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Asthma in the Preschool Age Child

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Epidemiology and Burden

Preschool asthma (i.e., wheeze in children 5 years of age and younger) is a common condition. Indeed, a UK study reported that between 1990 and 1998, there was an increase in the prevalence of parent-reported preschool “wheeze ever” (from 16% to 29%), “current wheeze” (from 12% to 26%), “diagnosis of asthma” (from 11% to 19%), and “admission for wheeze” (from 6% to 10%).¹ This high prevalence of wheeze in preschool children results in a high burden of disease. For example, US National Surveillance of Asthma statistics² report the highest average annual asthma physician office visits, hospital outpatient department visits, emergency department visits, and hospitalizations in the preschool period than other age groups (Fig. 44.1)—a pattern also found in other countries.³

Episodes of preschool wheeze are frequently associated with signs of an upper respiratory tract infection (URTI).⁴ A wide range of infectious agents triggers these episodes (exacerbations). In a prospective cohort study done in Copenhagen, both respiratory viruses (e.g., picornaviruses, respiratory syncytial virus [RSV], and coronavirus) and bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*) were isolated from the hypopharynx in just over half of preschool wheeze episodes. Bacteria alone were isolated in just over a third of wheeze episodes, and respiratory viruses alone were isolated in 10% of episodes.⁵ In preschool children with clinically severe wheeze, human rhinovirus species C (HRVC) is often isolated, especially in those admitted to hospital.^{6,7} While an increased virulence of HRVC has been suggested for this association,⁸ there is accumulating evidence that gene-environment interaction is important. For some children this may be due to genetic susceptibility.⁹ In other children, allergy may be important, potentially because of impaired innate immune response leading to increased viral replication.¹⁰

Diagnosis

Asthma is considered an inflammatory disease presenting with episodic or persistent respiratory symptoms associated with variable airflow obstruction to endogenous or exogenous stimuli.¹¹ However, preschool children with wheeze do not always have airway inflammation between wheezing episodes. As in adults and older children, asthma in preschool is based on recurrent (i.e., two or more) episodes of airflow obstruction and reversibility with appropriate inhaled medication. The diagnosis should be considered in children aged 12 months and older with no suspicion of another

condition.¹² Wheeze is the most specific sign of airflow obstruction; it refers to the presence of a continuous musical tone or squeaking commonly heard on auscultation in early expiration or at the end of inspiration. Accompanying signs of obstruction include cough, tachypnea, accessory muscle use, hypoxemia, and, in severe cases, alteration of the mental state. Significant clinical improvement with bronchodilators or corticosteroids is required to document reversibility or, alternatively, fluctuation of symptoms spontaneously over time.

In infants, there is some inconsistency about the diagnostic label applied for wheeze heard on auscultation. A frequent condition in this age group is bronchiolitis—a condition that is associated with signs of a respiratory infection, predominantly, but not exclusively, associated with primary RSV infection of the lower respiratory tract. Infants with bronchiolitis typically do not display significant reversibility, either to bronchodilators or other asthma medications, and in this condition a therapeutic trial is not indicated.^{13,14} Although the diagnosis of bronchiolitis is clinical, its varied definition results in diagnostic confusion. In Canada and the United States, a diagnosis of bronchiolitis is a first episode of wheezing in children up to the age of 1 and 2 years, with lower respiratory signs that include wheeze. By contrast, in the United Kingdom and South Africa, the diagnosis of bronchiolitis is mainly limited to infants under 6 months of age, typically with fine crackles but without wheezing.¹⁵ Consequently, wheeze in children, particularly those between 6 months and 2 years, with a first or second episode of respiratory difficulty, and no observed clinical response to asthma medication falls into a clinically unclear area, and is thus frequently labeled as “preschool wheeze” while awaiting a firm diagnosis. However, preschool wheeze is not a diagnosis, but only a symptom underlying an, as yet, poorly defined pathological entity. By careful observation including, when indicated, a therapeutic trial—clinicians should aim to make a definitive, if not at least a presumptive, diagnosis to apply appropriate therapy. In this regard, a therapeutic trial of asthma medication (bronchodilators with oral corticosteroids [OCS], in case of a moderate or severe exacerbation) would be indicated in children aged 12 months and older to document reversibility.

The diagnosis of preschool asthma (defined previously) is best made on the observation of a trained health care professional (or alternatively a convincing parental history) of two or more episodes with signs of airflow obstruction and reversibility. A thorough history and examination is essential to make a presumptive or conclusive diagnosis of asthma and to exclude alternative diagnoses that may cause respiratory symptoms in infancy and early childhood. There are two important caveats to parent-reported wheeze: the

ABSTRACT

Wheeze in preschool children (5 years of age and younger) is common. The majority of severe episodes are triggered by viral colds. Unlike atopic asthma in adults and young people, the underlying pathology of this condition is poorly understood, and the label of “preschool wheeze” should therefore not be regarded as a diagnosis but a description of symptoms. It is important to consider other causes of wheeze, but, for the most part, serious conditions such as cystic fibrosis and foreign body aspiration are associated with atypical features on careful history and examination. There remain significant uncertainties about the optimal management of children with this condition. Short-acting bronchodilators are indicated for the acute treatment of wheeze, and current evidence suggests that daily inhaled corticosteroid therapy is an effective preventive therapy, at least in a subgroup of children. Some trials suggest that preemptive therapy with inhaled corticosteroids may be as effective as regular inhaled corticosteroids. Since wheeze is intermittent for the majority of children, preemptive therapy is a logical approach. However, more studies are needed to confirm whether preemptive inhaled corticosteroids are as, or more, effective than regular preventer therapy.

