

Viral Infections and Wheezing in Preschool Children



Alexa M.A. Doss, MD^{*}, Jeffrey R. Stokes, MD¹

KEYWORDS

• Wheezing • Asthma • Preschool • Viral infection

KEY POINTS

- Wheezing is common in childhood with approximately 50% of children experiencing at least 1 wheezing episode within their first 6 years of life while only 8% of children have asthma.
- Lower lung function, in children who wheeze, is set by 6 years of life.
- Respiratory syncytial virus (RSV) and rhinovirus account for most viruses detected in children with RSV causing the most wheezing episodes in children aged less than 1 year. Rhinovirus causes more wheezing episodes in children aged 1 year and older.
- Asthma indices can help predict which wheezing children will develop asthma.
- Inhaled corticosteroids (ICS) are commonly used to treat wheezing in preschool children. Both intermittent and daily ICS can be used. The effectiveness of oral corticosteroids in this age range is inconclusive.

INTRODUCTION

Wheezing is common in childhood; approximately 50% of children will have at least one wheezing episode in their first 6 years of life, yet only 8% of children will develop asthma.¹ Respiratory viral infections are triggers for childhood wheezing with respiratory syncytial virus (RSV) and rhinovirus being the 2 most common infections to cause wheezing in early childhood.² Children with viral-induced wheezing comprise a cohort that can go on to develop asthma.

Asthma is chronic, high morbidity disease which requires long-term medical management. In childhood, there is a male predominance of asthma diagnoses in children aged 0–9 years, yet the reverse is observed in late adolescence through adulthood.^{3,4} Up to 60% of asthmatic children have at least one asthma exacerbation per year.^{4,5}

Division of Pediatric Allergy, Immunology, and Pulmonary Medicine, St. Louis Children's Hospital, St Louis, MO, USA

¹ Present address: 6170 Kingsbury Avenue, Saint Louis, MO 63112.

^{*} Corresponding author. 1 Children's Place, CB 8116, Saint Louis, MO 63110.

E-mail address: alexa.altman@wustl.edu

Immunol Allergy Clin N Am 42 (2022) 727–741

<https://doi.org/10.1016/j.iac.2022.05.004>

0889-8561/22/© 2022 Elsevier Inc. All rights reserved.

immunology.theclinics.com

Children with asthma aged 0 to 4 years have the highest rate of asthma-related health care visits, accounting for twice the rate of emergency department (ED) visits and 3 times the rate of hospitalizations compared with adolescents with asthma.^{5,6} In addition to health care visits and hospitalizations, approximately 50% of school-aged asthmatics are absent from one or more day of school per year.⁶

WHEEZING PHENOTYPES

Multiple wheezing phenotypes have been identified in childhood. Classifying these wheezing phenotypes helps guide management and identifies the children who will experience future wheezing episodes. The Tuscan Children's Respiratory Study (TCRS) prospectively followed 1246 newborns and defined 4 childhood wheezing phenotypes: never wheeze (no wheezing episodes, 51.5%), transient early wheeze (wheezing episodes that stopped after age 3 years, 19.9%), late-onset wheeze (first wheezing episode after age 4 years, 15%), and persistent wheeze (wheezing episodes beginning before age 3 years and persisted, 13.7%).¹ The TCRS saw that patterns of lung function and atopy by age 6 years persisted through age 16 years with children who had higher atopy and immunoglobulin E (IgE) levels in the late-onset wheezers and persistent wheezers.⁷ Additionally, lower lung function seen in the transient early wheezers and persistent wheezers at age 6 also persisted through age 16.⁷ The TCRS results indicate that the lung function deficits detected in children with asthma are present by age 6 years and not due to their ongoing disease process.¹

The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study used latent class analysis to identify respiratory phenotypes in 2810 participants from the Netherlands birth cohort.⁸ In addition to the 4 phenotypes identified by the TCRS and described above, the PIAMA study identified a fifth phenotype of intermediate-onset wheeze (onset of wheeze after age 2 years and persisted).⁸ The Avon Longitudinal Study of Parents and Children (ALSPAC) study also used latent class analysis to evaluate 6265 United Kingdom birth cohort participants and, in addition to those phenotypes found in the TCRS and PIAMA study, identified a sixth phenotype of prolonged early wheeze (wheezing episodes that stopped at age 5 years).⁹ The ALSPAC study evaluated lung function at 24 years of age and found lower lung function in the persistent wheeze and transient-early wheeze compared with the never wheeze phenotype as also shown with the TCRS cohort.¹⁰ Both the ALSPAC and PIAMA study showed the intermediate-onset, late-onset, and persistent wheeze phenotypes were strongly associated with indoor allergen sensitization seen by age 4 years.⁸

The Childhood Asthma Research and Education (CARE) Network identified 4 phenotypes based on atopy and wheezing from 1708 preschool children: (1) minimal sensitization (30%), (2) sensitization with indoor pet exposure (25%), (3) sensitization with tobacco smoke exposure (25%) and (4) multiple sensitizations plus eczema (20%).¹¹ The probability of wheezing per 2-year period was highest in groups 2 and 4.¹¹ As CARE had data from 5 clinic trials, treatment response was available and showed that daily inhaled corticosteroids (ICS) improved the frequency of exacerbations in groups 2 and 4 only.¹¹ The Urban Environment and Childhood Asthma birth cohort prospectively evaluated 442 inner city children and identified 5 phenotypes: (1) low wheeze/low atopy (26%), (2) low wheeze/high atopy (18%), (3) transient wheeze/low atopy (17%), (4) high wheeze/low atopy (23%), and (5) high wheeze/high atopy (15%).¹² Indoor allergen exposure in the first year of life differed in the high and low wheezing phenotypes with the 2 high wheezing phenotypes having the lowest cumulative exposure to indoor allergens.¹² Asthma rates were greatest in

high wheezing/high atopy and high wheezing/low atopy, at 70% and 67%, respectively. Children exhibiting the high wheezing/high atopy phenotype also had the greatest lung function impairment.¹²

