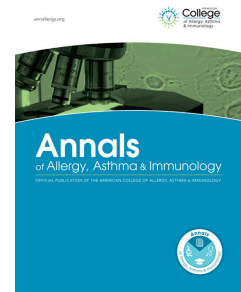


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Prevention and Treatment of Recurrent Viral-Induced Wheeze in the Preschool Child

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1 Introduction

2 Wheezing is common during the preschool years, with nearly 50% of children having at least one
3 episode of wheezing in their first 6 years of life.¹ Of those children that wheeze before the age of three,
4 at least 40% continue to wheeze by the age of six. Preschool children with wheezing episodes
5 experience disease-related morbidity, with a 50% higher rate of outpatient visits, nearly twice the rate
6 of emergency department (ED) visits, and nearly 3 times the rate of hospitalization compared to older
7 children.² In addition to causing acute wheezing episodes, viral respiratory tract infections early in life
8 have been associated with recurrent wheezing and the eventual development of childhood asthma.³
9 However, only 4.4% of children 4 years old and younger in the United States are diagnosed with
10 asthma.⁴

11 Viral respiratory tract infections have long been identified as the most frequent trigger of wheezing
12 episodes in young children, typically rhinovirus and respiratory syncytial virus.⁵ Infection induced
13 wheezing can initially present with acute respiratory syncytial virus (RSV) bronchiolitis, which is a
14 frequent antecedent to recurrent infection-induced wheezing episodes. Among infants presenting to an
15 emergency department with wheezing, respiratory viruses have been detected in the nasal washings of
16 >80% of infants.⁶ Among a birth cohort of children at risk for subsequent asthma, a viral etiology was
17 detected in 90% of wheezing episodes during the first 3 years of life.⁷

18 Recurrent wheezing due to viral infections can subsequently progress to asthma with viral-induced
19 exacerbations.⁵ In between these wheezing episodes, children may have minimal to no respiratory
20 symptoms or may wheeze in the context of other triggers such as exercise or allergen exposure.
21 Children with recurrent wheezing and other risk factors for the development of asthma may respond
22 differently to treatment options for viral induced wheezing episodes. For example, children who

wheeze secondarily to rhinovirus may respond to better to medications, such as corticosteroids, compared to children wheezing secondarily to RSV.⁸

The variable expression of early life wheezing phenotypes (Table 1) complicates the assessment and management of patients. Recognition of different phenotypic characteristics and patterns of disease expression may help guide and predict future asthma diagnosis in the recurrently wheezing preschool child (Table 1). The earliest classification was derived from the Tucson Children's Respiratory Study (TCRS), which prospectively enrolled 1246 newborns between May 1980 and October 1984 and noted 4 wheezing patterns (or phenotypes); children who never wheezed by 6 years of age (51.5%), children who wheezed by 3 years of age, but not afterwards (transient early wheezing, 20%), children who wheezed both before 3 years of age and between 4 and 6 (persistent wheezing, 14%) and those children who did not wheeze before 3 years but did between 4 and 6 years of age (late-onset wheezing, 15%).¹ In children who begin wheezing during the preschool years, the patterns of wheezing and levels of lung function were established by 6 years old and did not appear to change significantly by age 16.⁹ Subsequent studies, most using unsupervised methodologies such as latent class analyses, have found similar phenotypical patterns. In the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study, 2180 children from the Netherlands exhibited five respiratory phenotypes, most similar to the Tucson Study, with an additional intermediate-onset wheeze pattern.¹⁰ The Avon Longitudinal Study of Parents and Children (ALSPAC) British birth cohort of 6265 children identified six phenotypes, including a prolonged early wheeze peaking at 30 months and declining to low prevalence by 69 months.¹¹ These phenotype patterns continued through adolescence.¹² Both the PIAMA and ALSPAC birth cohorts demonstrated that intermediate-onset, late-onset and persistent wheeze were associated with an increased likelihood of an asthma diagnosis by the age of eight as well as being strongly associated with indoor allergen sensitization.¹⁰ Only intermediate-onset and persistent wheeze were associated with food sensitization.¹⁰ The Urban Environment and Childhood Asthma (URECA) study identified five

respiratory phenotypes, which were based predominantly on wheezing frequency and atopic status.¹³

Asthma was present at comparable rates in the high wheeze/low atopy phenotype (67%) and in the high wheeze/high atopy (70%) phenotype. Data from five clinical trials of 1708 preschool children in the Childhood Asthma Research and Education (CARE) Network noted phenotype differences based on eczema, eosinophil counts and allergen sensitization (aeroallergen and food).¹⁴ Those children with sensitization and indoor pet exposure and those with multiple sensitization and eczema had the highest probability of exacerbations. These studies confirm the existence of multiple trajectories of respiratory symptoms, and thus differing prognoses, in early life, and further research is needed to determine the underlying mechanistic basis for each of these phenotypes (i.e. disease endotypes).

Using data from large cohorts, several models have been developed to help prospectively identify children at heightened risk of asthma development. Based on data from the TCRS, the Asthma Predictive Index was developed to help predict the likelihood of persistent asthma by 6 years of age.¹⁵ This Index has since been modified and used in pediatric clinical trials for the CARE Network.¹⁶ For a positive modified Asthma Predictive Index (mAPI) (Table 2) a child 3 year old or younger has to have experienced at least four wheezing episodes in the previous year in addition to having one either major or two minor criteria (Table 2). In a high-risk cohort, a positive mAPI greatly increased the future asthma probability (e.g., 30% pretest probability to 90% posttest probability).¹⁷ The Pediatric Asthma Risk Score (PARS) used data from the Cincinnati Childhood Allergy and Air Pollution Study to predict asthma outcomes in a birth cohort of 762 children.¹⁸ In addition to parental asthma, eczema, and wheezing apart from colds, additional factors that predicted asthma included early wheezing, sensitization to 2 or more food or aeroallergens, and African American race. The PARS performed better than the API in predicting children with mild to moderate asthma. A systematic review of 12 asthma prediction models assessed in children up to 4 years of age and predicted asthma diagnosis by school age.¹⁹ Some of the

predictors included factors such as comorbid atopic disease, family history of asthma or allergy, eosinophilia, total IgE, and evidence of food or aeroallergen sensitization.