KEYWORDS

preschool wheeze
preschool asthma
inhaled therapy

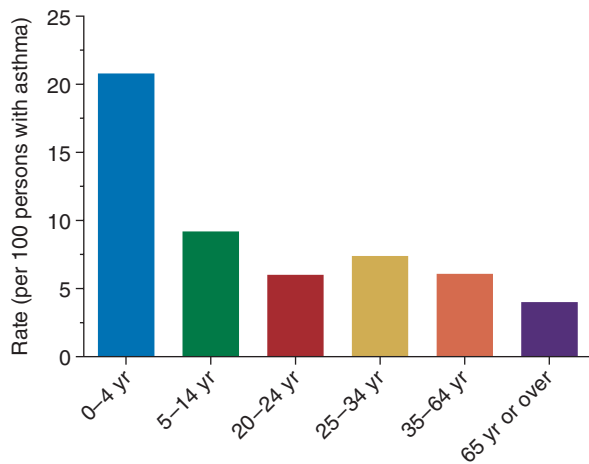


Fig. 44.1 Emergency department visits for acute wheeze (risk-based) for the United States. (Data are the age-specific average annual rates for 2007–2008, from the U.S. National Surveillance of Asthma report [2]).

accuracy of the vocabulary and the lower sensitivity of ears compared with a stethoscope. When taking a history, wheeze should be separated from other respiratory sounds by asking about “a high-pitched whistling or squeaking sound from the chest, not the throat.” Parental reporting of wheeze cannot be regarded as the gold standard. For example, in a large population-based study, 17% of families did not define wheeze as a whistling noise, despite being given a description of wheeze in a questionnaire.¹⁶ Showing parents a video of common respiratory signs and then asking them to identify the closest match help distinguish wheeze from other sounds such as stridor and upper airway rattles.¹⁷ However, direct observation of signs of airflow obstruction and reversibility during an exacerbation by a trained health care professional remains the preferred approach. In a child with a prior documented exacerbation or a convincing history of an exacerbation, who does not present with clinical signs of airflow obstruction, an alternative approach is to document reversibility with a 12-week trial of maintenance inhaled corticosteroids (ICS), with parent-reported change in the frequency and severity of chronic and acute symptoms. This treatment should be discontinued if there is no benefit; many would want to exclude the possibility that the child had in fact recovered spontaneously by having a trial period of stopping treatment.

Parents should be asked about the nature and duration of symptoms, exacerbating factors, family history, and presence of atopy, rhinitis, and smoking in the home or car. History and examination should focus on eliminating the other important diagnoses that may cause respiratory symptoms in infancy and early childhood. Alternative diagnoses include structural abnormalities, gastroesophageal reflux, congenital heart disease, foreign body, chronic aspiration, chronic airway infection, and the consequences of extreme prematurity. Red flags for alternative diagnoses include prominent upper airway symptoms, symptoms from the first day of life, sudden onset of symptoms, chronic moist cough, symptoms worse after meals, and weight loss (Table 44.1).¹⁸ Examination should pay attention to clubbing, wasting, severe tonsillar hypertrophy, severe chest deformity, fixed monophonic or asymmetrical wheeze, and cardiac murmurs. A 2016 review of the diagnostic

Table 44.1 Differential Diagnosis of Preschool Wheeze

Diagnosis	Clinical Features
Aspiration syndromes (e.g., gastroesophageal reflux, H-type fistula)	Vomiting, poor weight gain, coughing during feeding, and abdominal distension with H type fistula
Inhaled foreign body	Prior episode of coughing or choking (this may be absent), chronic cough
Immune deficiency	Wheeze with infections that are severe, persistent, unusual, or recurrent
Cystic fibrosis	Cough in first weeks of life, poor weight gain
Primary ciliary dyskinesia	Rhinorrhea in first weeks of life, term respiratory distress, with or without situs invertus
Bronchomalacia	Harsh, monophonic expiratory sound
Bronchopulmonary dysplasia/ chronic lung disease of prematurity	Premature birth, home oxygen
Cardiac abnormality	Tachycardia, hepatomegaly, pulmonary crackles
Post infectious obliterative bronchiolitis	History of previous viral infection (especially adenovirus), tachypnea

Table 44.2 American Thoracic Society Recommendations for the Diagnostic Evaluation of Infants With Recurrent or Persistent Wheeze Despite Appropriate Inhaled Treatment

Investigation	Recommendation	Quality of Evidence
Fiberoptic bronchoscopy	Should be done	Very low
Bronchoalveolar lavage	Should be done	Very low
24-hour esophageal pH monitoring	Should be done	Very low
Gastroesophageal scintigraphy instead of pH monitoring	Not preferred to pH monitoring	Very low
Swallowing function study	Should be done	Very low

Ren CL, Esther CR, Debley JS, et al. Official American Thoracic Society Clinical Practice Guidelines: diagnostic evaluation of infants with recurrent or persistent wheezing. *Am J Respir Crit Care Med.* 2016;194:356-373.

evaluation of infants with recurrent or persistent wheezing (despite adequate inhaled asthma therapy) by the American Thoracic Society recommends flexible bronchoscopy, pH monitoring, and a swallowing study; however, the evidence to support these recommendations was found to be of low quality (Table 44.2).¹⁹

Investigations should be tailored to the medical history, physical examination, and suspected diagnosis. For the majority of wheezy preschool children, no investigations are needed. For the minority of children with clinically very severe wheeze (and no red flags on history and examination), it is reasonable to perform a chest radiograph and assess the possibility of sensitization to outdoor and indoor allergens as contributing factors. Exposure to cigarette smoke should be ascertained for all children,²⁰ with a firm recommendation for a smoke-free environment.

