



Management of preschool recurrent wheezing and asthma: a phenotype-based approach

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Purpose of review

The purpose of this review is to summarize the recent evidence on the management of preschool children with wheezing and asthma, and to propose a phenotype-based approach to the management of these children.

Recent findings

Recent studies have begun to identify populations of preschool children that are likely to benefit from inhaled corticosteroids (ICS) therapy and defined ICS regimens: daily ICS in preschool children with persistent asthma, and pre-emptive high-dose intermittent ICS among preschool children with intermittent disease reduce the risk of exacerbation. In addition, among preschool children with mild persistent asthma, the presence of aeroallergen sensitivity and/or blood eosinophil counts of 300/ μ L or greater are predictors of good response to daily ICS therapy. Other studies identified intermittent azithromycin as a therapy to prevent, and potentially to treat, acute exacerbations.

The uncertainty of the role of oral corticosteroids (OCS) as a therapy for acute exacerbations continues, as a recent meta-analysis showed that OCS did not prevent hospitalizations or urgent visits, and did not reduce the need for additional courses of OCS. Whereas previous epidemiologic studies suggested acetaminophen may increase risk of exacerbations, a clinical trial clearly demonstrated acetaminophen use, compared to ibuprofen use, does not increase exacerbation risk among preschool children with mild-persistent asthma.

Summary

Recent studies have shown potential for phenotypic-driven therapies for the management of preschool children with asthma. Targeting airway bacteria has emerged as a promising therapeutic approach, but its effect on antibiotic resistance still needs to be investigated. Finally, more studies are required to evaluate if oral corticosteroids provide any benefits for acute episodic wheeze.

Keywords

acetaminophen, asthma, azithromycin, corticosteroids, preschool children, wheeze, wheezing

INTRODUCTION

Wheezing is a common clinical condition during early childhood: approximately 50% of children experience at least one episode before 6 years of age [1]. Wheezing and asthma among preschool children are heterogeneous conditions with many phenotypes, which differ in the age of onset, expression of symptoms, the presence of atopic characteristics, treatment response, and in their long-term outcomes [1–4]. Early childhood wheezing and asthma phenotypes are also likely to differ in their pathophysiology. Although routine bronchoscopies are not being performed among preschoolers, studies that have utilized biomarkers to indirectly explore airway inflammation have suggested heterogeneous patterns of inflammation: eosinophil activation [5], leukotriene production [6], and neutrophil activation [7].

Optimizing asthma management among preschool children is essential as preschoolers experience disproportional morbidity and healthcare utilization compared with school-age children with asthma [8,9]. The goal of this review is to summarize the recent data on the management of preschool

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KEY POINTS

- Daily inhaled corticosteroid therapy among preschool children with persistent asthma, and pre-emptive high-dose intermittent inhaled corticosteroids among preschool children with intermittent asthma or viral-triggered wheezing reduced the risk of exacerbations by approximately 40%.
- Among preschool children with mild persistent asthma, the presence of aeroallergen sensitivity and/or blood eosinophil counts of 300/ μ L or greater is a significant predictor of daily inhaled corticosteroid response. If a child does not respond to the initial step 2 therapy, an alternative step 2 therapy (e.g. leukotriene receptor antagonist) should be investigated before escalating to step 3 therapy.
- In children with recurrent wheezing in the setting of lower respiratory tract illnesses, clinicians may consider a therapeutic trial of azithromycin early in the course of respiratory tract illness in order to prevent severe exacerbation. If effective, it may be repeated with subsequent illnesses. Azithromycin may also be considered as a therapy for acute exacerbations among these children.
- The utility of oral corticosteroids for acute wheeze/asthma exacerbation among preschool children remains uncertain. Recent meta-analysis showed that oral corticosteroids did not prevent hospitalizations or urgent visits, and did not reduce the need for additional courses of oral corticosteroids.
- Compared with ibuprofen, acetaminophen use does not increase exacerbation risk among preschool children with mild persistent asthma.

children with wheezing and asthma, and to propose a phenotype-based approach to the management of these children.