CHILDHOOD VIRAL INFECTIONS

Viral infections are common among children; the average child will contract 6 to 8 viral infections per year, with increasing rates if the child attends daycare.¹³ Wheezing episodes are frequently triggered by respiratory viral infections.^{13,14} Viruses have been detected in 80% to 90% of children with wheeze and cough compared with 21% of healthy, asymptomatic children.^{2,14–16} RSV and rhinovirus, the most commonly detected viral pathogens with wheezing illnesses, account for 69% of all detected viral infections within the first 3 years of life.² Children who wheezed with RSV and/or rhinovirus at ages 0 to 3 years had an increased risk of asthma at age 6.¹⁷ The Childhood Origins of Asthma (COAST) prospective birth cohort of 289 newborns noted that children who wheezed with rhinovirus had nearly a 10-fold increase in wheezing by age 3 years, whereas children with RSV-induced wheezing were 2.6 times more likely to have wheezing by age 3 years.¹⁷

RHINOVIRUS

Rhinovirus is the most common virus to cause wheezing in children aged 1 year and older.^{14,18} Rhinoviruses (*Enterovirus* genus, Picornaviridae family) are classified into 3 species: A, B, and C.¹⁸ Rhinovirus A and C cause more severe illness in infants than B.¹⁸ Wheezing with rhinovirus infection is a strong predictor of future wheezing episodes, and this prediction is higher in atopic individuals.^{14,17} A cross-sectional emergency department (ED) study of 70 children presenting with wheezing showed most wheezing episodes were in children aged 2 to 16 years with rhinovirus infection and evidence of atopy or eosinophilic airway inflammation.¹⁴ Similar results were seen in the Childhood Asthma Study (CAS) prospective cohort of 234 Australian children at high risk for developing atopic disease.¹⁶ Preschool children wheezing with rhinovirus-C infection had 7 times greater risk of wheezing at age 5 and 10 years if atopic by 2 years of age compared with nonatopic children. Genetics, such as 17q21 variants are associated with rhinovirus wheezing in childhood and an increased risk of asthma.¹⁹

RESPIRATORY SYNCYTIAL VIRUS

RSV is the most common viral infection in infants younger than 1 year to cause wheezing.¹⁸ RSV (*Orthopneumovirus* genus and the Paramyxoviridae family) has 2 main antigenic groups, A and B with RSV-A causes more severe illness.¹⁸ Although RSV is the leading cause of hospitalization in infants aged younger than 1 year in the United States, most RSV infections are mild or asymptomatic.^{18,20} RSV is the most prominent virus to cause wheezing in infancy; however, it is not significant in adolescents. The TCRS reported that the prevalence of RSV lower respiratory tract illnesses before age 3 years was associated with a significant increase in risk of subsequent wheezing during the first 10 years but was not significant by age 13.²¹

Palivizumab is a monoclonal antibody given to high-risk infants to prevent severe RSV infection.²² In the Netherlands, 429 otherwise healthy preterm infants (33–35 weeks estimated gestational age) were enrolled in a double-blind, placebo-controlled trial to receive palivizumab or placebo during RSV season.²² In the first year of life, the palivizumab cohort had a 61% relative risk reduction of total wheezing

days compared with placebo.²² The percentage of physician-diagnosed asthma was similar between the 2 groups: 10% of those treated with palivizumab and 9.9% with placebo.²³ There was no statistical significant difference in lung function between the 2 groups.²³

Both viral-induced wheezing and aeroallergen sensitization are risk factors for asthma development in childhood. The COAST birth cohort study sought to determine the developmental sequence for asthma diagnosis.² This was a prospective, birth-cohort of 285 children at high risk for allergic disease and asthma followed through 13 years of age.^{2,24} Children who were sensitized to aeroallergens had a greater risk of developing viral wheeze than nonsensitized children.² Additionally, the earlier in life sensitization occurred, the higher the rate of asthma at age 13.²⁴ This study demonstrated that allergic sensitization precedes rhinovirus wheezing and that viral wheezing did not increase the likelihood of developing allergic sensitization.²

CHILDHOOD BACTERIAL INFECTIONS

In addition to viral infections, airway bacteria can also influence the development of asthma.¹⁸ Upper airway bacteria colonization is common, and the colonized species can influence wheeze in childhood.²⁰ The most common bacterium found in upper airways in childhood include *Staphylococcus*, *Streptococcus*, *Moraxella*, *Haemophilus*, *Dolosigranulum*, and *Corynebacterium*.²⁰ In children aged 0 to 3 years, pathogenic bacteria have been identified in 86% of wheezing episodes with 31% of episodes without viral detection.²⁵ Although certain bacterial pathogens are associated with wheezing and asthma, a diverse airway microbiome can be protective against wheezing illnesses.¹⁸ Many studies have demonstrated colonization with *S. pneumoniae*, *M. catarrhalis*, and *H. influenzae* in infants are associated with an increased incidence of recurrent wheezing and asthma in childhood, whereas *Corynebacterium*, *Staphylococcus*, and *Dolosigranulum* are more often found in the absence of respiratory symptoms and viral detection.^{18,26}

Bacterial colonization before the first upper respiratory infection influences the development of asthma.^{16,27} The CAS prospective birth cohort of 234 Australian children at high risk for atopic disease were evaluated for bacteria and viruses when asymptomatic at scheduled screenings and with respiratory illness.¹⁶ Infants who had early asymptomatic colonization with *Streptococcus* were subject to an increased risk of asthma 3-fold to 4-fold.¹⁶

Because bacteria and viruses are so prevalent in childhood, studies have evaluated the effects of different bacterial and viral combinations. Cross-sectional cohort studies have demonstrated increased *Moraxella* and *Haemophilus* in rhinovirus bronchiolitis, whereas RSV bronchiolitis had increased *Streptococcus* and *Haemophilus* species.²⁰ Rhinovirus and *S. pneumoniae* detection was associated with increased moderate asthma exacerbations.²⁷ In the absence of rhinovirus, *S. pneumoniae* was associated with increased upper respiratory symptoms and moderate asthma exacerbations.²⁷