Natural History

The first complete picture of the natural history of preschool wheeze originated from the Tucson Children's Respiratory Study.²¹ Retrospective analysis of this longitudinal dataset from 1246 newborns assessed at both 3 years and 6 years revealed distinct temporal patterns of wheeze that were associated with different factors. First, there are "transient infant wheezers" (the majority of wheezers in this cohort) who wheezed occasionally during the first 3 years of life and then did not wheeze after the age of 3 years. This pattern was not significantly associated with markers of atopy, such as blood eosinophilia or high levels of serum immunoglobulin E (IgE), but was associated with lower lung function (measured in infants prior to their first episode of wheezing) and maternal smoking during pregnancy. Although many of these preschoolers probably met the definition of preschool asthma (obstruction and reversibility with asthma therapy), this pattern was not significantly associated with parent-reported ongoing asthma symptoms at and beyond 6 years of age, suggesting a transient asthma phenomenon. Second, there were "nonatopic wheezers" who begin wheezing at 3 years, but whose wheeze resolved by 6 years. Third, there are "atopic wheezers," whose preschool wheeze continued as allergic asthma after 6 years of age. Similar trajectories of preschool wheeze have subsequently been reported in other longitudinal cohorts, albeit with subtle differences. For example, an analysis of longitudinal data from the Leicestershire and Avon Longitudinal Study of Parents and Children (ALSPAC) cohorts found patterns consistent between the two cohorts. Those children with persistent wheeze and chronic cough, associated with atopy, have reduced lung function and a poorer prognosis, whereas those with early-onset non-persistent wheeze have a more favorable prognosis.²² To date, however, these important epidemiological studies have not produced a clinically useful method for predicting which preschool children will develop asthma symptoms at school age. Indeed, a systematic review of 12 asthma prediction models, including the asthma predictive index (API), found that although some models were better at predicting ongoing asthma at 6 years, and other models were better at ruling it out, no single model could accurately do both.²³ Thus the prediction of whether preschoolers with asthmalike symptoms will continue to have asthma at 6 years, from contemporaneously obtained information, cannot be achieved with sufficient precision in a large proportion of preschool children with wheeze. One main reason is that most children have symptoms only in preschool years and "outgrow" symptoms before the age of 6 years, although, unfortunately, some still have residual lung function impairment.²⁴ Another reason is the different prevalence of disease in various settings, such as the general population, a family physician practice, or a specialist clinic. When discussing outcomes with parents, clinicians therefore should make it clear that (1) wheezing is very common in the first few years of life, (2) there is a good chance that wheeze will resolve by school age and only a minority of affected children will become lifelong asthmatics, and (3) there is an increased chance of exhibiting ongoing asthma symptoms at school age if wheeze continues beyond 3 years of age, and particularly if it is associated with allergies, although accurate prediction of outcome is not possible.

As the pattern of wheeze changes over time, the subgroup of children who become persistent or recurrent wheezers needs careful follow-up and treatment (or at least a therapeutic trial) to improve symptoms and reduce the frequency and severity of exacerbations. Importantly, as a group, preschoolers with wheezing (confirmed or suspected asthma) are at an increased risk of attenuated lung function growth,²⁵ and those with more frequent or severe exacerbations appear to be most affected.

ENVIRONMENTAL FACTORS

Exposure to air pollution is associated with an increased risk of developing preschool wheeze. A longitudinal study of US children found that increased exposure to traffic-derived pollution at birth was associated with both preschool wheeze that subsequently resolved by 7 years (transient) and with wheeze that continued to 7 years (persistent).²⁶ In this study, exposure to traffic-derived air pollution from birth to 1 year of age and from 1 to 2 years of age were both associated with persistent wheeze.²⁶ There is emerging evidence that prenatal exposure to chemicals, especially bisphenol A and phthalates, increases risk of preschool asthma. For example, a recent study reported that metabolites of these compounds in the urine of pregnant Spanish women are associated with increased risk of wheeze in their offspring during the first 4 years of life.²⁷

CLINICAL PATTERNS OF WHEEZE

There have been several attempts to classify preschool asthma by pattern of symptoms, with a view to better targeting treatment (e.g., intermittent treatment for episodic symptoms). A classification suggested by a European Respiratory Society Task Force is to divide children into those with multiple-trigger wheeze, defined as episodes of wheeze associated with one or more triggers (including but not limited to URTIs and interval symptoms), versus those with episodic wheeze, defined as discrete episodes of wheeze (usually triggered solely by URTI) but without interval symptoms.²⁸ In cross-sectional surveys, episodic wheeze predominates in children younger than 3 years old.^{1,29,30} Whether wheeze patterns are clinically useful remains unclear, as these are unstable over time in the same child, and there is a high variation in the categorization of patterns between pediatricians.^{29,31}

Pathology

Increased bronchial airway smooth muscle (ASM), subepithelial eosinophilia, and increased reticular basement membrane thickening (a pattern found in adult atopic asthma) are reported in a highly selected group of preschool children with severe recurrent wheeze.³² Furthermore, increased ASM, but not the latter two features, was associated with an increased risk of having ongoing asthma at school age.³³ There are no reported data from bronchial biopsies in children with less severe disease. However, transient increases in urinary cysteinyl leukotriene metabolites and urinary eosinophil activation markers are reported during acute wheeze^{34,35}—whether these indirect markers reflect airway inflammation is unclear.