THE UTILITY OF INHALED CORTICOSTEROIDS FOR EXACERBATION PREVENTION

Inhaled corticosteroids (ICS) are recommended by asthma guidelines [10,11] as the first line of therapy for school-age children and adults with mild persistent asthma, as many studies have demonstrated the efficacy of these medications in terms of exacerbation prevention and reduction in asthma symptoms.

A recent meta-analysis confirmed the beneficial role of ICS among preschool children [12^{***}]. This meta-analysis investigated ICS treatment response among children aged 6 years or younger with asthma or recurrent wheezing (at least two episodes in the past year). The outcome of the analyses was severe exacerbations requiring systemic corticosteroids. The

main analysis, which included 15 studies involving 3278 participants, compared the effect of daily ICS to placebo, and revealed a 30% reduction in the risk of exacerbations with daily medium-dose ICS. The number needed to treat (NNT) was nine, that is, nine children needed to be treated with daily ICS in order to prevent one exacerbation. Intermittent ICS therapy compared with placebo (six studies with 588 participants) resulted in a 36% reduction in exacerbation. Findings from two studies (498 participants) comparing daily with intermittent ICS showed no significant differences in rates of severe exacerbations. These findings were extended in additional subgroup analyses that targeted specific populations of interest and revealed the following:

- (1) Daily ICS therapy compared with placebo among preschool children with persistent asthma (eight studies, 2505 participants) resulted in a 44% reduction in risk of exacerbations (NNT = 11).
- (2) Daily ICS therapy compared with montelukast among preschool children with persistent asthma resulted in a 41% reduction in exacerbations (one study, 202 participants).
- (3) Pre-emptive high-dose intermittent ICS compared with placebo among preschool children with intermittent asthma or viral-triggered wheezing (five studies, 422 participants) resulted in a 35% reduction in exacerbations (NNT = 6).

In summary, this recent meta-analysis has confirmed the role of ICS as the first-line therapy in preschool children with asthma or recurrent wheezing. It also helps the clinicians to determine ICS regimens: whereas daily ICS therapy should be considered for preschool children with persistent disease, pre-emptive high-dose intermittent ICS is a reasonable option for preschool children with intermittent disease.

PHENOTYPIC-DRIVEN APPROACH TO ASTHMA MANAGEMENT

Initial selection of asthma controller in preschool children with mild persistent asthma

The results of the meta-analysis described above [12^{***}] confirmed the efficacy of ICS in the management of preschool children with asthma. However, gaps in knowledge in the management of young children with asthma remain, including the following:

- (1) What are the characteristics of preschool children most likely to benefit from ICS therapy?

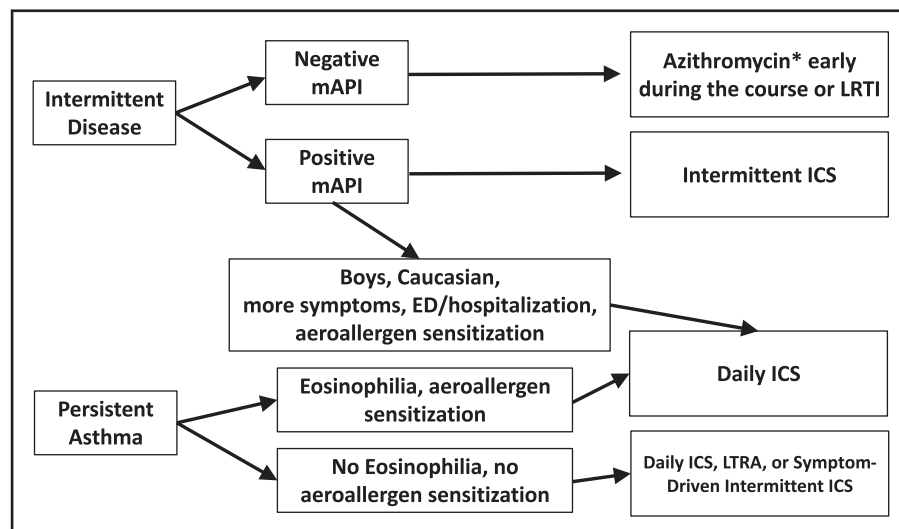


FIGURE 1. Phenotype-driven approach to the management of preschool children with asthma. If no response to intermittent azithromycin therapy, then consider pre-emptive high-dose intermittent ICS therapy. ICS, inhaled corticosteroids; LTRA, leukotriene receptor antagonist; LRTI, lower respiratory tract illness; mAPI, modified asthma predictive index.