PREDICTING ASTHMA IN CHILDHOOD

Although there are many wheezing infants, it is difficult to know from their clinical presentation who will develop asthma. Additionally, there is not a single biomarker to predict which children will develop asthma.²⁸ Predictive indices are useful in prospectively identifying those infants at risk to develop asthma and distinguishing them from the transient wheezers. The initial asthma predictive index (API) was established using data from the TCRS.²⁸ The API has been modified (mAPI) and used in clinical trials for the CARE network.²⁹ A positive mAPI is defined as 4 or more wheezing

Box 1**Modified asthma predictive index**

- A history of 4 or more wheezing episodes in the last year with at least one that was physician-diagnosed
- Must meet 1 major or 2 minor conditions

Major Criteria

- Parental history of asthma
- Physician-diagnosed atopic dermatitis
- Allergic sensitization to at least 1 aeroallergen

Minor Criteria

- Allergic sensitization to milk, egg, or peanut
- Wheezing unrelated to colds
- Blood eosinophils $\geq 4\%$

episodes in the prior year with at least 1 physician-diagnosed event accompanied with either 1 major or 2 minor criteria (**Box 1**). Major criteria for the mAPI include parental history of asthma, physician-diagnosed atopic dermatitis, or allergic sensitization to at least 1 aeroallergen. Minor criteria include allergic sensitization to milk, egg, or peanut, wheezing unrelated to colds, and blood eosinophilia 4% or greater. The mAPI has high a posttest probability at 72% for unselected populations and 90% in high-risk populations.³⁰

The Pediatric Asthma Risk Score (PARS) used data from the Cincinnati Childhood Allergy and Air Pollution study birth cohort of 762 children and identified 6 risk factors in children at age 3 years to predict asthma development at age 7 years (**Table 1**).³¹ In addition to parental asthma, atopic dermatitis, and wheezing unrelated to colds as identified in the API, risk factors included early wheezing, sensitization to 2 or more food allergens or aeroallergens, and African American race.³¹ PARS is a more effective system for predicting mild-to-moderate asthma compared with the API as children with mild asthma commonly have fewer risk factors and do not meet the API criteria.³¹

Table 1**Pediatric asthma risk score**

Yes/No Question	Point Value	Total Score	Risk of Asthma by Age 7
Parental Asthma	2	0–4	3%–11%
Eczema by Age 3	2		
Early Wheezing by Age 3	3	5–8	15%–32%
Wheezing when Healthy	3		
African Ancestry	2	9–14	40%–79%
Positive SPT to ≥ 2 Food or Aeroallergen	2		

Abbreviation: SPT, skin prick test.

TREATMENT**Daily Inhaled Corticosteroids**

ICS are effective in reducing the risk of asthma exacerbations in school-aged children, adolescents, and adults. As such, multiple trials have evaluated ICS in preschool-aged children. The Preventing Early Asthma in Kids (PEAK) trial was a double-blind, randomized, placebo-controlled, parallel group comparison of daily inhaled fluticasone

propionate with placebo in 285 children aged 2 to 3 years with a positive mAPI.²⁹ PEAK was designed to evaluate the efficacy of daily ICS use during a 2 year period and its effect preventing high-risk children from developing asthma.²⁹ Children on daily ICS had more episode-free days, fewer exacerbations, and decreased use of other controlled medications compared with children receiving placebo.²⁹ A 1 year observation period followed the 2 year treatment period. At the end of the observation year, there were no differences in the number of exacerbations, episode-free days, or lung function in the 2 groups.²⁹ Even though the use of ICS did not prevent asthma, it demonstrated patients who benefited from daily ICS: male sex, Caucasian, history of ED visit or hospitalization for asthma within the prior year, aeroallergen sensitization, and less than 80% episode-free days during the run-in period.²⁹

The Individualized Therapy for Asthma in Toddlers (INFANT) study was a randomized, double-blind, double-dummy clinical trial in 300 children aged 12 to 59 months with asthma requiring treatment with daily controller.³² The study included 3 crossover periods consisting of daily ICS, daily leukotriene receptor antagonists (LTRAs), and as-needed ICS treatment coadministered with albuterol.³² Seventy-four percent of the participants had a differential response to the 3 treatments with approximately 50% having the best response to daily ICS and 25% each with the best response to intermittent ICS or daily LTRA.³² Factors that predicted best control with daily ICS included aeroallergen sensitization and blood eosinophil count of 300/mL or greater.³² Additionally, serum eosinophilic cation protein levels of 10 mg/L or greater and sensitization to dog and/or cat predicted greater daily ICS response. The children without differential response had less disease activity.³² Serum IgE levels and mAPI status did not influence a differential response pattern. No factors were noted for improved response to as-needed ICS or LTRA.³²

Papi and colleagues³³ performed a randomized, parallel-group, three-group, double-blind, double-dummy, placebo-controlled study in 276 children aged 1 to 4 years with frequent wheeze randomized to receive daily ICS and as-needed short-acting beta agonist (SABA), daily placebo and as-needed ICS + SABA, or daily placebo and SABA. The daily ICS cohort exhibited the greatest number of symptom-free days at 70%, followed by as-needed ICS + SABA at 65%, and the SABA only group having the least number of symptom-free days at 61%.³³ There was a greater time to first exacerbation in the daily ICS group with no difference in time to first exacerbation in the 2 remaining groups.

Kaiser and colleagues³⁴ performed a meta-analysis using 15 studies of daily ICS versus placebo showing an overall reduction in exacerbation rate with daily ICS compared with placebo at 12.9% and 24.0%, respectively. They estimated that the treatment of 9 children would prevent an asthma exacerbation in 1 child.³⁴ Studies have examined increasing the ICS dose at the onset of acute exacerbation in patients adherent to daily ICS and found no difference in the rate of exacerbations requiring treatment with systemic corticosteroids compared with maintaining standard daily ICS.³⁵ This does not hold true for children who are not taking daily ICS and benefits have been observed in starting ICS at the onset of symptoms as discussed below.