Treatment

Compatible with the management objectives for older children and adults, the goals of children presenting with preschool asthma are to achieve good control of symptoms, maintain normal activity levels, and minimize future risk—that is, the prevention of future exacerbations, impaired lung growth and function, and side effects.³⁶ A diagnosis, at least a presumptive one, is essential to achieve this goal, as treatment varies according to the condition. In reviewing the treatment of preschool asthma, this chapter focuses on children who wheeze after 1 year of age and those younger than 1 year with recurrent wheeze. Treatment recommendations do not apply to infants less than 1 year presenting with a first episode of wheezing where bronchiolitis is suspected. The management of preschool wheeze and asthma includes both non-pharmacological and pharmacologic approaches.

TREATMENT—NONPHARMACOLOGICAL

All preschool children with suspected or confirmed asthma should have preschool asthma education, with an explanation of the condition, the role of relief and controller medication, and adequate inhalation technique.¹¹ They should be provided with a self-management plan with written instructions on how to achieve and maintain asthma control (“green zone”), how to manage deterioration (“yellow zone”), and when to consult the physician in case of an asthma attack (“red zone”). While shown effective in all age groups,³⁷ the only randomized trial that tested an educational guided self-management approach exclusively in preschoolers did not show a significant difference from usual care.³⁸ However, the authors recognized substantial contamination between groups, with close to half of control patients recalling that they received the same verbal instructions as those in the intervention; further, they acknowledged the absence of documented effectiveness of their recommended intervention—namely preemptive home administration of oral steroids in viral-induced wheezing. Given these study limitations, asthma self-management education remains indicated in preschoolers.¹¹

Avoidance of exposure to cigarette smoke and other irritants, and if sensitized, to aeroallergens, should be recommended. Although respiratory illnesses are the most frequent triggers, there is currently no proven, effective approach to avoid the common cold, other than reduced exposure to infected individuals. This is a difficult task when children are placed in childcare during the first years of life or in the presence of numerous siblings.

TREATMENT—PHARMACOLOGICAL

Challenge to Personalizing Therapy

Despite the worldwide move toward personalized medicine, most, if not all, preschool trials have failed to show convincing evidence that a particular approach is more beneficial for some children than others. Specifically, there is little evidence that children with positive and negative asthma predictive scores respond differently to therapeutic approaches.^{39,40} This is probably due in part to poor stability of these

phenotypes within the same child over time and high between-physician variability.^{29,31} Clearly, significant progress in personalized medicine hinges on the future identification of accurate, precise, and reproducible determinants of response, such as preschool lung function, inflammatory markers, genotype, metabolomics, and other “omics” obtainable in preschool children. Stratification on these determinants must then be proven to be associated with differential treatment response, in randomized clinical trials.

Until then, the therapy shown most effective for the majority of preschoolers with asthma in a rigorously designed trial should dictate the best management. The therapeutic section of this chapter is informed by a literature search that identified systematic reviews of randomized controlled trials and randomized controlled trials of children aged 1–5 years described as having preschool wheeze and/or asthma; trials related to wheeze arising from alternative diagnoses (as discussed previously) were specifically excluded whenever feasible. The pharmacological approach is presented by sections corresponding to the “green zone” (maintaining control) and “yellow zone” (managing deterioration) of a self-management plan and for the initial management of an exacerbation in the acute care setting.

Preventive Management—“Green Zone”

The evidence supporting therapy in preschool children is derived from randomized controlled trials and systematic reviews of trials, which included children with either asthma or preschool wheezing with specific or a variety of wheezing phenotypes (Fig. 44.2).

Daily Preventive Monotherapy

All identified trials pertained to the use of ICS or montelukast, as the leukotriene receptor antagonist (LTRA). With regard to first-line monotherapy, clearly the strongest evidence relates to the use of daily ICS. In a meta-analysis of children with preschool wheeze and asthma by Castro-Rodriguez and Rodrigo,⁴¹ daily ICS was associated with a 41% reduction in the risk of exacerbations of all severity (RR 0.59, 95% CI 0.52–0.67), risk of withdrawals due to exacerbations (RR 0.52, 95% CI 0.43–0.63), symptoms (standardized mean difference [SMD] 0.93, 95% CI 0.49–1.37), and β_2 -agonist use (SMD 0.63, 95% CI 0.30–0.63), and with a significant improvement in forced expiratory volume in one second (FEV₁) (weighted mean difference [WMD] 0.06L, 95% CI 0.05–0.09). A second meta-analysis of trials not included in the Castro-Rodriguez and Rodrigo review (noted previously) done by Ducharme et al⁴² pertained to a mixed population of preschoolers with or without atopy (or a positive API); again, daily ICS was found to reduce the risk of moderate exacerbations (i.e., exacerbations needing rescue OCS) by more than 40%, compared with placebo (RR 0.57, 95% CI 0.40–0.80) and was associated with a significantly greater percentage of asthma-free days (mean difference [MD] 5.52 days, 95% CI 2.22–8.81). However, daily ICS therapy is not curative and must be sustained to maintain benefit. For example, during the 1-year period after the cessation of ICS in the Prevention of Early Asthma in Kids (PEAK) trial, there was a similar frequency of symptoms in ICS- and placebo-treated children.⁴³

Only two pediatric trials have compared daily LTRAs to placebo in preschoolers. While daily montelukast was