Previous post-hoc analysis has shown that Caucasian children, boys, children with history of recent emergency department (ED) visit or hospitalization for asthma, and those with evidence of aeroallergen sensitization, had a more favorable response to daily low dose ICS [13]. However, this important question has not been prospectively investigated.

- (2) The meta-analysis described above [12^{***}] suggested similar treatment responses with intermittent and daily ICS therapy. However, are there characteristics of children who respond better to one of these approaches? If so, how are these children identified?
- (3) Are there characteristics that identify children who are more likely to benefit from other asthma controller therapy, such as leukotriene receptor antagonists (LTRAs)?

The Individualized Therapy for Asthma in Toddlers (INFANT) [14^{***}] of the NHLBI's AsthmaNet, which addressed several of these areas of uncertainty, investigated whether phenotypic features and biomarkers, among preschool with mild persistent asthma, would determine treatment response. The study population included children aged 12–59 months who required step 2 asthma therapy. Among the participants, 75% required oral corticosteroid (OCS) therapy over the previous year, 60% had positive modified asthma predictive index (mAPI) [15] status, and 42% had evidence of aeroallergen sensitivity. Study participants were randomized to three 16-week crossover periods with the following therapies: daily ICS, daily LTRA, and

as-needed ICS treatment co-administered with albuterol. Among the children, 74% experienced a differential (and thus preferred) response to one of these three treatments assessed by a composite asthma outcome, which included domains of risk and impairment. Patients without a preferred therapy had evidence of less severe disease and lower disease activity overall. Among the entire study population, the preferred therapy was daily ICS. The next step of the analysis investigated whether daily ICS response could be predicted based on patient characteristics and biomarkers. Daily ICS response was predicted by aeroallergen sensitization or blood eosinophil counts of 300/ μ l or greater. The highest likelihood of experiencing a daily ICS response was seen among children with both aeroallergen sensitization and blood eosinophil counts at least 300/ μ l. ICS therapy among these children resulted in more asthma control days (ACDs) and lower exacerbation risk compared with the other two therapies. Neither phenotypic features such as exacerbation history, sex, and mAPI status, nor biomarkers such as serum IgE levels and urinary leukotriene E4 concentrations were predictors of differential response.

In summary, the INFANT study [14^{***}] suggests that determining peripheral blood eosinophil counts and/or aeroallergen sensitivity may aid clinicians in choosing the initial therapy for preschool children with mild persistent asthma. If a child has evidence for aeroallergen sensitivity and/or blood eosinophil count at least 300/ μ l, the child would be most likely to experience a beneficial response to daily ICS. If a child does not respond to the initial step 2 therapy, an alternative step 2 therapy (e.g.

LTRA) should be investigated before escalating to step 3 therapy. In contrast, among children without aeroallergen sensitivity and/or blood eosinophil count at least 300/ μ l, initial therapy may include daily ICS, daily LTRA, or symptom-driven ICS use.

Macrolide therapy in preschool children with recurrent wheezing in the setting of lower respiratory tract illnesses

Many preschool-aged children with recurrent episodes of wheezing experience significant morbidity during acute episodes of lower respiratory tract illnesses (LRTIs), but have minimal symptoms consistent with persistent asthma between these episodes [16]. Although their disease is episodic, these young children experience disproportionately greater morbidity and healthcare utilization, mainly related to acute exacerbations [9]. Therefore, defining approaches for the prevention of acute exacerbations is highly desirable. Furthermore, exacerbation prevention is highly important, as it is unclear if the traditional therapy for acute exacerbations (i.e. OCS) provides clinical benefits (discussed below) [17,18].

