

Management of Wheezing in Preschool Children

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Diagnosis and management of asthma in preschool children are challenging. The Expert Panel Report 3 has recommendations for specific illness phenotypes to start long-term controller medication to reduce risk and impairment in children ages 0–4-year old. The use of daily-inhaled corticosteroids has shown to be effective in preschool children with persistent asthma, but there are also reports of growth retardation. For children with recurrent or intermittent wheezing without symptoms in between episodes, the intermittent use of controller medications may be an option for certain phenotypes. This review will discuss the available data on use of intermittent controller medications in preschool children with wheezing.

DIAGNOSIS AND MANAGEMENT OF ASTHMA in preschool children are more challenging than in older age groups. The diagnosis is challenging, as childhood wheezing may have multiple causes, and there is a lack of objective lung function measurements in this age group outside of research laboratories.¹ The management also faces many challenges, as preschool children have smaller airways and tidal volumes that may affect drug deposition. In addition, the efficacy of available asthma medications is unclear due to age dependency of drug delivery via the use of a nebulizer or metered dose inhalers with spacers, lack of sufficient studies in this age group and extrapolation of data to children <5 years of age, and different characterizations of wheezing phenotypes across the age groups. In consideration of these factors, the latest National Asthma Education and Prevention Program's Expert Panel Report 3 (EPR3),² the management of asthma is presented in 3 different age groups of children 0–4, children 5–11, and youths ≥12 years of age and adults.² The focus of this editorial is the management of asthma in children <5 years of age. The EPR3 recommends initiating long-term control therapy in children with at least 4 episodes of wheezing in the past year and positive values in modified Asthma Predictive Index (API).^{2–4}

Management of recurrent wheezing in this age group is complicated, as these children may not have persistent asthma with frequent symptoms. The management becomes even more complex, as it may be viewed as a window of opportunity to prevent potential development of asthma later in life. In addition, concerns regarding the safety of inhaled corticosteroids (ICSs) and their potential effects on growth exist for these very young children. Since many of these patients have asthma symptoms with respiratory illnesses and stay symptom free in between episodes, 2 treatment strategies have been studied and reported: daily and intermittent treatment with controller medications.

When it comes to management of preschool children with persistent asthma, the use of daily ICSs has been shown to be more effective than placebo.^{5,6} However, the risk associated with potential-reduced linear growth remains and needs to be balanced with clinical benefits. The use of low-dose fluticasone propionate daily for 2 years in preschool children at a high risk of developing asthma was associated with a lower rate of exacerbation and greater episode-free days when compared to placebo.⁴ Patients were followed for a 1-year observation phase, and at the end of the trial, the height increase was still 0.7 cm less than the placebo group. Furthermore, there was no disease-modifying effect noted in the observation phase.

For preschool children with episodic symptoms (and symptom free in between the episodes), the intermittent use of ICSs seems appealing as it may address these issues about the long-term use of ICSs as well as the noted difficulty for parents in administering the medication via a nebulizer or MDI with a facemask every day, leading to nonadherence.

In a recent publication, Zeiger and colleagues reported a randomized, double-blind, parallel group trial to determine whether a low dose of nebulized budesonide is superior to an intermittent high dose of nebulized budesonide starting at the onset of the respiratory tract illness.⁷ Children 12–53-months old were enrolled if they had at least 4 episodes of wheezing in the previous year, positive-modified API, and at least one exacerbation in the previous year. Patients were excluded if they were hospitalized more than twice for the wheezing episodes in the previous year or if they had more than 6 courses of systemic corticosteroids. A 2-week run-in period assured exclusion of those children with symptoms in between the respiratory tract infections. At the randomization visit, parents identified the early signs or symptoms of the respiratory episodes that would lead to developing wheezing, and these were used to determine when to start intermittent therapy. Patients were randomized to the daily

use of low-dose budesonide (0.5 mg nightly) or intermittent high dose of budesonide (1 mg twice daily for 7 days) starting at the onset of the respiratory tract illness in a double-blind, double-dummy fashion for 52 weeks. The primary outcome was the frequency of exacerbations as defined by the use of oral corticosteroids after consultation with a physician via phone or in person. Treatment failure and hence termination from the study was defined as 4 courses of systemic corticosteroids or any hospitalization, hypoxic seizure, or serious adverse events related to the study. Height and weight were measured at each visit. Two hundred seventy-eight patients were randomized, and 213 completed the study. The rate of exacerbation per patient-year did not differ between the treatment groups, and it was 0.95 [95% confidence interval (CI), 0.71 to 1.35] for the intermittent group compared to 0.97 (95% CI, 0.76 to 1.22) in the daily treatment group ($P=0.60$). Similarly, the time to the first and second exacerbation did not differ between the groups. The total number of respiratory episodes per patient-year was not different, nor was the frequency of treatments for respiratory tract illness in each treatment group. The intermittent group was exposed to a lesser amount of budesonide over the duration of the study compared to the daily group. There were no differences in height, weight, and head circumference of the patients in the treatment groups. Twelve patients in the intermittent group and 7 in the daily group experienced treatment failure ($P=0.3$). The authors concluded that daily use of budesonide was not superior to the intermittent high dose for 7 days started at the onset of symptoms known for progressing to wheezing episodes.

The use of intermittent controller medication has been studied previously. What is important to note in MIST and other trials are the patient population and timing of the start of therapy. Administration of 400 mcg of budesonide daily for 2 weeks, beginning 3 days after onset of first wheezing episode in infants, did not alter the number of wheezing episodes during the first 3 years of life compared to placebo, nor did it change the progression from episodic to persistent wheezing.⁸ In a similar study, 750 mcg of fluticasone propionate twice daily was started at the onset of an upper respiratory infection for 10 days in children 1 to 6 years over 6–12 months.⁹ Children in the fluticasone propionate group had significantly fewer exacerbations as defined by use of oral corticosteroid compared to the placebo group. They also had a significantly smaller gain in weight and height compared to placebo.

When budesonide (1 mg twice daily), montelukast (4 mg once daily), or placebo was started at the early onset of respiratory illness in children 1–5 years of age with recurrent wheezing, only children with modified API showed a modest symptom reduction during the episodes with budesonide and montelukast compared to placebo.¹⁰

With a different approach, the daily use of beclomethasone, as needed use of combination of beclomethasone and salbutamol and as needed salbutamol (albuterol), was compared in children 1–4-years old for 12 weeks.¹¹ Children were randomized to treatment arms if they had symptoms requiring use of rescue medications for 7 days out of the 2-week screening period. The authors reported that the percentage of symptom-free days was significantly higher only in the daily use of the ICS group compared to the as needed salbutamol group. Use of montelukast daily or intermittently has also been investigated with inconclusive results.^{12,13}

In conclusion, the MIST study is the first one to compare 2 promising strategies: daily low-dose corticosteroids and high-dose intermittent corticosteroid—in a parallel design.^{4,10} However, it is important to note that the result of this study cannot be extrapolated to all the children, but only to those as defined in the inclusion criteria.

Current data provide the opportunity for future trials, and while emerging evidence in managing asthma in preschool children is compiling, the wheezing phenotype needs to be defined clearly at each study, as the proposed strategies may not be extrapolated to all wheezing phenotypes. Treatment approaches need to be individualized for the best results.

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Received for publication June 14, 2012; accepted after revision June 15, 2012.