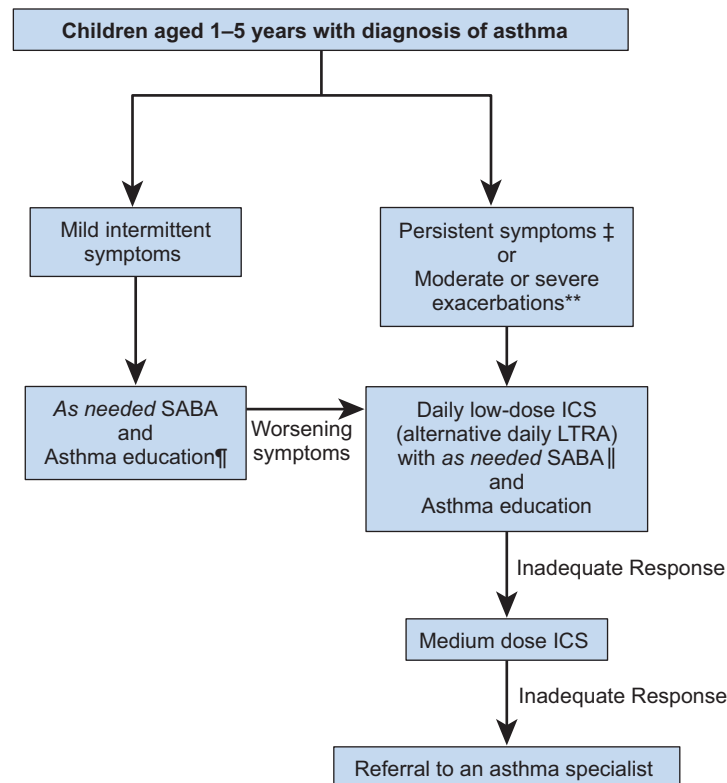


Fig. 44.2 Diagnostic algorithm for treatment of wheeze in preschool children (1–5 years of age). ICS, Inhaled corticosteroids; OCS, oral corticosteroids; SABA, inhaled short-acting β_2 -agonists. ¶, Asthma education including environmental control and a written self-management plan; ‡, eight or more (≥ 8) days/month with symptoms, ≥ 8 days/month with use of SABA, ≥ 1 night awakening due to symptoms/month, any exercise limitation/month or any absence from usual activities to asthma symptoms; **, episodes requiring rescue oral corticosteroids or hospital admission; ||, ICS are more effective than LTRA. (Figure adapted from Ducharme FM, Dell SD, Radhakrishnan D, et al. Diagnosis and management of asthma in preschoolers: a Canadian Thoracic Society and Canadian Paediatric Society position paper. *Can Respir J Vol.* 2015;22:135-143 and reproduced with permission).

associated with a reduction in the number of overall exacerbations in one trial,⁴⁴ it was not associated with a reduction in exacerbations requiring rescue oral steroids,⁴⁴ or in asthma-free days.^{44,45} When data were reanalyzed after including only children with an apparent episodic (viral-triggered) wheeze or episodic asthma phenotype, no statistically significant group reduction in the number of episodes requiring rescue OCS was associated with daily montelukast versus placebo (OR 1.20, 95% CI; 0.70–2.06).⁴⁶

What Is the Best Preventive Strategy for Specific Wheezy Children?

In the absence of head-to-head trials comparing daily ICS to daily montelukast, the best strategy may only be gauged at present by the size of the effect of each monotherapy compared with placebo. Children showed a greater magnitude of response with ICS than with montelukast. Compared with placebo, potential markers of the best ICS responders were explored. A subgroup analysis of the systematic review by Castro-Rodriguez and Rodrigo⁴¹ suggested a stronger effect for reducing exacerbations in children with a clinical diagnosis of asthma than in those with wheezing (RR 0.50 vs. 0.65, $P = .04$), with no apparent effect of other patient characteristics such as age, atopy, or treatment characteristics such as specific ICS, delivery mode, or duration of therapy.

In contrast, in a post hoc analysis of the PEAK trial, preschoolers with a health care utilization in the preceding year, those with aeroallergen sensitization, boys, and Caucasians were better responders to ICS compared with placebo.⁴⁷ These apparent conflicting determinants attest to the need for replication.

In the future, the identification of consistent and strong determinants of response is needed to better identify responders, with a confirmatory trial of different therapies, stratified on the presence/absence of determinants (as noted previously) to validate their discriminative ability, will be required. Until then, given the strength of the evidence supporting ICS as opposed to LTRA over placebo, the preferred daily monotherapy should be ICS.

Adjunct Therapy

To date, there are no published trials exploring adjunct therapy to ICS in this age group.⁴⁸

In summary, the best daily management for preschoolers with repeated wheezing episodes or persistent symptoms is daily low-dose ICS, although it appears slightly more effective in those with a clinical diagnosis of asthma than yet undiagnosed children (i.e., preschool wheezers). The evidence for montelukast is less compelling, partly because of the paucity of trials and apparent lesser efficacy. In view of the difficulty in the recognition of specific phenotypes, initiation of therapy with

daily ICS in any child with clinically significant symptoms is reasonable.

Preemptive Therapy—Yellow Zone

For children with apparent episodic asthma, another approach is the preemptive initiation of an asthma controller when exposed to a known trigger or at the onset of an exacerbation (i.e., intermittent therapy). Preemptive management refers to the initiation of therapy by parents at the onset of an exacerbation. Short-acting β 2-agonists are effective in children aged 1 year and over, and should be the first-line relief medication in the yellow zone of the self-management plan.⁴⁹ Preemptive administration of ICS, LTRA, and OCS has been formally tested in the context of randomized controlled trials and summarized in systematic reviews.^{42,48}

Preemptive Inhaled Corticosteroids

Six trials, identified by systematic review, compared preemptive ICS to placebo in children less than 6 years. With the exception of one trial in infants and toddlers using 400 μ g/day of nebulized budesonide,⁵⁰ all trials used a high-dose ICS over 5–10 days (i.e., 1500 μ g/day or greater of budesonide or beclomethasone in hydrofluoroalkane [HFA] equivalent).⁴² Preemptive low-moderate ICS dose was not effective in preschoolers with mild episodic viral wheeze/asthma.⁵⁰ In children with moderate-to-severe viral induced episodic asthma, preemptive high-dose ICS significantly reduced the risk of exacerbations requiring rescue OCS by more than 30% (RR 0.68 [95% CI; 0.53–0.86]; Fig. 44.3A), but was not

associated with a significant group difference in the proportion of asthma-free days.⁴² Although children with moderate to severe URTI/viral-induced asthma respond to preemptive high-dose ICS, this approach has not been tested in head-to-head comparisons with other groups of children, including those with mild viral-induced asthma and those with persistent asthma, so a clear phenotype-specific response remains to be confirmed.