Intermittent Inhaled Corticosteroids

Many preschool children only wheeze with viral infections and are symptom free between episodes. Given this pattern, intermittent ICS has been studied to evaluate the efficacy of as-needed therapy compared with daily ICS. The Maintenance and Intermittent Inhaled Corticosteroids in Wheezing Toddlers (MIST) trial enrolled 278 children aged 12 to 53 months with a positive mAPI and recurrent wheezing episodes (at least 1 in the 12 months before the trials) in a randomized, double-blind, parallel group

study.³⁶ Treatment groups included intermittent, high-dose budesonide for 7 days at the start of symptom onset or daily, low-dose budesonide with corresponding placebos.³⁶ There was no significant difference in the number of exacerbations requiring systemic corticosteroids, time to first or second exacerbation, or treatment failures between the groups.³⁶ The mean ICS exposure was 69% less in the intermittent regimen than daily regimen, 46 mg versus 150 mg, respectively.³⁶

The Prevention of Asthma in Childhood study enrolled 411 1-month-old infants of asthmatic mothers in a double-blind, randomized, placebo control trial.³⁷ Treatment consisted of budesonide or placebo given for 2 weeks after a 3 day episode of wheezing. No statistical differences were seen in the number of symptom-free days, duration of acute episodes, or persistent wheezing between the 2 groups.³⁷

Ducharme and colleagues³⁸ performed a randomized, parallel-group, placebo-controlled trial with triple blinding in 5 institutions in Quebec in 129 children aged 1 to 6 years to receive as-needed ICS versus placebo.³⁸ Participants were required to have 3 or more wheezing episodes in their lifetime. The children were randomized to ICS twice daily for 10 days at the onset of upper respiratory tract infection or placebo.³⁸ At the end of the 6 to 12 months treatment period, the ICS cohort required less treatment with systemic corticosteroids, 8% in the treatment group compared with 18% in placebo.³⁸ A statistically significant difference was observed in height with greater slowing of height in the treatment group at 6.23 cm compared with 6.56 cm in the placebo cohort.³⁸

Kaiser and colleagues³⁴ meta-analysis of 5 studies involving 422 participants aged 6 years or younger treating with intermittent high-dose ICS with intermittent asthma or recurrent viral-triggered wheezing reduced the risk of exacerbation by 35% compared with placebo. They estimated that the treatment of 6 children will prevent an asthma exacerbation in 1 child.³⁴ In meta-analysis of 2 studies comparing daily ICS to intermittent ICS in 498 children with ages ranging 12 to 59 months, there was no difference in rates of severe exacerbation.³⁴ When deciding treatment of daily versus intermittent ICS preschool children with persistent symptoms, elevated blood eosinophils or aeroallergen sensitization benefited from daily ICS over intermittent treatment. Those children who had no wheezing episodes between respiratory infections, who are male, Caucasian, and visited the ED or were hospitalized in the past year due to wheezing or have aeroallergen sensitization, may have greater benefit from daily ICS. In all other children aged 5 years and younger, intermittent ICS should be sufficient.

Leukotriene Receptor Antagonists

Valovirta and colleagues³⁹ evaluated 1771 patients aged 6 months to 5 years in a double-blind, double-dummy, parallel group study randomized to receive daily montelukast, intermittent montelukast, or placebo in a 52-week study. Enrollment requirements included episodes of asthma symptoms in the preceding year that required SABA treatment, at least 1 treatment with oral corticosteroids (OCS) or hospitalization for asthma with asymptomatic periods between episodes. There were no significant differences in the daily versus intermittent montelukast group compared to placebo in the total number of asthma attacks that required treatment with corticosteroids or unscheduled medical visits. There was a reduction in beta-agonist use in both montelukast groups compared to placebo.³⁹

The PREvention of Virally Induced Asthma trial was a multicenter, double-blind, parallel-group study of 549 children aged 2 to 5 years with a history of intermittent asthma symptoms.⁴⁰ Children were randomized to either daily montelukast or placebo for the 12 month treatment period. In children treated with montelukast, the average yearly asthma exacerbation rate was significantly lower than that of the placebo group by

31.8%. In addition, montelukast extended the time to the first exacerbation by 2 months and lowered the rate of inhaled corticosteroid use.

The Acute Intermittent Management Strategies (AIMS) trial was a randomized, double-blind, placebo-controlled study evaluating 238 children aged 12 to 59 months with a history of at least 2 wheezing respiratory tract infections in the preceding year with one episode within the last 6 months.⁴¹ There were 3 treatment groups consisting of montelukast, ICS, and placebo with all treatment arms including albuterol as needed for the 12 months study period. There was no significant difference in episode-free days, OCS use, health-care use, linear growth, or quality of life among the 3 treatment groups. In participants with a positive mAPI, both montelukast and ICS improved breathing scores, interference with activity scores, and total symptom scores compared with placebo. For those with a negative mAPI, the study showed improvement only in the interference with activity score in the cohort receiving montelukast. Similar to the INFANT trial, 25% of children with asthma responded best to LTRA, though mAPI did not determine which treatment (daily ICS, intermittent PRN, or LTRA) the children would respond to best.³²

A Cochrane meta-analysis was performed on 5 studies evaluating LTRAs as maintenance and intermittent therapy for episodic wheezing in children aged 1 to 6 years.⁴² Although individual studies did show some benefit of LTRA therapy, the authors determined that there was no evidence of benefit from maintenance or intermittent LTRA treatment compared with placebo in decreasing the number of viral-induced wheezing episodes requiring rescue OCS.