Treatment Approaches to Preschool Children with Recurrent Wheezing

Inhaled Corticosteroids

Daily Inhaled Corticosteroids

By virtue of the established efficacy of inhaled corticosteroids in the management of persistent asthma in school age children and adolescents, and the clinical similarities between early life recurrent wheezing and subsequent asthma, multiple trials have examined the role of ICS in preschool children with recurrent, viral-triggered wheezing.

The Prevention of Early Asthma in Kids (PEAK) trial was a randomized, placebo controlled trial of 285 children with a positive mAPI with ICS or placebo for 2 years to assess whether daily inhaled corticosteroids given for 2 years can modify the development of asthma in these high risk 2-3 year olds.¹⁶ Sensitization to food or aeroallergens was noted in 60% of the children. During the 2 year treatment period, ICS use was effective, as it was associated with more episode-free days, fewer exacerbations, and less use of other controller medications. After two years of treatment, the children were observed off treatment for a third year. At the end of the third year, no differences were seen between the two groups in exacerbations, episode-free days or lung function. Those children treated with ICS had a decrease in growth compared to the placebo, mostly during the first 12 months of treatment. Characteristics of the participants with a greater benefit of ICS therapy were male sex, Caucasian race, history of an ED visit or hospitalization for asthma within the year preceding the trial, sensitization to aeroallergen, and having fewer than 80% episode-free days during the run-in period.²⁰

The Individualized Therapy for Asthma in Toddlers (INFANT) trial was a multicenter, randomized, double-blind, double-dummy, cross-over clinical trial with 230 children ages 12 to 59 months requiring Step 2 daily asthma therapy evaluating the response to 3 treatment options; daily inhaled corticosteroids, as needed inhaled corticosteroids and daily leukotriene receptor antagonist.²¹ There was a differential response demonstrable in 74% of children, with the probability of best response highest for daily ICS, especially in those children with aeroallergen sensitization and blood eosinophil counts $\geq 300/\mu\text{L}$. In addition, serum eosinophilic cation protein (ECP) levels $\geq 10 \mu\text{g/L}$ and pet sensitization predicted a better response to daily ICS. The child's mAPI status and total IgE levels did not predict a differential response pattern. Those children without a differential response had less disease activity overall. No predictors were noted for those that would respond better to as needed ICS or daily LTRAs.

Intermittent Inhaled Corticosteroids

Given the intermittent nature of disease in children with recurrent wheezing episodes in the setting of respiratory tract infections, several trial have examined the role of ICS administered only during acute respiratory tract illnesses.

The Prevention of Asthma in Childhood (PAC) study was a single center, randomized, double-blind, prospective study involving 411 one-month infants with a maternal history of asthma.²² After a three-day episode of wheezing, children were treated with a two-week course of inhaled budesonide or placebo. The primary objective was the efficacy of intermittent inhaled corticosteroids (ICS) use to reduce subsequent respiratory symptoms over three years. Overall, there was no significant difference in symptom-free days, mean duration of acute symptoms, or persistent wheezing between the two groups.

The use of high dose inhaled corticosteroids was evaluated in 129 children 1 to 6 years old with a history of three or more episodes of wheezing.²³ This parallel group, randomized, placebo-controlled trial with triple blinding assigned children to 750 µg of fluticasone propionate or placebo twice a day at the onset of an upper respiratory tract infection. Treatment continued up to 10 days over the 6 to 12 month treatment period. In the children treated with ICS, only 8% needed oral corticosteroids with upper respiratory tract infections compared to 18% in the placebo group. During this time, no differences were noted in cortisol level, but those receiving ICS had a slight (but statistically significant) decrease in gain in height (6.23 cm) compared to the children treated with placebo (6.56 cm).

The Acute Intermittent Management Strategies (AIMS) trial was a randomized, double blind, placebo-controlled study, with 238 children ages 12 to 59 months that had at least 2 respiratory tract infections leading to wheezing episodes within the last year and one within the preceding 6 months.²⁴ These children had evidence of moderate to severe episodes based on oral corticosteroid use or urgent care visits. Over 12 months each respiratory tract illness treatment plan consisted of albuterol 4 times daily and either 7 days of 1 mg inhalation of budesonide twice daily, 4 mg montelukast, or placebo. Overall, no differences in proportion of episode free days, oral corticosteroid use, health care use, quality of life or linear growth between the three groups were noted. However, among children with a positive mAPI, budesonide reduced the trouble breathing, and interference with activity, and total symptom scores compared to placebo.

The Maintenance and Intermittent Inhaled Corticosteroids in Wheezing Toddlers (MIST) study evaluated 278 children 12-53 months of age with recurrent wheezing, a positive mAPI, and one exacerbation within the last year.²⁵ Participants were randomly assigned in a double blind parallel group fashion to one year of treatment of intermittent budesonide inhalation 1 mg twice a day at the start of a URI, or daily 0.5 mg budesonide with corresponding placebos. At the conclusion of the study, no differences were noted in the number of severe exacerbations requiring oral corticosteroids, time to first or second

exacerbations, or the frequency of treatment failures between the two groups. Those children on intermittent high dose ICS had a mean ICS exposure that was 104 mg less (150 mg vs 46 mg) than the daily low dose group.

In a meta-analysis, 15 studies involving 3278 children ≤ 6 years old found that daily ICS reduced severe wheezing exacerbations. Furthermore, a subgroup analysis of five studies including 422 children showed intermittent high dose ICS also reduced severe exacerbations relative to placebo.²⁶ Another meta-analysis identified 29 studies (3592 subjects) evaluated a minimum of 4 weeks of treatment of inhaled corticosteroids versus placebo.²⁷ Children were infants (1-23 months) or preschoolers (2-5 years old) with a diagnosis of wheezing or asthma. Those children who received inhaled corticosteroids had fewer wheezing/asthma exacerbations compared to placebo (18.0% vs 32.1%).

