LTRAs, or long-acting β -agonists, if control of symptoms is not achieved with low-dose ICSs. These recommendations are based on extrapolated data based on studies in older children and adults.

Although not endorsed by the NAEPP, intermittent treatment of acute wheezing episodes for a predefined period of time with controller therapy is used in practice. Supporting this approach, a recent study of 129 nonatopic preschool children with moderate-to-severe virus-induced wheezing demonstrated a 50% reduction in use of rescue oral corticosteroids during wheezing episodes when high-dose fluticasone or placebo was used intermittently at the onset of illness.¹⁰ Bacharier et al¹¹ examined the effectiveness of episodic use of a high-dose ICS, an LTRA, or placebo during respiratory tract illnesses in 238 preschool children with moderate-to-severe intermittent wheezing. Both budesonide and montelukast given at the onset of respiratory tract illness modestly improved symptom scores only during the illness but did not decrease oral corticosteroid use or symptoms apart from the illness.

In addition to efficacy, other factors need to be considered when selecting treatment regimens. These include ease of administration, side effects, and adherence. In this regard continuous therapy with ICSs in children is associated with an average height decrease of 1 cm in toddlers⁷ and older children. A modest decrease in height growth from baseline was noted in nonatopic children with recurrent wheezing treated with high-dose intermittent ICSs¹⁰ compared with placebo, but no height effect was demonstrated in the Bacharier et al trial.¹¹ There are also potential concerns of adrenal insufficiency, thrush, cataracts, and decreased bone mineral density associated with corticosteroid use.⁶ The ease of oral administration of LTRAs is desirable for many, although these medications have been associated with a variety of side effects as well.⁶

Taken together, these data suggest that children with positive API scores or those with a history of wheezing exacerbations requiring oral corticosteroids might demonstrate a greater response to either an ICS or montelukast. However, the NAEPP guidelines recommend ICSs as the preferred therapy with recurrent wheezing given the strength of the data supporting their use. For children with negative API scores, neither treatment led to significant improvement compared with use of a β -agonist alone. It could be argued that intermittent controller therapy could be used in place of daily therapy; however, it is unknown which characteristics would predict those children who will respond to high-dose intermittent controller therapy in an equivalent manner to continuous therapy. It is possible that this variable response might be due to the pattern of inflammation present within the child's airway, such as neutrophilic or eosinophilic inflammation. Furthermore, wheezing phenotypes currently are imperfectly defined and have not been studied sufficiently within the context of therapeutic trials to fully understand their contribution to the heterogeneity of response to therapy in the preschool-aged group.

Lastly, the use of oral corticosteroids in short courses to gain prompt control of symptoms when exacerbations occur has recently been questioned. Panickar et al¹² compared oral prednisolone with placebo in 687 hospitalized preschool children with virus-induced wheezing and demonstrated no benefit in length of hospitalization, symptom scores, or albuterol use. This study suggests that nonatopic preschool children (only 8% with physician-diagnosed "hay fever") with severe wheezing episodes might not respond to corticosteroids; however, the systemic corticosteroids were given during hospitalization, when the exacerbation was already severe, and more than one third of these children had no prior history of wheezing. Therefore additional evidence is needed before general recommendations can be made.

TABLE II. Summary of key studies relevant to the management of infants and toddlers at risk for asthma