The Wheeze And Intermittent Treatment study was a multicenter, randomized, placebo-controlled, parallel-group study to assess the efficacy of intermittent montelukast.⁴³ Enrollment included 1358 children aged 10 months to 5 years with a history of 2 or more wheezing episodes, 1 in the preceding 3 months. Children were allowed to continue their baseline medications that could include bronchodilators and ICS. Montelukast or placebo was started at home at the onset of wheezing or viral infection for more than a 12-month period. The intermittent montelukast cohort required fewer courses of OCS. No differences were seen in the number of wheezing episodes, duration of wheezing episodes, or unscheduled medical visits. In 2004 and updated in 2020, the US Food and Drug Administration added a black box label to montelukast stating that serious mental health side effects may include suicidal thoughts or actions have been reported in patients.⁴⁴

Oral Corticosteroids

OCS are a mainstay of treatment of asthma exacerbation; however, in preschool children, OCS have not been consistently shown to be beneficial in wheezing episodes.^{45,46} This may be due to the fact that many preschool children who wheeze do not develop asthma. One of the earlier studies looking at hospital admission rates recruited 74 participants aged 7 to 54 months who were evaluated in the ED for acute wheezing.⁴⁷ In this double-blind trial, participants received either a dose of intramuscular methylprednisone or placebo.⁴⁷ Patients were evaluated 3 hours after treatment with 20% of the methylprednisone cohort being admitted to the hospital compared with 43% of the placebo cohort. This was more significant in children aged 7 to 24 months with only 18% of the treatment group requiring admission compared with 50% of the placebo group. The older children aged 24 to 54 months had a smaller difference in admission rates with 23% versus 31% requiring admission.⁴⁷

Another study involving 230 children aged 6 to 35 months presenting to the ED with acute respiratory distress were randomized to 3 days of oral prednisone versus placebo.⁴⁸ Children were hospitalized at similar rates between the 2 groups but those

treated with OCS had a shorter hospital duration by 1 day, 2 versus 3 days, in treatment versus placebo cohorts, respectively. Additionally, when compared with the placebo cohort, the treatment group had decreased need for additional asthma medication and shorter duration of symptoms by 1 day compared with the placebo group.

An Australian ED randomized, double-blind, placebo-controlled trial evaluated 624 children aged 24 to 72 months presenting to the ED with virus-associated wheeze.⁴⁹ Participants were treated with oral prednisone for 3 days or placebo. The average length of stay was decreased in the treatment group at 370 minutes compared with 540 minutes in the placebo group. This study found that in children with more severe symptoms, children who used albuterol before ED presentation and previously diagnosed with asthma were more likely to improve with OCS use. Another ED study treated 687 infants aged 10 to 60 months without bronchiolitis who presented to the ED with acute viral wheezing.⁵⁰ In this double-blind, placebo controlled study, children were randomized to prednisolone for 5 days versus placebo. There was no significant difference noted in the duration of hospitalization, albuterol use, or 7-day symptom score.

Seventy-nine children aged 3 to 23 months were evaluated for the effects of OCS in rhinovirus wheeze.⁵¹ Children with an initial, acute, moderate-severe wheezing episode were randomized to receive 3 days of oral prednisone versus placebo and were followed for 12 months. Oral steroids improved short-term respiratory symptoms during the initial 2 weeks posttreatment. Long-term outcomes did not differ between treatment groups and included future wheezing episodes and controller medication for asthma. The use of home-administered OCS for viral-induced wheezing was evaluated in 108 children aged 1 to 5 years with a previous history of hospital admission for viral-induced wheeze.⁵² These children were subsequently randomized to 5 days of OCS or placebo to use at that start of their next viral wheezing episode. There was no difference in daytime or nighttime lower respiratory tract symptoms, need for rescue medications, or hospital admission between the 2 groups or in children with above-average eosinophil priming determined by the level of serum eosinophil cationic protein greater than 20 mg/L and eosinophil protein X > 40 mg/L.

The following post hoc analysis focuses on OCS given for outpatient exacerbations in children who did not require ED evaluation. Beigelman and colleagues⁵³ performed a post hoc analysis on high-risk children enrolled in the AIMS trial and MIST trial; the investigators did not find any difference in total symptom score or length of symptoms during outpatient exacerbations among children who were treated or not treated with OCS. There were no risk factors that predicted which group of children would have greater benefit from OCS. Positive mAPI, atopic dermatitis, and family history of asthma are factors that would have been expected to yield greater benefit from OCS, although these groups did not have any additional benefit than those without atopic risk factors. Furthermore, there was also no difference noted in OCS treatment in patients on daily ICS versus no controller therapy as half of the children in the MIST trial were receiving daily ICS. This analysis shows minimal evidence to support the use of OCS in preschool children treated at home for intermittent viral wheezing.

The national and international asthma guidelines address OCS in young children with exacerbations. Updated asthma guidelines released by the Global Initiative for Asthma support consideration for OCS in children aged 5 years and younger if the child requires ED evaluation for hospital admission for exacerbation; OCS are not listed as a recommendation for outpatient exacerbation management.⁵⁴ The expert panel working group of the National Heart, Lung, and Blood Institute released an update to the national asthma management guidelines in 2020.³⁵ For children 4 years

and younger with acute exacerbation, this group states to consider OCS if the child has a severe exacerbation or a history of severe exacerbations.³⁵ OCS can be beneficial in reducing hospital-based care in young children with a diagnosis of asthma, use of bronchodilators, and more severe wheezing episodes who seek ED evaluation; OCS are not in the list of recommendations for outpatient exacerbation management.⁴⁹ Additional studies are still needed in young children to best determine which subgroups will receive the greatest benefit from OCS.

Azithromycin

Bacteria, specifically *S. pneumoniae* and *M. catarrhalis*, are often detected in children who wheeze, both with and without the presence of viral infections.¹⁸ As such, azithromycin has been studied in wheezing children. In the Copenhagen Prospective Study on Asthma in Childhood 2000 birth cohort, 72 children aged 1 to 3 years with a history of recurrent asthma symptoms were enrolled in a study to assess the duration of wheezing episodes when treated with azithromycin.⁵⁵ Children were randomized to receive 3 days of azithromycin or placebo with each wheezing episode of 3 consecutive days in duration. Azithromycin shortened the duration of symptoms to 3.4 days compared to 7.7 with placebo, corresponding to a calculated reduction in episode length of 63.3%. Greater improvement was seen when the treatment was started earlier in the episode; however, treatment did not significantly affect the time to next episode of respiratory symptoms.