As summarized above, daily ICS is the mainstay of therapy directed for exacerbation prevention in preschool children. However, this therapy has limitations, which are given as follows:

- (1) Inhaled corticosteroid reduces the rate of exacerbation by approximately 40%, but does not completely prevent them [12²²].
- (2) Inhaled corticosteroid therapy is associated with small, but significant, reduction in linear growth, and the effect may be nonreversible among young and low-weight children [19].
- (3) Low adherence was documented to daily ICS regimens, potentially due to parent's concern of medication side effects [20].

Based on these limitations of ICS therapy, and the potential lack of efficacy of OCS when given for acute exacerbations, additional approaches to prevent exacerbations have recently been investigated. Macrolides have beneficial anti-inflammatory effects in other inflammatory chronic lung diseases [21]: they reduce neutrophilic inflammation, which is dominant during respiratory infections, in a mouse model of viral lower respiratory tract infection [22], and among infants hospitalized with viral bronchiolitis [23]. In addition, macrolides may provide benefits in children with episodic wheeze based on their effect on the airway microbiome, as accumulating evidence suggests that bacteria are important determinants of asthma inception and

progression [24,25²⁴]. Finally, azithromycin given during acute severe respiratory syncytial virus bronchiolitis may reduce post-bronchiolitis wheezing through its effects on the airway microbiome [26].

The Azithromycin for Preventing the Development of Upper Respiratory Tract Illness into Lower Respiratory Tract Symptoms in Children (APRIL) clinical trial performed by AsthmaNet investigated whether early administration of azithromycin started prior to the onset of severe LRTI symptoms, in preschool children with severe episodic wheeze, would prevent the progression to severe LRTI episodes that would trigger the use of OCS [27²⁵].

The study population included 607 children aged 12–71 months with significant episodic wheeze and minimal day-to-day impairment. Approximately 50% had positive mAPI status. Participants were randomized to receive either parent-initiated azithromycin (12 mg/kg/day for 5 days) or placebo started early during each predefined RTI based on individualized action plan, which was designed to reflect a collection of signs and symptoms that, based on parents' perception, would lead to exacerbation. No asthma controllers were used during the study. Early initiation of azithromycin reduced the risk of progressing to severe LRTI by 36%, a magnitude of effect that is comparable to the effect of ICS therapy. In addition, azithromycin significantly decreased illness severity during episodes that progressed to severe LRTI. There was no difference in treatment effects between those with and without a positive mAPI, suggesting a therapeutic option for children with negative mAPI, a group of children traditionally under-represented in asthma studies. Induction of azithromycin-resistant organisms was infrequent: over the duration of the study [27²⁵], 17% of participants treated with azithromycin and 11% of participants treated with placebo acquired azithromycin-resistant organisms, with *Staphylococcus aureus* being the most common azithromycin-resistant organism isolated.

On the basis of the results of the APRIL trial, the authors suggested that in children with recurrent severe wheeze in the context of LRTI, clinicians may consider a therapeutic trial of azithromycin early in the course of RTI [27²⁵]. If effective, clinicians should consider repeating such therapy with subsequent illnesses.

Another recent study [28²⁶] suggested the utility of azithromycin therapy during significant LRTI.

The trial included children aged 1–3 years, from the Copenhagen Prospective Studies on Asthma in Childhood 2010 cohort. All participants had recurrent asthma-like symptoms (troublesome lung symptoms) that lasted at least 3 days, but not pneumonia. One hundred and fifty-eight asthma-like

episodes in 72 children were randomized to a 3-day course of oral azithromycin (10 mg/kg/day) or placebo. Azithromycin therapy resulted in a 63% reduction in the duration of respiratory symptoms after initiation of therapy: 3.4 days for children treated with azithromycin versus 7.7 days for children treated with placebo. The intervention was more effective when the therapy was initiated earlier during the course of the illness: duration of symptoms was reduced by 83% if the treatment was initiated before day 6 of illness versus 36% if initiated on or after day 6. In general, the presence of three types of bacteria (*Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*) detected in upper airway secretions in 67% of the episodes, did not modify the treatment effect. However, azithromycin was more effective in episodes positive for *H. influenzae*. The investigators did not evaluate the effect of azithromycin on the induction of antibiotic resistance. Although asthma-like symptoms were reduced by azithromycin therapy, these results should be interpreted with caution as the investigators could not detect effect on relevant clinical outcomes that are often utilized in outpatient asthma studies, such as the need for OCS use and/or urgent care visits, as these events were extremely uncommon in this study population.