Leukotriene Modifiers

The cysteinyl leukotrienes (cysLTs) have been identified as important mediators in the complex pathophysiology of asthma. CysLTs are detectable in the blood, urine, nasal secretions, sputum, and bronchoalveolar lavage (BAL) fluid of patients with chronic asthma. Similar to heightened levels in asthmatics, 20 infants with a history of prolonged or persistent wheeze (mean 14.9 months) and a history of viral illness at wheeze onset (10/20), had significant elevations of leukotrienes in BAL despite the fact that 12/20 infants were receiving daily ICS therapy (≤ 450 mcg/day).²⁸ These findings suggest that, similar to asthma pathophysiology, cysLTs play a role in the pathophysiology of viral-induced wheeze.

Among the children in the AIMS trial in children with a positive mAPI, montelukast treatment reduced the wheezing, trouble breathing score, and interference with activity and total symptom score.²⁴ Only the improvement with the interference with activity score by montelukast was significant in children with a negative mAPI score.

A multicenter, randomized, double-blind, double-dummy, parallel group enrolled 589 children 6 months to 5 years of age who were treated with either daily montelukast, intermittent montelukast or placebo over 52 weeks.²⁹ No significant differences were noted in the number of asthma attacks requiring an unscheduled visit to a doctor, urgent care, or emergency department, or treatment with corticosteroids (inhaled or systemic) between the montelukast and placebo children. In post hoc analysis, both montelukast arms improved symptoms compared to placebo over the 12-day treatment episode treatment.

The Wheeze And Intermittent Treatment (WAIT) trial assessed the efficacy of intermittent use of montelukast for children 10 months to 5 years of age with two or more episodes of wheezing with one episode in the preceding 3 months.³⁰ In a parallel group, randomized, placebo-controlled fashion montelukast or placebo was started at home at the onset of each viral infection or wheezing episode over 12 months. Children were allowed to continue their baseline medications that could include bronchodilators and ICS. No difference was noted between the two groups with respect to unscheduled medical visits due to wheezing, number of wheezing episodes, or duration of wheezing episodes. Over the course of the trial, those children on montelukast received less oral corticosteroids. A subset of children with a specific polymorphism in the 5-lipoxygenase promoter region noted a decrease in medical visits for wheezing.

The Prevention of Virally Induced Asthma (PREVIA) was a 12-month double blind, parallel-group study of 549 children 2 to 5 years of age with a history of intermittent asthma symptoms treated with either montelukast or placebo daily.³¹ In children treated with montelukast, the average yearly asthma exacerbation rate was significantly lower than that seen in the placebo group (1.6 vs. 2.34). In addition, montelukast extended the time to first exacerbation and rate of inhaled corticosteroid use.

Brodie and colleagues performed a meta-analysis of the use of leukotriene receptor antagonists as maintenance and intermittent therapy for episodic viral wheezing in preschool children (1 to 6 years of age).³² Only five studies were eligible for inclusion, including the WAIT and PREVIA studies. Despite findings in individual studies, the author's conclusion was there is no evidence of benefit compared to placebo with maintenance or intermittent LTRA treatment in reducing the number of children with one or more viral-induced episodes requiring rescue oral corticosteroids, and little evidence of significant clinical benefit for other secondary outcomes.

Azithromycin

While respiratory viruses are frequently detected in wheezing in preschoolers, bacteria such as *Streptococcus pneumoniae* or *Moraxella catarrhalis* are also often present.³³ The COPSAC₂₀₀₀ birth cohort examined airway aspirates during acute wheezing episodes. In those children, both viruses and bacteria were identified in 55% of the episodes, bacteria only in 31% and viruses only in 10% of the samples. The role of these bacteria in the pathogenesis of wheezing episodes remains uncertain, but given the association between their presence and wheezing episodes, several trials have examined the role of the macrolide antimicrobial azithromycin on these episodes.

The Azithromycin for Preventing the Development of Upper Respiratory Tract Illness Into Lower Respiratory Tract Symptoms in Children (APRIL) study enrolled 607 children aged 12 through 71 months with a history of recurrent, severe lower respiratory tract illnesses (LRTIs).³³ In a randomized, double-blind, placebo controlled fashion, children were administered either azithromycin or placebo at the first sign of a respiratory tract illness prior to developing lower respiratory tract illness (LRTI) symptoms (and continued for 5 days) over a period of 12 through 18 months. Azithromycin significantly reduced the risk of progressing to a severe LRTI by 37%. No significant difference was noted in response to azithromycin

between those children with a positive or a negative mAPI. Given concerns about development of antimicrobial resistance, oropharyngeal swabs were tested for azithromycin resistance in a subset of participants. At randomization, an azithromycin resistant organism was detected in 5 out of 41 (12.2%) children treated with azithromycin, and 4 out of 45 (8.9%) those treated with placebo. At the end of the study, 6 out of 36 (16.7%) who received azithromycin and 4 out of 37 (10.8%) who did not receive azithromycin acquired azithromycin resistant organisms.

The Copenhagen Prospective Studies on Asthma in Childhood 2000 (COPSAC₂₀₀) also noted the association of airway bacteria and respiratory viruses associated with episodes of asthma-like symptoms.³⁴ Seventy-two, 1-3 year olds diagnosed with recurrent asthma-like symptoms were enrolled during a total of 158 episodes. Each episode of asthma-like symptoms lasting at least 3 days was randomly assigned to either a 3 day course of azithromycin (79 episodes) or placebo (79 episodes). The mean duration of episode in azithromycin treated children was decreased by 63%, 3.4 days compared to placebo 7.7 days. If treatment was started prior to day 6, the improvement was 83%. The treatment effect was not significantly altered by the use of controller medications such as ICS or montelukast. Bacterial resistance patterns were not evaluated in this study.