The Azithromycin for Preventing the Development of Upper Respiratory Tract Illness into Lower Respiratory Tract Symptoms in Children study was a randomized, double-blind, placebo-controlled, parallel-group trial evaluating intermittent azithromycin for respiratory tract infections.⁵⁶ Participants included 607 children aged 12 to 71 months with a history of recurrent severe lower respiratory tract infections with minimal impairment between episodes. Children were treated with 5 days of azithromycin or placebo at the onset of respiratory tract illness before lower respiratory tract illness developed. A total of 937 respiratory tract infections were treated during a period of 12 to 18 months. Azithromycin significantly reduced the risk of progression to a severe lower respiratory tract infection by 37%. Antimicrobial resistance was evaluated in a subset of participants throughout the study. At initial randomization, azithromycin-resistant organisms were isolated from 5 of 41 treatment participants and 4 of 45 placebo participants. At the completion of the study, azithromycin-resistant organisms were identified in an additional 3 patients per group: 8 of 40 in the treatment cohort and 7 of 41 in the placebo cohort. As the placebo cohort had a similar rate of azithromycin resistance, this secondary outcome measure was not statistically significant. Further studies are needed to evaluate the potential increased risk in resistance.

The use of azithromycin in the prevention of future wheezing episodes has been looked at in this recent prospective, double-blind, placebo-controlled study of 200 children aged 1 to 18 months admitted with RSV bronchiolitis assigned to 14 days of azithromycin or placebo.⁵⁷ Despite evidence of biologic activity on nasal interleukin-8 levels, azithromycin did not reduce the risk of post-RSV recurrent wheeze during the 2 to 4 year observation period (47% in the azithromycin group vs 36% in the placebo group). There were no differences in the number of days with respiratory symptoms, annualized days with albuterol use, or number of subsequent antibiotic courses or OCS courses. A greater number of participants in the azithromycin group were given a diagnosis of asthma by the end of the trial data collection compared with placebo at 15.6% and 8.7%, respectively. The hazard ratio for having an asthma diagnosis by the end of data collection was 1.95. Although azithromycin is an option for treatment in intermittent wheezing children, it has not been effective for asthma

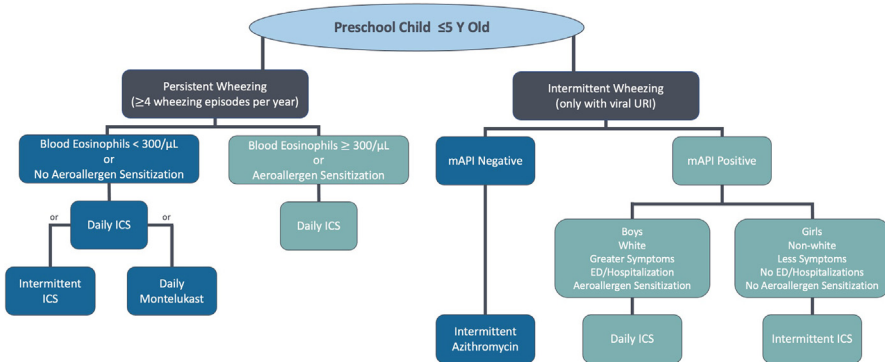


Fig. 1. Treatment Recommendations for Preschool Children with Wheeze. ICS, inhaled corticosteroid; mAPI, modified asthma predictive index.

prevention. **Fig. 1** illustrates the therapeutic options for the treatment of wheezing episodes in preschool children.

SUMMARY

Wheezing is common in childhood, although only a small percentage of these children develop asthma. The child's wheezing phenotype and asthma predictive indices help predict the likelihood of future asthma diagnosis. Lung function patterns are established in childhood where lung function deficits are established by 6 years of life. Viral infections are common in childhood with RSV accounting for most wheezing episodes in children aged less than 1 year and rhinovirus in children aged 1 year and greater. Many treatment options exist for wheezing children, including those that wheeze persistently or only due to viral infections. In atopic persistent wheezing children, daily ICS has been shown to be most effective. In nonatopic persistent wheezers, options include daily ICS, intermittent ICS, and daily montelukast. Intermittent wheezing children with a negative mAPI are best suited for intermittent azithromycin. Children intermittently wheezing with a positive mAPI and positive risk factors respond best to daily ICS, whereas those without risk factors can be treated with intermittent ICS. The benefit of OCS for exacerbations in this age is still inconclusive, although there is greater evidence to support OCS in those requiring ED evaluation or hospital admission.

CLINICS CARE POINTS

- Rhinovirus is the most common virus to cause wheezing in children aged 1 year and older. Wheezing with rhinovirus infection is a strong predictor of future wheezing episodes, and this prediction is higher in atopic individuals.
- Respiratory syncytial virus (RSV) is the most common virus to cause wheezing in children aged 1 year and younger. RSV lower respiratory tract illnesses before age 3 years is associated with a significant increase in risk of subsequent wheezing during the first 10 years but is not significant by age 13.
- The modified asthma predictive index and the pediatric asthma risk score are tools to identify infants at risk to develop asthma.
- Many treatment options are available for preschool children who wheeze:

- Those with persistent wheeze and elevated blood eosinophils or aeroallergen sensitization are best treated with daily inhaled corticosteroids (ICS).
- Persistent wheezing without eosinophilia or aeroallergen sensitization can be treated with daily ICS, intermittent ICS, or daily leukotriene receptor antagonist (LTRA).
- Intermittent wheezing with a negative modified (mAPI) can be treated with intermittent LTRA.
- Intermittent wheezing with a positive mAPI and risk factors of male gender, Caucasian, greater symptoms, prior emergency department visit or hospitalization, or aeroallergen sensitization may be best treated with daily ICS. Those without the above risk factors can be treated with intermittent ICS.
- The effectiveness of oral corticosteroids in this age range is inconclusive.