Citation	Population (ref)	Treatment studied	Primary outcome	Findings
Bisgaard et al ⁹	549 children 2 to 5 y old with intermittent asthma and history of exacerbation with upper respiratory tract infections	12-mo randomized DBPC parallel-group trial of montelukast (4 or 5 mg daily) compared with placebo	No. of asthma exacerbation episodes defined as any 3 consecutive days with daytime symptoms and at least 2 treatments of β -agonist per day, ≥ 1 -d use of rescue oral/inhaled corticosteroids, or a hospitalization	Daily montelukast was better than placebo in reducing the rate of and time to first exacerbation and supplementary ICS courses. Most exacerbations were mild and did not require oral steroids. Montelukast did not reduce oral corticosteroid courses. <i>Post hoc</i> analyses did not demonstrate an effect of age or atopic status on response to therapy. No significant differences in adverse events were seen between treatment groups.
Bisgaard et al ¹³	625 children 1 to 3 y old with recurrent wheezing	12-mo randomized, parallel-group, open-label study comparing daily use of fluticasone-CFC, 100 μ g twice daily, with VHC/FM compared with sodium cromoglycate-CFC, 5 mg, 4 times daily with VHC/FM	A symptom-free day was defined as a symptom score on a diary card of 0 for 1 d (rating scale of 0-3)	The efficacy of fluticasone was superior to that of sodium cromoglycate, with fewer cases of symptom worsening, exacerbations, and requirements for oral steroid treatment and more symptom-free days and days without use of rescue treatment. No significant differences in adverse events were seen between treatment groups.
Bacharier et al ¹¹	238 children 12 to 59 mo old with moderate-to-severe intermittent wheezing	12-mo randomized DBPC study comparing 7 d of either budesonide inhalation suspension (1 mg twice daily), montelukast (4 mg daily), or placebo in addition to albuterol with each identified respiratory tract illness	Episode-free days	Intermittent budesonide and montelukast modestly improved symptom scores during respiratory tract illnesses but did not improve episode-free days or decrease oral corticosteroid use compared with placebo. Children with positive API scores or those who required oral corticosteroids for wheezing in the past year demonstrated the most benefit. No significant differences in adverse events were seen between treatment groups.
Bacharier et al ⁸	285 children 2 and 3 y old with mAPI	2-y treatment phase of daily use of fluticasone-CFC, 88 μ g twice daily, with VHC/FM compared with masked placebo; the objective was to determine whether demographic and atopic features predict response to ICSs in preschool children at high risk for asthma.	Episode-free days and oral corticosteroid use for exacerbations; urgent care or ED visits or supplemental controller medications	More favorable responses to ICSs than placebo in high-risk preschool children over a 2-y period were more likely in those with an ED visit or hospitalization for asthma within the past year, children with aeroallergen sensitization, boys, and white subjects.

(Continued)

TABLE II. (Continued)

Citation	Population (ref)	Treatment studied	Primary outcome	Findings
Baker et al ¹⁴	480 children 6 mo to 8 y with moderate persistent asthma	12 wk, randomized DBPC study comparing budesonide through a nebulizer comparing 0.25 mg once daily, 0.25mg twice daily, 0.5 mg twice daily, or 1 mg daily to placebo	Asthma symptom scores from diary cards	All dosing regimens produced statistically significant improvement in various clinical efficacy measures for asthma control compared with placebo. The lowest dose used, 0.25 mg daily, was efficacious but with fewer efficacy parameters than seen with the other doses administered. All treatment groups showed numeric improvement in FEV ₁ , but only the 0.5-mg twice-daily dose was significantly different from placebo. Adverse events for the entire group and responses to ACTH in a subgroup of children who underwent cortisol testing before and at the end of the treatment period were no different in budesonide-treated patients compared with those seen in placebo-treated patients.
Ducharme et al ¹⁰	129 nonatopic preschool children 1 to 6 y old with moderate-to-severe virus-induced wheezing	40-wk randomized DBPC study, 750 µg of fluticasone propionate HFA or placebo twice daily, beginning at the onset of an upper respiratory tract infection and continuing for a maximum of 10 d compared with placebo used during wheezing exacerbations	Rescue oral corticosteroid use	This study demonstrated a 50% reduction in use of rescue oral corticosteroids during wheezing episodes when high-dose fluticasone was used intermittently at the onset of illness compared with placebo. Treatment with fluticasone was associated with a smaller gain in height and weight.
Guilbert et al ⁷	285 children 2 to 3 years of age with positive mAPI score and recurrent wheezing	2-y treatment phase of daily use of fluticasone-CFC, 88 µg twice daily, with VHC/FM compared with masked placebo	Episode-free days	During treatment, benefits compared with placebo at the end of the 2-y treatment period in multiple illness burden outcomes that favored continuous ICS therapy, including (1) a significant increase in proportion of episode-free days and (2) lower rate of exacerbations and supplementary use of controller medication. Treatment with fluticasone was associated with a smaller gain in height (1.1 cm), which lessened off treatment (0.7 cm).