Preemptive Leukotriene Receptor Antagonists

In three placebo-controlled trials,^{40,45,51} the effect of preemptive montelukast (4 mg) was not significantly different from that of placebo for preventing exacerbations requiring rescue OCS (OR 0.77, 95% CI; 0.48–1.25), or reducing asthma-free days.⁴² When limited to a subgroup of children with only viral-induced wheezing derived from a single study,⁵² there was no significant effect on exacerbations requiring rescue oral steroids, although a small but statistically significant reduction was observed in unscheduled medical attendances due to wheeze (RR 0.83, 95% CI; 0.71–0.98).⁴⁶ With only one 3-arm placebo-controlled trial⁴⁰ comparing preemptive LTRA to preemptive high-dose ICS in preschoolers with moderate-to-severe intermittent wheezing, neither was associated with less rescue OCS or more episode-free days.

Preemptive Oral Corticosteroids

OCS initiated by parents at the onset of URTI symptoms, or after not responding to a first dose of bronchodilator, were tested in two trials of children aged 1–5 years with

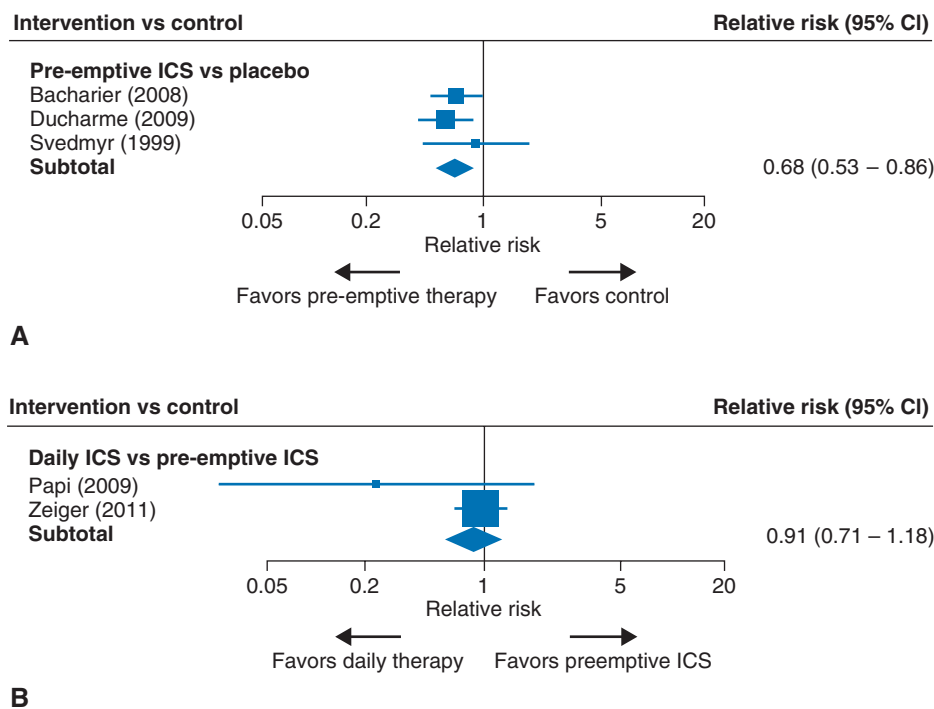


Fig. 44.3 (A) Comparison of preemptive inhaled corticosteroids (ICS) with preemptive placebo. In preschool children with moderate-to-severe viral induced episodic asthma, preemptive high-dose ICS reduced the risk of exacerbations requiring rescue oral corticosteroids. In these studies, prescription of oral steroids is used as a marker for clinically severe wheeze. (B) Comparison of daily ICS with preemptive high-dose ICS. Results are described as pooled relative risk of preschool children with wheeze or asthma experiencing exacerbations treated with rescue oral corticosteroids. The wide confidence interval underlines the lack of power to draw firm conclusions about the relative efficacy of daily low-dose ICS versus preemptive high-dose ICS. (Figure adapted from Ducharme FM, Tse SM, Chauhan B. Diagnosis, management, and prognosis of preschool wheeze. *Lancet*. 2014;383:1593-1604 and reproduced with permission).

recurrent viral-induced wheeze.^{53,54} There was no statistically significant group difference with regard to symptoms, emergency department visits, or hospital admission. The absence of a benefit of preemptive OCS on symptoms during episodes was subsequently confirmed by a post hoc analysis of two randomized controlled trials testing other preemptive strategies.⁵⁵

Step-Up of Daily Therapy Dose at the Onset of an Exacerbation

There are no identified trials with preschoolers on daily ICS exploring the strategy of increasing the ICS dose at the onset of an exacerbation compared with maintaining the usual dose. Since no beneficial effect was observed in school-aged children and adults,⁵⁶ this strategy does not appear promising.

Which Preemptive Strategy Is Most Effective?