DISCLOSURES

A.M.A. Doss-nothing to disclose. J.R. Stokes: Research grants from NIH, Avillion LLP, Sanofi-Aventis/SA, and Regeneron Pharmaceuticals.

REFERENCES

1. Martinez FD, Wright AL, Taussig LM, et al. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995;332(3):133–8.
2. Jackson DJ, Evans MD, Gangnon RE, et al. Evidence for a causal relationship between allergic sensitization and rhinovirus wheezing in early life. *Am J Respir Crit Care Med* 2012;185(3):281–5.
3. Johnson CC, Havstad SL, Ownby DR, et al. Pediatric asthma incidence rates in the United States from 1980 to 2017. *J Allergy Clin Immunol* 2021;148(5):1270–80.
4. Pate CA, Zahran HS, Qin X, et al. Asthma Surveillance - United States, 2006–2018. *MMWR Surveill Summ* 2021;70(5):1–32.
5. Akinbami LJ, Moorman JE, Garbe PL, et al. Status of childhood asthma in the United States, 1980–2007. *Pediatrics* 2009;123(Suppl 3):S131–45.
6. Zahran HS, Bailey CM, Damon SA, et al. Vital signs: asthma in children - United States, 2001–2016. *MMWR Morb Mortal Wkly Rep* 2018;67(5):149–55.
7. Morgan WJ, Stern DA, Sherrill DL, et al. Outcome of asthma and wheezing in the first 6 years of life. *Am J Respir Crit Care Med* 2005;172(10):1253–8.
8. Savenije OE, Granell R, Caudri D, et al. Comparison of childhood wheezing phenotypes in 2 birth cohorts: ALSPAC and PIAMA. *J Allergy Clin Immunol* 2011;127(6):1505–12.e14.
9. Oksel C, Granell R, Mahmoud O, et al. Causes of variability in latent phenotypes of childhood wheeze. *J Allergy Clin Immunol* 2019;143(5):1783–90.e11.
10. Henderson J, Granell R, Heron J, et al. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax* 2008;63(11):974–80.
11. Fitzpatrick AM, Bacharier LB, Guilbert TW, et al. Phenotypes of recurrent wheezing in preschool children: identification by latent class analysis and utility in prediction of future exacerbation. *J Allergy Clin Immunol Pract* 2019;7(3):915–24.e7.
12. Bacharier LB, Beigelman A, Calatroni A, et al. Longitudinal phenotypes of respiratory health in a high-risk urban birth cohort. *Am J Respir Crit Care Med* 2019;199(1):71–82.
13. Heikkinen T, Jarvinen A. The common cold. *Lancet* 2003;361(9351):51–9.

14. Rakes GP, Arruda E, Ingram JM, et al. Rhinovirus and respiratory syncytial virus in wheezing children requiring emergency care. *Am J Respir Crit Care Med* 1999; 159(3):785–90.
15. Johnston SL, Pattemore PK, Sanderson G, et al. Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. *BMJ* 1995; 310(6989):1225–9.
16. Teo SM, Mok D, Pham K, et al. The infant nasopharyngeal microbiome impacts severity of lower respiratory infection and risk of asthma development. *Cell Host Microbe* 2015;17(5):704–15.
17. Lemanske RF Jr, Jackson DJ, Gangnon RE, et al. Rhinovirus illnesses during infancy predict subsequent childhood wheezing. *J Allergy Clin Immunol* 2005; 116(3):571–7.
18. Jackson DJ, Gern JE, Lemanske RF. The contributions of allergic sensitization and respiratory pathogens to asthma inception. *J Allergy Clin Immunol* 2016; 137(3):659–65.
19. Caliskan M, Bochkov YA, Kreiner-Moller E, et al. Rhinovirus wheezing illness and genetic risk of childhood-onset asthma. *N Engl J Med* 2013;368(15):1398–407.
20. Altman MC, Beigelman A, Ciaccio C, et al. Evolving concepts in how viruses impact asthma: a work group report of the microbes in allergy committee of the american academy of allergy, asthma & immunology. *J Allergy Clin Immunol* 2020;145(5):1332–44.
21. Stein RT, Sherrill D, Morgan WJ, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999;354(9178):541–5.
22. Blanken MO, Rovers MM, Molenaar JM, et al. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. *N Engl J Med* 2013;368(19):1791–9.
23. Scheltema NM, Nibbelke EE, Pouw J, et al. Respiratory syncytial virus prevention and asthma in healthy preterm infants: a randomised controlled trial. *Lancet Respir Med* 2018;6(4):257–64.
24. Rubner FJ, Jackson DJ, Evans MD, et al. Early life rhinovirus wheezing, allergic sensitization, and asthma risk at adolescence. *J Allergy Clin Immunol* 2017; 139(2):501–7.
25. Carlsson CJ, Vissing NH, Sevelsted A, et al. Duration of wheezy episodes in early childhood is independent of the microbial trigger. *J Allergy Clin Immunol* 2015; 136(5):1208–14.e5.
26. Bisgaard H, Hermansen MN, Buchvald F, et al. Childhood asthma after bacterial colonization of the airway in neonates. *N Engl J Med* 2007;357(15):1487–95.
27. Kloepfer KM, Lee WM, Pappas TE, et al. Detection of pathogenic bacteria during rhinovirus infection is associated with increased respiratory symptoms and asthma exacerbations. *J Allergy Clin Immunol* 2014;133(5):1301–7.e3.
28. Castro-Rodríguez JA, Holberg CJ, Wright AL, et al. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162(4):1403–6.
29. Guilbert TW, Morgan WJ, Krawiec M, et al. The prevention of early asthma in kids study: design, rationale and methods for the childhood asthma research and education network. *Controlled Clin Trials* 2004;25(3):286–310.
30. Chang TS, Lemanske RF, Guilbert TW, et al. Evaluation of the modified asthma predictive index in high-risk preschool children. *J Allergy Clin Immunol Pract* 2013;1(2):152–6.
31. Biagini Myers JM, Schauburger E, He H, et al. A pediatric asthma risk score to better predict asthma development in young children. *J Allergy Clin Immunol* 2019;143(5):1803–10.e2.