In summary, azithromycin therapy may be a therapeutic approach for young children with recurrent and severe episodic wheeze, either as a prevention modality or as a treatment for acute exacerbations. Obviously, more information is needed on the potential development of antibiotic-resistant pathogens that may be associated with episodic and repeated azithromycin therapy. However, this treatment approach may prevent multiple OCS courses, a treatment that is of questionable efficacy [17[■],18] and is associated with side effects [29].

Montelukast therapy in preschool children with episodic wheeze

A recent meta-analysis investigated the utility of montelukast for the prevention of acute exacerbation requiring OCS among preschool children with acute episodic viral wheeze [30]. Neither maintenance montelukast therapy (more than 2 months) nor intermittent montelukast therapy resulted in a significant reduction in the rate of exacerbations requiring systemic corticosteroids.

Another recent study [31] highlighted the importance of personalized medicine by suggesting that genetic variability in the arachidonate 5-lipoxygenase (*ALOX5*) gene promoter, which was shown to modify montelukast response in adults,

may determine treatment response to intermittent montelukast also in preschool children. The results of this study [31] did not show clear benefits for the prevention of unscheduled visits for wheezing in the whole cohort, but identified a genotype that may increase montelukast treatment response.

THE DEBATABLE UTILITY OF ORAL CORTICOSTEROIDS AS A THERAPY FOR ACUTE EXACERBATIONS

The use of OCS for acute wheeze/asthma exacerbation among preschool children continues to be a topic of controversy [17[■]]. Traditionally, preschool children presenting with acute exacerbation have been treated with OCS based on the assumption that airway inflammation can be attenuated and this would improve acute respiratory symptoms. This assumption is based on extrapolation from studies performed in the setting of acute asthma exacerbations among school-age children and adolescents where OCS has been an effective therapy [32]. However, episodic wheeze in preschool children and asthma in older children are clinical conditions that differ in their pathophysiology and in the patterns of underlining airway inflammation [18]. Indeed, studies performed over the past decade failed to demonstrate efficacy of OCS when given during acute episodic wheeze among preschool children [33,34], and several editorials have questioned the utility of this traditional intervention [35–37]. Furthermore, the most recent version (2016) of the international asthma (GINA) guidelines [11] concluded that the evidence to support OCS therapy in the outpatient setting (parent-initiated therapy) among preschool children is weak, but still recommended OCS use in the acute care/hospital setting [11].

A recent meta-analysis investigated the efficacy of OCS in the treatment of acute wheezing episodes in asthmatic preschoolers [38[■]]. The pooled analyses (11 studies, involving 1733 participants) showed that oral corticosteroids did not prevent hospitalizations or urgent visits, and did not reduce the need for additional courses of oral corticosteroids. The authors concluded that the current evidence is inadequate to make any broad clinical recommendations regarding the utility of OCS in preschoolers with acute episodic wheeze [38[■]].

Stratifying the meta-analysis [38[■]] by the setting of the intervention yielded some unexpected findings. Analysis of randomized trials that investigated the utility of parent-initiated OCS in the outpatient setting (three studies) showed that children treated with OCS were twice as likely to be hospitalized compared with children treated with

placebo. The authors hypothesized that behavioral changes that sometimes are associated with OCS therapy may have affected the decision to admit these children; however, the exact reason for this unexpected finding is not clear. Additional stratified analyses showed that systemic corticosteroids may reduce rate of hospitalizations when administered in the ED setting (two studies), and may decrease the need for additional courses of systemic corticosteroids among hospitalized children (two studies). However, after excluding two studies that also included school-aged children, a population that is more likely to benefit from systemic corticosteroids, the effect of systemic corticosteroid became nonsignificant.