There are no published trials comparing the use of preemptive OCS with either of the two other strategies. Only one trial compared preemptive nebulized budesonide to preemptive montelukast or placebo: there was no statistically significant group difference, despite a nonsignificant trend favoring ICS over LTRA for rescue oral steroids and symptom-free days.⁴⁰ Consequently, there is insufficient evidence to firmly conclude on the equivalence or superiority of any of these three preemptive options.⁴² However, in view of the absence of a significant effect of preemptive LTRA or OCS on episode-free days, rescue OCS, health care utilization, or symptom severity compared with placebo, the strength of the evidence clearly supporting preemptive high-dose ICS over placebo for reducing exacerbations requiring rescue OCS would support this latter strategy over the former two in preschoolers with episodic moderate to severe viral induced asthma.

Daily Versus Preemptive Asthma Controller: What Is the Best and Safest Approach?

With regard to efficacy, two trials of preschool children with recurrent moderate to severe episodic viral-induced wheeze or asthma, with and without a positive API, compared daily low-dose ICS with preemptive high-dose ICS: there was no statistically significant group difference with regard to the need for rescue OCS (0.91 [0.71–1.18]).⁴² In these two trials, initiation of OCS therapy was used as a marker for clinically severe wheeze. The wide confidence interval (see Fig. 44.3B) underlines the lack of power to draw firm conclusions about the relative efficacy of daily low doses versus preemptive high-doses of ICS.⁴² However, daily ICS trials included a variety of children with interim symptoms, atopy, or recurrent viral-induced asthma, such that this approach appears as the most effective first-line therapy irrespective of apparent phenotype and is recommended as such by most national and international guidelines.^{12,36,57,58} By contrast, preemptive high-dose ICS was tested in younger preschool children with moderate or severe viral-induced wheezing with no or minimal interim symptoms, such that this approach may be best reserved to those with two or more exacerbations requiring an emergency department visit or rescue OCS, who failed to respond to daily ICS.¹² Because of the risk of ICS overuse by parents and physicians, the preemptive high-dose

ICS strategy should be reserved for preschool children who remain poorly controlled, despite good compliance with a medium dose of daily ICS, under the supervision by asthma specialists with close monitoring of potential side effects and follow-up of efficacy.

Safety Profile. Clinical trials conducted in preschoolers have seldom documented potential adverse effects systematically (specifically growth), and impact on adrenal function has been insufficiently studied. Concerning the former, only two trials were identified in a systematic review of randomized controlled trials. In the subgroup of toddlers or infants ($n = 903$), the change in the baseline of height (cm) during 1 year of ICS (MD -0.58 , 95% CI: -0.55 to -0.20 , $P = .003$) was of similar magnitude than that observed in prepubertal school-aged children (MD -0.46 , 95% CI: -0.75 to -0.16 , $P = .004$).⁵⁹ In another trial, daily ciclesonide up to 200 $\mu\text{g}/\text{day}$ for 24 weeks was not linked with any detectable impairment in growth or adrenal function in children less than 6 years.⁶⁰ This systematic review, including mostly prepubertal school-aged children, showed a significant molecule- and dose-dependency in the magnitude of growth suppression associated with ICS.⁵⁹ Compared with placebo, repeated intake of preemptive high-dose ICS has been associated with a group difference of 0.6 cm, equivalent to a 4 percentile point difference in growth,³⁰ analogous to that reported with daily low ICS dose.⁴³ The potential for overuse of preemptive high-dose ICS by both parents and physicians has led to calls for caution in the use of this strategy. In the absence of solid data for preschool children, the selection of the safest molecules and careful monitoring of growth seems to be the most prudent approach for any child receiving daily or preemptive ICS.

TREATMENT—INITIAL MANAGEMENT OF EXACERBATIONS IN THE ACUTE CARE SETTING

As for older children and adults, the initial step is to assess asthma severity and apply severity-specific management. Several signs suggest increasing severity of airflow obstruction, namely accessory muscle use, wheezing, oxygen saturation at or below 92%,¹² decreased air entry, agitation, or apathy.⁶¹ Use of validated standardized clinical scores, such as the 12-point pediatric respiratory assessment measure (PRAM, Fig. 44.4),⁶² has been shown to be effective and practical to apply guidelines and reduced hospital admissions.^{63,64}

Bronchodilators

Short-acting β_2 -agonists are the most effective bronchodilators, with a significant bronchodilator effect documented in children aged 1 year and over.⁴⁹ In a meta-analysis of children aged 1–18 years, with moderate or severe airflow obstruction, the addition of ipratropium bromide to β_2 -agonists has been shown to be superior to β_2 -agonists alone.⁶⁵ The administration of salbutamol by metered dose inhaler with a spacer was more cost-effective and associated with fewer side effects than by nebulizer in young children (1–4 years) with moderate and severe acute asthma.⁶⁶ In these patients, repeating the dose of β_2 -agonists at 20 minutes, the time of peak action, led to better and more sustained bronchodilation.⁶⁷ Supplemental oxygen should be provided for children with hypoxemia.