Mandhane et al, evaluated azithromycin in the ED setting for wheezing episodes in preschool children.³⁵ Children were treated either with 5 days of azithromycin (110 children) or placebo (112 children) after an ED visit for wheezing. Several phenotypes of children were included in the study with 29% of the children with first time wheeze at enrolment, 35% in the azithromycin group and 36% in the placebo group used ICS, and 40% children treated with azithromycin had a previous diagnosis of asthma compared to 35% in the placebo group. No differences were noted between the active treatment and placebo group in median time to resolution of respiratory symptoms, median number of days

of Short-Acting Beta-Agonist use, and time to exacerbation in the following six months. Subgroup analysis demonstrated no differences in outcomes for children with their first or repeat episode of wheezing. The study by Mandhane et al. included children presenting to the ED with acute wheezing, whereas the APRIL study focused on early use of azithromycin to prevent episodes and the study from COPSAC included children with lower respiratory tract symptoms of at least 3 days' duration but who did not require ED care.³³⁻³⁵ Based upon these studies, the exact role of azithromycin in young children with recurrent wheeze remains uncertain, with the greatest evidence for its role in episode prevention more so than for episodes of sufficient severity to warrant emergency department care.

Oral corticosteroids

Despite their widespread use, clinical trials of oral corticosteroids in preschool children with wheezing have not demonstrated consistent clinical benefit. One of the early studies recruited 74 children 7 to 54 months of age with recurrent wheezing who were evaluated in an ED and treated with a dose of intramuscular methylprednisone or placebo.³⁶ Three hours after dosing, 8/30 (20%) of the children treated with methylprednisone were admitted compared to 15/35 (43%) those treated with placebo. In another study, children 6 to 35 months, excluding those with recurrent wheeze or asthma, noted that the use of oral corticosteroids in the ED did not change the need for hospitalization, but decreased the length of hospitalization, duration of symptoms and duration of oral corticosteroids.³⁷ In a study involving 624 children ages 24-72 months evaluated in local ED with viral-associated wheezing were treated with either prednisone or placebo in a randomized fashion.³⁸ The median total length of time in the ED/hospitalized was 540 minutes for the placebo group, while the prednisolone group's time was 370 minutes ($p=0.0227$). In this trial, children younger than 2 were not evaluated, eliminating those with likely viral bronchiolitis. In addition, those children with more severe symptoms, using albuterol prior to the emergency room presentation, and a prior diagnosis of asthma were more likely to improve with

oral corticosteroids. Cornelli et al found no benefit of dexamethasone in infants 12 months and younger with a first episode of wheezing presenting to the ED with acute moderate-severe bronchiolitis.³⁹ In 79 children with a first wheezing illness due to rhinovirus treatment with oral prednisolone improved short-term outcomes such as respiratory symptoms but long-term outcomes such as future wheezing episodes or controller medication for asthma were no different than the placebo treated children.⁴⁰ In children with a higher initial viral load, oral corticosteroids may offer some improvement with less recurrence of wheezing and time to start asthma controller medication.^{40,41} Panickar et al, wished to avoid the infant with bronchiolitis so they evaluated children 10-60 months of age presenting to ED with acute viral wheezing.⁴² Of the 700 children randomized, 687 were included in the intention to treat analysis. Overall, no significant difference was noted in duration of hospitalization between prednisolone treated children (11.0 hours) and placebo (13.9 hours).

The use of home administered oral corticosteroids for viral induced wheezing was evaluated in 108 children 1 to 5 years of age.⁴³ Children had a history of previous hospital admission for viral induced wheeze. Parents started oral daily corticosteroids for 5 days or placebo at the start of an episode of viral wheeze. Corticosteroids did not have an effect on daytime or nighttime lower respiratory tract symptoms, need for rescue medications, or need for hospital admission even in children with evidence of eosinophilic priming.

In a *post hoc* analysis on the high-risk children in the AIMS trial, investigators did not find any difference in the symptom burden, as reflected by the areas under the curve (AUCs) of total symptoms or individual symptom scores, in children that were or were not treated with oral corticosteroids.⁴⁴ The *post hoc* analysis on the 278 children in the MIST trial had similar findings, with no difference in symptom burden or resolution between episodes treated with or without oral corticosteroids.⁴⁴ While children in the AIMS trial were not receiving daily controller therapy, half of the children in the MIST were receiving daily ICS.

Based upon these studies, there is no compelling evidence for efficacy of OCS when given (or managed) at home to preschool children with episodic viral wheeze. Among preschool children requiring ED care, particularly those with diagnosis of asthma, receipt of bronchodilators before ED arrival, or a more severe wheezing episode, OCS use reduces duration of hospital-based care.⁴⁵ However, Additional studies are needed to best determine which subgroups of children derive the greatest benefit from OCS. For an in depth review of oral corticosteroids in this preschool wheezers see the Pro/Con discussion by Beigleman, Durrani and Guilbert.⁴⁶

Conclusion

Recurrent viral wheeze remains a clinical challenge affecting a majority of preschool children. Over the past 2 decades, this condition has been the focus of many clinical trials, which now provide an increasingly robust evidence base for management. Additional research is needed to define optimal strategies, to best match therapies to specific phenotypes and endotypes, and will eventually begin to include therapies directed specifically at the viral triggers themselves.

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3 episode of wheezing in their first 6 years of life.¹ Of those children that wheeze before the age of three,
4 at least 40% continue to wheeze by the age of six. Preschool children with wheezing episodes
5 experience disease-related morbidity, with a 50% higher rate of outpatient visits, nearly twice the rate
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By virtue of the established efficacy of inhaled corticosteroids in the management of persistent asthma in school age children and adolescents, and the clinical similarities between early life recurrent wheezing and subsequent asthma, multiple trials have examined the role of ICS in preschool children with recurrent, viral-triggered wheezing.