(Continued)

TABLE II. (Continued)

Citation	Population (ref)	Treatment studied	Primary outcome	Findings
Kemp et al ¹⁵	359 children 6 mo to 8 y old with mild persistent asthma	12-wk randomized DBPC study of once-daily budesonide (0.25, 0.50, or 1.0 mg) compared with placebo through a Pari LC-Jet Plus nebulizer with facemask	Nighttime/daytime asthma symptoms	All budesonide inhalation suspension doses produced significant improvements in nighttime/daytime symptoms and significant decreases in rescue medication use compared with placebo. Significant improvements in FEV ₁ were observed in the 0.5- and 1.0-mg budesonide inhalation suspension groups. There were no differences between doses of budesonide. Adverse events and basal and ACTH-stimulated cortisol levels were similar among all groups.
Knorr et al ¹⁶	689 children 2 to 5 y old with persistent asthma	12-wk randomized DBPC study comparing montelukast, 4 mg daily, with placebo	Daytime and overnight asthma symptoms	Daily montelukast therapy reduced symptom burden and oral corticosteroid use compared with placebo. No significant differences in adverse events were seen between treatment groups.
Panickar et al ¹²	687 hospitalized preschool children with virus-induced wheezing; one third of the children had no prior history of wheezing	29-mo randomized DBPC trial comparing a 5-d course of oral prednisolone (10 mg once a day for children 10-24 mo of age and 20 mg once a day for older children) with placebo	Duration of hospitalization	No benefit was noted in length of hospitalization, symptom scores, or albuterol use. This study suggests that nonatopic preschool children with severe wheezing episodes might not respond to corticosteroids. No significant differences in adverse events were seen between treatment groups.
Qaqundah et al ¹⁷	359 children 1 to 4 y old with persistent asthma	12-wk randomized DBPC study comparing fluticasone-HFA, 88 µg twice daily, with VHC/FM	Mean percentage change from baseline to end point in 24-h daily (composite of daytime and nighttime) asthma symptom scores	Fluticasone-HFA significantly reduced 24-h symptom scores and nighttime symptom scores over the trial period compared with placebo. Daytime asthma symptom scores, albuterol use, and the percentage of symptom-free days were not statistically different. No significant differences in adverse events were seen between treatment groups.
Shapiro et al ¹⁸	178 children 4 to 8 y old	12-wk randomized DBPC comparing budesonide doses of 0.25, 0.50, or 1.0 mg twice daily administered by a jet nebulizer with facemask	Nighttime and daytime asthma symptom scores	All doses of budesonide inhalation suspension were superior to placebo in improving nighttime and daytime asthma symptom scores, reducing use of breakthrough medication, and improving morning peak expiratory flow. There were no differences between doses of budesonide. No significant differences in adverse events were seen between treatment groups.

(Continued)

TABLE II. (Continued)

Citation	Population (ref)	Treatment studied	Primary outcome	Findings
Szeffler et al ¹⁹	Children 2 to 8 y old with either mild persistent asthma or recurrent wheezing	52-wk randomized open-label study comparing budesonide administered by nebulizer (0.5 mg once daily) to the LTRA montelukast (4 or 5 mg once daily)	Time to first additional medication for asthma worsening at 52 wk	No difference was noted in the time to first addition of step-up therapy for asthma worsening or time to the first course of oral corticosteroids at 52 wk between the treatment groups, although at some intermediate time points, there was an advantage for the budesonide group. The 2 groups did not differ in proportion of asthma-free days or rate of exacerbations requiring oral corticosteroids. No significant differences in adverse events were seen between treatment groups.

ACTH, Adenocorticotrophic hormone; CFC, chlorofluorocarbon; DBPC, double-blind, placebo-controlled; ED, emergency department; HFA, hydrofluoroalkane; *mAPI*, modified Asthma Predictive Index; VHC/FM, valved holding chamber spacer/face mask.

Therefore, in children with recurrent wheeze, the beneficial effects of asthma therapies need to be balanced with regular assessments of asthma risk and symptom control and consideration of reduction, substitution, or discontinuation of medication to capitalize on the benefit and lessen the risk of treatment.

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