PRAM scoring table

Criteria	Description	Score	
O ₂ saturation	95%	0	
	92-94%	1	
	< 92%	2	
Suprasternal retraction	Absent	0	
	Present	2	
Scalene muscle contraction	Absent	0	
	Present	2	
Air entry*	Normal	0	
	↓ at the base	1	
	↓ at the apex and the base	2	
	Minimal or absent	3	
Wheezing [§]	Absent	0	
	Expiratory only	1	
	Inspiratory (± expiratory)	2	
	Audible without stethoscope or silent chest (minimal or no air entry)	3	
PRAM score: (max. 12)			
Score	0-3	4-7	8-12
Severity	Mild	Moderate	Severe

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Fig. 44.4 The pediatric respiratory assessment measure (PRAM) scoring table. *, In case of asymmetry, the most severely affected (apex-base) lung field (right or left, anterior or posterior) will determine the rating of the criterion. §, In case of asymmetry, the two most severely affected auscultation zones, irrespective of their location (right upper lobe, right middle lobe, right lower lobe, left upper lobe, left lower lobe), will determine the rating of the criterion. (Reproduced with the permission of Francine M. Ducharme. Reprinted from *The Journal of Pediatrics*, Vol. 137, Issue 6. Chalut DS, Ducharme FM, Davis GM. The Preschool Respiratory Assessment Measure (PRAM): A responsive index of acute asthma severity. Pages 762-768, Copyright © 2000, with permission from Elsevier.)

Oral Corticosteroids

National and international guidelines recommend the addition of OCS in preschoolers with moderate or severe airflow obstruction and in those with poor responses to bronchodilators. This view is consistent with a systematic review of randomized controlled trials, confirming a 25% reduction in hospital admission rate in children treated with systemic corticosteroids compared with placebo in pediatric trials that collectively included about 50% preschoolers⁶⁸; one trial included only preschoolers,⁶⁹ whereas the other four pediatric trials included both preschool and school-aged children.⁷⁰⁻⁷³ The efficacy of OCS was challenged by a 2009 placebo-controlled trial in children aged 10 months to 5 years, with viral-induced wheezing showing no apparent effect on the duration of hospital stay; young age and viral infection were

suspected explanations for the negative findings.⁷⁴ By contrast, a recent cohort study conducted in children aged 1-17 years presenting with a moderate or severe asthma exacerbation and treated with a severity-specific treatment protocol with β 2-agonists, ipratropium bromide, and OCS reported a very low treatment failure rate of 17%.⁷⁵ After adjusting for baseline severity (i.e., PRAM score and oxygen saturation), the presence of symptoms between exacerbations, viral detection, and fever were significant predictors of failure of emergency management. Of note, age was not significantly associated with treatment response. These data suggest that a higher rate of respiratory infections, rather than age, may explain the apparent higher treatment failure observed in preschoolers presenting with acute asthma.

In summary, the evidence specific to preschoolers to support the efficacy of OCS in those with repeated episodes of airflow

obstruction and who meet the criteria for asthma is scarce; consequently, it remains debated whether one should restrict or liberalize its use in preschool children with ongoing wheeze, despite an initial adequate dose of inhaled bronchodilator therapy. By contrast, children who are younger than a year, with a first episode of wheezing, who do not meet the operational definition of asthma (obstruction and reversibility with asthma medication) are unlikely to benefit from OCS, irrespective of severity or setting. In children falling between these two extremes, OCS should be used sparingly and on an individual trial basis only.

Inhaled Corticosteroids

A systematic review of eight randomized controlled trials of children (and an unspecified proportion of preschoolers) presenting to the emergency department with an acute asthma exacerbation concluded that there was a beneficial effect of ICS alone in reducing the rate of hospital admission. Although there was no significant group difference in hospital admission rate between groups, the power was insufficient to conclude regarding the equivalence between ICS versus OCS for preventing hospital admission, relapse, and the need to rescue OCS. Although promising, the evidence is thus insufficient to recommend replacing oral steroids by high-dose ICS therapy (which is also more costly), either in emergency management, or upon discharge from the emergency department.⁷⁶

Magnesium Sulfate

Treatment with intravenous magnesium sulfate showed a significant benefit in children and adults with acute severe asthma, but not in those with milder severity.⁷⁷ Several pediatric trials are ongoing and will help confirm the best route (nebulized vs. intravenous) and indication for magnesium sulfate in children, including preschoolers.

Antibiotics

The observation that bacterial colonization of the hypopharynx is common during episodes of preschool wheeze (discussed previously) led researchers to assess the efficacy of azithromycin. In a randomized placebo controlled trial that recruited infants from the COPSAC cohort, Stokholm et al⁷⁸ found that a course of azithromycin started 3 days into an episode reduced the mean duration of subsequent

troublesome lower respiratory symptoms by about 4 days. Since improvement of symptoms with azithromycin may be due to an improvement in (clinically trivial) bronchitic cough, and not wheeze,⁷⁹ azithromycin cannot be recommended at this time.

FUTURE DIRECTIONS

As most of the airflow obstruction reported by 7 years of age in children with asthma is not attributable to prenatal or perinatal programming, there is a window of opportunity for interventions in the preschool years to prevent early airway remodeling. This may imply finding novel strategies to prevent key triggers such as viral infections, to reduce the frequency and severity of viral-induced exacerbations, and to improve the monitoring of preschool lung function to identify “unrecognized” persistent airway obstruction. Although there are no long-term trials to determine if sustained controller therapy introduced early could prevent lung function impairment in school-aged children with asthma symptoms, it seems prudent to initiate controller therapy early.

Until determinants of a differential response to therapy are identified, the best approach for preschool children with recurrent or chronic wheeze is the administration of daily-ICS at the lowest effective dose. A proven effective alternative for children with moderate and severe viral-induced exacerbations is preemptive high-dose ICS, with safeguards to prevent overuse by parents and physicians. Future advances in objective markers of phenotype would enable major advances in personalized therapy. Trials are needed to clarify the role of adjunct therapy and immunotherapy in this young age group. Meanwhile, careful regular reassessments remain the cornerstone of an appropriate follow-up to ensure an adequate response and enable timely reduction to the minimal effective dose.

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Access the reference list online at ExpertConsult.com.

Suggested Reading

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