32. Fitzpatrick AM, Jackson DJ, Mauger DT, et al. Individualized therapy for persistent asthma in young children. *J Allergy Clin Immunol* 2016;138(6):1608–18.e12.
33. Papi A, Nicolini G, Baraldi E, et al. Regular vs prn nebulized treatment in wheeze preschool children. *Allergy* 2009;64(10):1463–71.
34. Kaiser SV, Huynh T, Bacharier LB, et al. Preventing exacerbations in preschoolers with recurrent wheeze: a meta-analysis. *Pediatrics* 2016;137(6):e20154496.
35. Cloutier MM, Baptist AP, Blake KV, et al. 2020 Focused updates to the asthma management guidelines: a report from the national asthma education and prevention program coordinating committee expert panel working group. *J Allergy Clin Immunol* 2020;146(6):1217–70.
36. Zeiger RS, Mauger D, Bacharier LB, et al. Daily or intermittent budesonide in preschool children with recurrent wheezing. *N Engl J Med* 2011;365(21):1990–2001.
37. Bisgaard H, Hermansen MN, Loland L, et al. Intermittent inhaled corticosteroids in infants with episodic wheezing. *N Engl J Med* 2006;354(19):1998–2005.
38. Ducharme FM, Lemire C, Noya FJD, et al. Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. *N Engl J Med* 2009;360(4):339–53.
39. Valovirta E, Boza ML, Robertson CF, et al. Intermittent or daily montelukast versus placebo for episodic asthma in children. *Ann Allergy Asthma Immunol* 2011;106(6):518–26.
40. Bisgaard H, Zielen S, Garcia-Garcia ML, et al. Montelukast Reduces Asthma Exacerbations in 2- to 5-Year-Old Children with Intermittent Asthma. *Am J Respir Crit Care Med* 2005;171(4):315–22.
41. Bacharier LB, Phillips BR, Zeiger RS, et al. Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. *J Allergy Clin Immunol* 2008;122(6):1127–35.e8.
42. Brodlie M, Gupta A, Rodriguez-Martinez CE, et al. Leukotriene receptor antagonists as maintenance and intermittent therapy for episodic viral wheeze in children. *Cochrane Database Syst Rev* 2015;2020(1):CD008202.
43. Nwokoro C, Pandya H, Turner S, et al. Intermittent montelukast in children aged 10 months to 5 years with wheeze (WAIT trial): a multicentre, randomised, placebo-controlled trial. *Lancet Respir Med* 2014;2(10):796–803.
44. Clarridge K, Chin S, Eworuke E, et al. A boxed warning for montelukast: the FDA perspective. *J Allergy Clin Immunol Pract* 2021;9(7):2638–41.
45. Beigelman A, Durrani S, Guilbert TW. Should a preschool child with acute episodic wheeze be treated with oral corticosteroids? A Pro/Con Debate. *J Allergy Clin Immunol Pract* 2016;4(1):27–35.
46. Stokes JR, Bacharier LB. Prevention and treatment of recurrent viral-induced wheezing in the preschool child. *Ann Allergy Asthma Immunol* 2020;125(2):156–62.
47. Tal A, Levy N, Bearman JE. Methylprednisolone therapy for acute asthma in infants and toddlers: a controlled clinical trial. *Pediatrics* 1990;86(3):350–6.
48. Csonka P, Kaila M, Laippala P, et al. Oral prednisolone in the acute management of children age 6 to 35 months with viral respiratory infection-induced lower airway disease: a randomized, placebo-controlled trial. *J Pediatr* 2003;143(6):725–30.
49. Foster SJ, Cooper MN, Oosterhof S, et al. Oral prednisolone in preschool children with virus-associated wheeze: a prospective, randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2018;6(2):97–106.
50. Panickar J, Lakhnapaul M, Lambert PC, et al. Oral prednisolone for preschool children with acute virus-induced wheezing. *N Engl J Med* 2009;360(4):329–38.

51. Jartti T, Nieminen R, Vuorinen T, et al. Short- and long-term efficacy of prednisolone for first acute rhinovirus-induced wheezing episode. *J Allergy Clin Immunol* 2015;135(3):691–698 e9.
52. Oommen A, Lambert PC, Grigg J. Efficacy of a short course of parent-initiated oral prednisolone for viral wheeze in children aged 1–5 years: randomised controlled trial. *Lancet* 2003;362(9394):1433–8.
53. Beigelman A, King TS, Mauger D, et al. Do oral corticosteroids reduce the severity of acute lower respiratory tract illnesses in preschool children with recurrent wheezing? *J Allergy Clin Immunol* 2013;131(6):1518–25.
54. Reddel HK, Bacharier LB, Bateman ED, et al. Global initiative for asthma strategy 2021. executive summary and rationale for key changes. *Arch Bronconeumol* 2022;58(1):35–51.
55. Stokholm J, Chawes BL, Vissing NH, et al. Azithromycin for episodes with asthma-like symptoms in young children aged 1–3 years: a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2016;4(1):19–26.
56. Bacharier LB, Guilbert TW, Mauger DT, et al. Early administration of azithromycin and prevention of severe lower respiratory tract illnesses in preschool children with a history of such illnesses. *JAMA* 2015;314(19):2034.
57. Beigelman A, Srinivasan M, Goss CW, et al. Azithromycin to prevent recurrent wheeze following severe respiratory syncytial virus bronchiolitis. *NEJM Evid* 2022;1(4). <https://doi.org/10.1056/EVIDoa2100069>.