The Prevention of Early Asthma in Kids (PEAK) trial was a randomized, placebo controlled trial of 285 children with a positive mAPI with ICS or placebo for 2 years to assess whether daily inhaled corticosteroids given for 2 years can modify the development of asthma in these high risk 2-3 year olds.¹⁶ Sensitization to food or aeroallergens was noted in 60% of the children. During the 2 year treatment period, ICS use was effective, as it was associated with more episode-free days, fewer exacerbations, and less use of other controller medications. After two years of treatment, the children were observed off treatment for a third year. At the end of the third year, no differences were seen between the two groups in exacerbations, episode-free days or lung function. Those children treated with ICS had a decrease in growth compared to the placebo, mostly during the first 12 months of treatment. Characteristics of the participants with a greater benefit of ICS therapy were male sex, Caucasian race, history of an ED visit or hospitalization for asthma within the year preceding the trial, sensitization to aeroallergen, and having fewer than 80% episode-free days during the run-in period.²⁰

The Individualized Therapy for Asthma in Toddlers (INFANT) trial was a multicenter, randomized, double-blind, double-dummy, cross-over clinical trial with 230 children ages 12 to 59 months requiring Step 2 daily asthma therapy evaluating the response to 3 treatment options; daily inhaled corticosteroids, as needed inhaled corticosteroids and daily leukotriene receptor antagonist.²¹ There was a differential response demonstrable in 74% of children, with the probability of best response highest for daily ICS, especially in those children with aeroallergen sensitization and blood eosinophil counts $\geq 300/\mu\text{L}$. In addition, serum eosinophilic cation protein (ECP) levels $\geq 10 \mu\text{g/L}$ and pet sensitization predicted a better response to daily ICS. The child's mAPI status and total IgE levels did not predict a differential response pattern. Those children without a differential response had less disease activity overall. No predictors were noted for those that would respond better to as needed ICS or daily LTRAs.

Intermittent Inhaled Corticosteroids

Given the intermittent nature of disease in children with recurrent wheezing episodes in the setting of respiratory tract infections, several trial have examined the role of ICS administered only during acute respiratory tract illnesses.

The Prevention of Asthma in Childhood (PAC) study was a single center, randomized, double-blind, prospective study involving 411 one-month infants with a maternal history of asthma.²² After a three-day episode of wheezing, children were treated with a two-week course of inhaled budesonide or placebo. The primary objective was the efficacy of intermittent inhaled corticosteroids (ICS) use to reduce subsequent respiratory symptoms over three years. Overall, there was no significant difference in symptom-free days, mean duration of acute symptoms, or persistent wheezing between the two groups.

The use of high dose inhaled corticosteroids was evaluated in 129 children 1 to 6 years old with a history of three or more episodes of wheezing.²³ This parallel group, randomized, placebo-controlled trial with triple blinding assigned children to 750 µg of fluticasone propionate or placebo twice a day at the onset of an upper respiratory tract infection. Treatment continued up to 10 days over the 6 to 12 month treatment period. In the children treated with ICS, only 8% needed oral corticosteroids with upper respiratory tract infections compared to 18% in the placebo group. During this time, no differences were noted in cortisol level, but those receiving ICS had a slight (but statistically significant) decrease in gain in height (6.23 cm) compared to the children treated with placebo (6.56 cm).

The Acute Intermittent Management Strategies (AIMS) trial was a randomized, double blind, placebo-controlled study, with 238 children ages 12 to 59 months that had at least 2 respiratory tract infections leading to wheezing episodes within the last year and one within the preceding 6 months.²⁴ These children had evidence of moderate to severe episodes based on oral corticosteroid use or urgent care visits. Over 12 months each respiratory tract illness treatment plan consisted of albuterol 4 times daily and either 7 days of 1 mg inhalation of budesonide twice daily, 4 mg montelukast, or placebo. Overall, no differences in proportion of episode free days, oral corticosteroid use, health care use, quality of life or linear growth between the three groups were noted. However, among children with a positive mAPI, budesonide reduced the trouble breathing, and interference with activity, and total symptom scores compared to placebo.

The Maintenance and Intermittent Inhaled Corticosteroids in Wheezing Toddlers (MIST) study evaluated 278 children 12-53 months of age with recurrent wheezing, a positive mAPI, and one exacerbation within the last year.²⁵ Participants were randomly assigned in a double blind parallel group fashion to one year of treatment of intermittent budesonide inhalation 1 mg twice a day at the start of a URI, or daily 0.5 mg budesonide with corresponding placebos. At the conclusion of the study, no differences were noted in the number of severe exacerbations requiring oral corticosteroids, time to first or second

exacerbations, or the frequency of treatment failures between the two groups. Those children on intermittent high dose ICS had a mean ICS exposure that was 104 mg less (150 mg vs 46 mg) than the daily low dose group.

In a meta-analysis, 15 studies involving 3278 children ≤ 6 years old found that daily ICS reduced severe wheezing exacerbations. Furthermore, a subgroup analysis of five studies including 422 children showed intermittent high dose ICS also reduced severe exacerbations relative to placebo.²⁶ Another meta-analysis identified 29 studies (3592 subjects) evaluated a minimum of 4 weeks of treatment of inhaled corticosteroids versus placebo.²⁷ Children were infants (1-23 months) or preschoolers (2-5 years old) with a diagnosis of wheezing or asthma. Those children who received inhaled corticosteroids had fewer wheezing/asthma exacerbations compared to placebo (18.0% vs 32.1%).

Leukotriene Modifiers

The cysteinyl leukotrienes (cysLTs) have been identified as important mediators in the complex pathophysiology of asthma. CysLTs are detectable in the blood, urine, nasal secretions, sputum, and bronchoalveolar lavage (BAL) fluid of patients with chronic asthma. Similar to heightened levels in asthmatics, 20 infants with a history of prolonged or persistent wheeze (mean 14.9 months) and a history of viral illness at wheeze onset (10/20), had significant elevations of leukotrienes in BAL despite the fact that 12/20 infants were receiving daily ICS therapy (≤ 450 mcg/day).²⁸ These findings suggest that, similar to asthma pathophysiology, cysLTs play a role in the pathophysiology of viral-induced wheeze.