An editorial accompanying this meta-analysis suggested that OCS use for acute episodic wheeze in preschool children should be limited, as there is no evidence that OCS provide any overall benefits and their use may be associated with unpredictable outcomes and adverse events [35].

ACETAMINOPHEN USE DOES NOT INCREASE EXACERBATION RISK AMONG PRESCHOOL CHILDREN WITH MILD-PERSISTENT ASTHMA

Febrile illnesses are very common events during early childhood. Acetaminophen, which is commonly used during these illnesses, is the most commonly used pediatric medication in the United States [39]. Observational data and post-hoc analyses have linked acetaminophen use to exacerbations of asthma symptoms, decreased lung function, and to unscheduled asthma visits [40–42]. These reports resulted in concerns that led some physician to recommend complete avoidance of acetaminophen in asthmatic children [43]. The main limitation of these studies, and any observational study/retrospective analysis, is the risk for indication bias: acetaminophen is usually prescribed for fever relief during respiratory infections, which are a known risk factor for asthma inception and asthma exacerbations. Therefore, it may well be that acetaminophen use is a marker for these infections and not an actual risk factor. Thus, the most reliable way to explore whether acetaminophen is a risk factor for asthma exacerbations is by a randomized trial.

The Acetaminophen versus Ibuprofen in Children with Asthma (AVICA) trial was conducted to address this research question [44²²]. Three hundred preschool children with mild persistent asthma were randomized to receive either acetaminophen or ibuprofen when needed for the relief of fever or pain over the following 48 weeks. All study

outcomes were comparable between children treated with acetaminophen or ibuprofen: the number of asthma exacerbations, the proportion of participants with at least one asthma exacerbation, the percentage of asthma-control days, the amount of albuterol rescue inhaler use, or the number of asthma unscheduled healthcare utilization [44²²]. This clinical trial clearly demonstrated acetaminophen use, compared with ibuprofen use, does not increase exacerbation risk among preschool children with mild persistent asthma, suggesting that the concerning findings from previous epidemiologic studies were likely confounded by indication bias. However, and as noted by the investigators, since the AVICA study did not include a placebo arm, the unlikely possibility that both ibuprofen use and acetaminophen use may be associated with parallel increases in either asthma exacerbations or symptoms could not be excluded.

CONCLUSION AND PROPOSED TREATMENT APPROACH

On the basis of the evidence described in this study, we propose the following phenotype-based approach for the long-term management of preschool children with asthma (Figure 1). Preschool children with mild persistent asthma and evidence of aeroallergen sensitivity and/or blood eosinophil counts of 300/ μ l or greater should receive daily ICS therapy. If a child does not respond to this initial step 2 therapy, or if the child does not have evidence for aeroallergen sensitivity or eosinophilia, an alternative step 2 therapy (e.g. LTRA or symptom-derived ICS therapy) should be considered.

Pre-emptive high-dose intermittent ICS or oral azithromycin, both as interventions given early in the course of RTI, have been shown to be efficacious to prevent severe exacerbations. It is still not clear which children respond better to each of these therapies; therefore, and due to ongoing concerns of potential induction of antibiotics resistance, we recommend that children with positive mAPIs receive an initial trial of intermittent ICS and to consider intermittent azithromycin for children who do not respond to intermittent ICS or those with negative mAPIs. Daily ICS is another therapeutic option for children with intermittent disease, positive mAPI, and characteristics that have shown to be associated with ICS response: boys, Caucasian, atopic, and significant disease activity.

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Some of the treatment approaches that are discussed in this manuscript, such as intermittent inhaled corticosteroids and intermittent azithromycin, are not FDA-

approved for either prevention or treatment of wheezing episodes.

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Conflicts of interest

A.B.: None. L.B.B. has received consultancy fees from GlaxoSmithKline, Merck, DBV Technologies, Teva, Boehringer Ingelheim, Sanofi, Vectura, Cephalon, and Meda; received payment for lectures from Genentech/Novartis, Teva, Boehringer Ingelheim, AstraZeneca, and Merck; and received payment for development of educational presentations from WebMD/Medscape.

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