Among the children in the AIMS trial in children with a positive mAPI, montelukast treatment reduced the wheezing, trouble breathing score, and interference with activity and total symptom score.²⁴ Only the improvement with the interference with activity score by montelukast was significant in children with a negative mAPI score.

A multicenter, randomized, double-blind, double-dummy, parallel group enrolled 589 children 6 months to 5 years of age who were treated with either daily montelukast, intermittent montelukast or placebo over 52 weeks.²⁹ No significant differences were noted in the number of asthma attacks requiring an unscheduled visit to a doctor, urgent care, or emergency department, or treatment with corticosteroids (inhaled or systemic) between the montelukast and placebo children. In post hoc analysis, both montelukast arms improved symptoms compared to placebo over the 12-day treatment episode treatment.

The Wheeze And Intermittent Treatment (WAIT) trial assessed the efficacy of intermittent use of montelukast for children 10 months to 5 years of age with two or more episodes of wheezing with one episode in the preceding 3 months.³⁰ In a parallel group, randomized, placebo-controlled fashion montelukast or placebo was started at home at the onset of each viral infection or wheezing episode over 12 months. Children were allowed to continue their baseline medications that could include bronchodilators and ICS. No difference was noted between the two groups with respect to unscheduled medical visits due to wheezing, number of wheezing episodes, or duration of wheezing episodes. Over the course of the trial, those children on montelukast received less oral corticosteroids. A subset of children with a specific polymorphism in the 5-lipoxygenase promoter region noted a decrease in medical visits for wheezing.

The Prevention of Virally Induced Asthma (PREVIA) was a 12-month double blind, parallel-group study of 549 children 2 to 5 years of age with a history of intermittent asthma symptoms treated with either montelukast or placebo daily.³¹ In children treated with montelukast, the average yearly asthma exacerbation rate was significantly lower than that seen in the placebo group (1.6 vs. 2.34). In addition, montelukast extended the time to first exacerbation and rate of inhaled corticosteroid use.

Brodie and colleagues performed a meta-analysis of the use of leukotriene receptor antagonists as maintenance and intermittent therapy for episodic viral wheezing in preschool children (1 to 6 years of age).³² Only five studies were eligible for inclusion, including the WAIT and PREVIA studies. Despite findings in individual studies, the author's conclusion was there is no evidence of benefit compared to placebo with maintenance or intermittent LTRA treatment in reducing the number of children with one or more viral-induced episodes requiring rescue oral corticosteroids, and little evidence of significant clinical benefit for other secondary outcomes.

Azithromycin

While respiratory viruses are frequently detected in wheezing in preschoolers, bacteria such as *Streptococcus pneumoniae* or *Moraxella catarrhalis* are also often present.³³ The COPSAC₂₀₀₀ birth cohort examined airway aspirates during acute wheezing episodes. In those children, both viruses and bacteria were identified in 55% of the episodes, bacteria only in 31% and viruses only in 10% of the samples. The role of these bacteria in the pathogenesis of wheezing episodes remains uncertain, but given the association between their presence and wheezing episodes, several trials have examined the role of the macrolide antimicrobial azithromycin on these episodes.

The Azithromycin for Preventing the Development of Upper Respiratory Tract Illness Into Lower Respiratory Tract Symptoms in Children (APRIL) study enrolled 607 children aged 12 through 71 months with a history of recurrent, severe lower respiratory tract illnesses (LRTIs).³³ In a randomized, double-blind, placebo controlled fashion, children were administered either azithromycin or placebo at the first sign of a respiratory tract illness prior to developing lower respiratory tract illness (LRTI) symptoms (and continued for 5 days) over a period of 12 through 18 months. Azithromycin significantly reduced the risk of progressing to a severe LRTI by 37%. No significant difference was noted in response to azithromycin

between those children with a positive or a negative mAPI. Given concerns about development of antimicrobial resistance, oropharyngeal swabs were tested for azithromycin resistance in a subset of participants. At randomization, an azithromycin resistant organism was detected in 5 out of 41 (12.2%) children treated with azithromycin, and 4 out of 45 (8.9%) those treated with placebo. At the end of the study, 6 out of 36 (16.7%) who received azithromycin and 4 out of 37 (10.8%) who did not receive azithromycin acquired azithromycin resistant organisms.

The Copenhagen Prospective Studies on Asthma in Childhood 2000 (COPSAC₂₀₀) also noted the association of airway bacteria and respiratory viruses associated with episodes of asthma-like symptoms.³⁴ Seventy-two, 1-3 year olds diagnosed with recurrent asthma-like symptoms were enrolled during a total of 158 episodes. Each episode of asthma-like symptoms lasting at least 3 days was randomly assigned to either a 3 day course of azithromycin (79 episodes) or placebo (79 episodes). The mean duration of episode in azithromycin treated children was decreased by 63%, 3.4 days compared to placebo 7.7 days. If treatment was started prior to day 6, the improvement was 83%. The treatment effect was not significantly altered by the use of controller medications such as ICS or montelukast. Bacterial resistance patterns were not evaluated in this study.

Mandhane et al, evaluated azithromycin in the ED setting for wheezing episodes in preschool children.³⁵ Children were treated either with 5 days of azithromycin (110 children) or placebo (112 children) after an ED visit for wheezing. Several phenotypes of children were included in the study with 29% of the children with first time wheeze at enrolment, 35% in the azithromycin group and 36% in the placebo group used ICS, and 40% children treated with azithromycin had a previous diagnosis of asthma compared to 35% in the placebo group. No differences were noted between the active treatment and placebo group in median time to resolution of respiratory symptoms, median number of days

of Short-Acting Beta-Agonist use, and time to exacerbation in the following six months. Subgroup analysis demonstrated no differences in outcomes for children with their first or repeat episode of wheezing. The study by Mandhane et al. included children presenting to the ED with acute wheezing, whereas the APRIL study focused on early use of azithromycin to prevent episodes and the study from COPSAC included children with lower respiratory tract symptoms of at least 3 days' duration but who did not require ED care.³³⁻³⁵ Based upon these studies, the exact role of azithromycin in young children with recurrent wheeze remains uncertain, with the greatest evidence for its role in episode prevention more so than for episodes of sufficient severity to warrant emergency department care.

Oral corticosteroids

Despite their widespread use, clinical trials of oral corticosteroids in preschool children with wheezing have not demonstrated consistent clinical benefit. One of the early studies recruited 74 children 7 to 54 months of age with recurrent wheezing who were evaluated in an ED and treated with a dose of intramuscular methylprednisone or placebo.³⁶ Three hours after dosing, 8/30 (20%) of the children treated with methylprednisone were admitted compared to 15/35 (43%) those treated with placebo. In another study, children 6 to 35 months, excluding those with recurrent wheeze or asthma, noted that the use of oral corticosteroids in the ED did not change the need for hospitalization, but decreased the length of hospitalization, duration of symptoms and duration of oral corticosteroids.³⁷ In a study involving 624 children ages 24-72 months evaluated in local ED with viral-associated wheezing were treated with either prednisone or placebo in a randomized fashion.³⁸ The median total length of time in the ED/hospitalized was 540 minutes for the placebo group, while the prednisolone group's time was 370 minutes ($p=0.0227$). In this trial, children younger than 2 were not evaluated, eliminating those with likely viral bronchiolitis. In addition, those children with more severe symptoms, using albuterol prior to the emergency room presentation, and a prior diagnosis of asthma were more likely to improve with

oral corticosteroids. Cornelli et al found no benefit of dexamethasone in infants 12 months and younger with a first episode of wheezing presenting to the ED with acute moderate-severe bronchiolitis.³⁹ In 79 children with a first wheezing illness due to rhinovirus treatment with oral prednisolone improved short-term outcomes such as such as respiratory symptoms but long-term outcomes such as future wheezing episodes or controller medication for asthma were no different than the placebo treated children.⁴⁰ In children with a higher initial viral load, oral corticosteroids may offer some improvement with less recurrence of wheezing and time to start asthma controller medication.^{40,41} Panickar et al, wished to avoid the infant with bronchiolitis so they evaluated children 10-60 months of age presenting to ED with acute viral wheezing.⁴² Of the 700 children randomized, 687 were included in the intention to treat analysis. Overall, no significant difference was noted in duration of hospitalization between prednisolone treated children (11.0 hours) and placebo (13.9 hours).

The use of home administered oral corticosteroids for viral induced wheezing was evaluated in 108 children 1 to 5 years of age.⁴³ Children had a history of previous hospital admission for viral induced wheeze. Parents started oral daily corticosteroids for 5 days or placebo at the start of an episode of viral wheeze. Corticosteroids did not have an effect on daytime or nighttime lower respiratory tract symptoms, need for rescue medications, or need for hospital admission even in children with evidence of eosinophilic priming.

In a *post hoc* analysis on the high-risk children in the AIMS trial, investigators did not find any difference in the symptom burden, as reflected by the areas under the curve (AUCs) of total symptoms or individual symptom scores, in children that were or were not treated with oral corticosteroids.⁴⁴ The *post hoc* analysis on the 278 children in the MIST trial had similar findings, with no difference in symptom burden or resolution between episodes treated with or without oral corticosteroids.⁴⁴ While children in the AIMS trial were not receiving daily controller therapy, half of the children in the MIST were receiving daily ICS.

Based upon these studies, there is no compelling evidence for efficacy of OCS when given (or managed) at home to preschool children with episodic viral wheeze. Among preschool children requiring ED care, particularly those with diagnosis of asthma, receipt of bronchodilators before ED arrival, or a more severe wheezing episode, OCS use reduces duration of hospital-based care.⁴⁵ However, Additional studies are needed to best determine which subgroups of children derive the greatest benefit from OCS. For an in depth review of oral corticosteroids in this preschool wheezers see the Pro/Con discussion by Beigleman, Durrani and Guilbert.⁴⁶

Conclusion

Recurrent viral wheeze remains a clinical challenge affecting a majority of preschool children. Over the past 2 decades, this condition has been the focus of many clinical trials, which now provide an increasingly robust evidence base for management. Additional research is needed to define optimal strategies, to best match therapies to specific phenotypes and endotypes, and will eventually begin to include therapies directed specifically at the viral triggers themselves.

- Recurrent wheezing in preschool children is common, results in substantial morbidity and health care utilization, and is most-frequently triggered by viral respiratory tract infections.
- Inhaled corticosteroids, given continuously or intermittently, have been demonstrated to reduce the risk of virus-induced wheezing episodes.
- Early administration of azithromycin reduces the risk of severe lower respiratory tract illnesses in preschool children.
- The effect of oral corticosteroids on wheezing episodes in young children varies by degree of episode severity.

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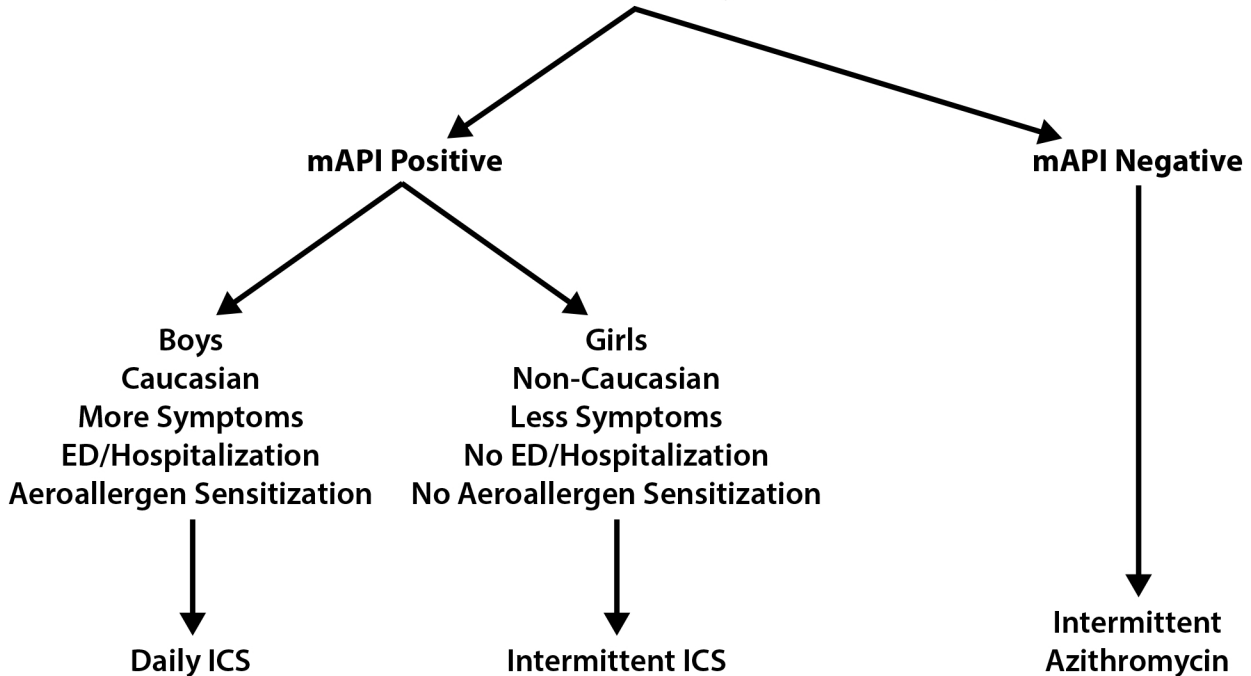
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Intermittent Wheezing (only with viral URIs)





Persistent Wheezing (≥ 4 episodes a year, lasting > 1 day and affecting sleep)

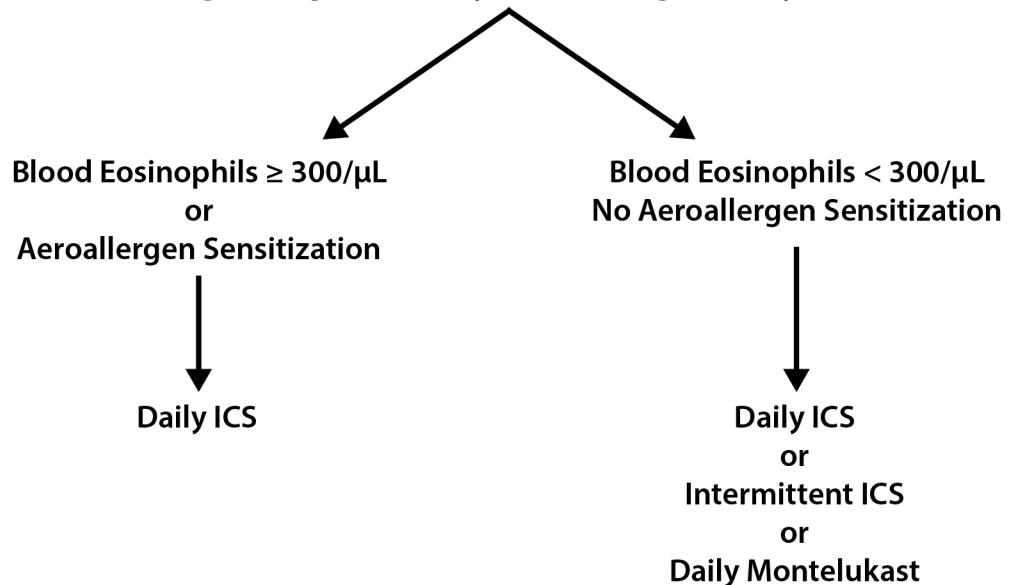


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Table 1. Phenotypes

Study	TCRS	PIAMA	ALSPAC	URECA	CARE
Country	USA	Netherlands	UK	USA	USA
Study type	Prospective 1246 children	Birth cohort 2810 children	Birth cohort 6265 children	Prospective inner city 442 children	5 clinical trials 1708 children
Assessed age	At 6 years of age	At 8 years of age	At 7.5 and 16.5 years	At 7 years of age	At 71 months
Phenotypes	1: Never/Infrequent Wheeze (51%) 2: Transient Early Wheeze (20%) 3: Late-Onset Wheeze (15%) 4: Persistent Wheeze (14%)	1: Never/Infrequent Wheeze (75%) 2: Transient Early Wheeze (17%) 3: Intermediate-Onset Wheeze (3%) 4: Late-Onset Wheeze (2%) 5: Persistent Wheeze (3%)	1: Never/Infrequent Wheeze (61%) 2: Transient Early Wheeze (16%) 3: Prolonged-Early Wheeze (9%) 4: Intermediate-Onset Wheeze (2%) 5: Late-Onset Wheeze (5%) 6: Persistent Wheeze (6%)	1: Low wheeze/low atopy (26%) 2: Low wheeze/high atopy (18%) 3: Transient wheeze/low atopy (17%) 4: High wheeze/low atopy (23%) 5: High wheeze/high atopy (15%)	1: Minimal sensitization (30%) 2: Sensitization with indoor pet exposure (25%) 3: Sensitization with tobacco smoke exposure (25%) 4: Multiple sensitization and eczema (20%)

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Table 2

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Major Criteria	Minor Criteria
Parental Asthma (physician diagnosed)	Wheezing unrelated to colds
Atopic Dermatitis (physician diagnosed)	Blood eosinophils $\geq 4\%$
Aeroallergen sensitization	Food allergen sensitization (milk, egg, or peanut)