

Management approaches to intermittent wheezing in young children

Caroline C. Horner and Leonard B. Bacharier

Purpose of review

To review the recently published studies addressing various treatment approaches for episodic wheezing in young children.

Recent findings

A landmark study demonstrated that short courses of oral corticosteroids initiated at the first sign of an upper respiratory tract infection decreased wheezing episode frequency and severity. Since then, alternative treatment strategies have been investigated. Montelukast decreased short-term daytime cough and delayed exacerbations following hospitalization for respiratory syncytial virus bronchiolitis, and led to fewer exacerbations without decreasing oral corticosteroids use among children with intermittent asthma. Preschool children with frequent wheezing at high risk for asthma receiving daily inhaled corticosteroids experienced lower rates of exacerbations requiring oral corticosteroids. Episodic use of inhaled corticosteroids, initiated at the early signs of an upper respiratory infection, led to modest reduction in symptoms, but not oral corticosteroid use. Among young children with 'preasthma', inhaled corticosteroids initiated after 3 days of wheezing did not affect the frequency or severity of wheezing episodes.

Summary

Evidence for the preferred treatment strategies for intermittent wheezing in young children remains incomplete. Most of the studies represent heterogeneous populations and lack adequate statistical power to evaluate relevant outcomes. Based on the evidence, there is rationale for further investigation of several management strategies, including corticosteroids and/or leukotriene receptor antagonists administered daily or episodically.

Keywords

asthma exacerbation, corticosteroids, leukotriene modifiers, wheezing

Abbreviations

ICS inhaled corticosteroid
OCS oral corticosteroid
URI upper respiratory infection

© 2007 Lippincott Williams & Wilkins
1528-4050

Introduction

Intermittent wheezing, typically with viral illnesses, occurs commonly in young children and is often described as an entity distinct from asthma. Children with episodic wheeze form a heterogeneous group; some have risk factors associated with persistence of wheezing (i.e. persistent wheezers), while others experience a self-limited process (i.e. transient wheezers) [1]. Wheezing with viral upper respiratory infections (URIs) is the most common form of wheezing at all ages [2] and often presents with moderate to severe episodes that lead to use of oral corticosteroids (OCSs) and often hospitalization. Although the current National Asthma Education and Prevention Program classification of mild intermittent asthma may include these children, some physicians propose that this term is unsuitable to describe the severe episodes some children experience. There are no published criteria to differentiate episodic wheezing of varying etiology from intermittent asthma and, therefore, treatment for children is not diagnosis-specific. Multiple sources of variability in this condition, including asthma risk factors and the timing of the intervention, make episodic wheezing difficult to study and render it difficult to compare the findings from different study populations.

Development of effective intervention strategies could have a major influence on the prevention and management of intermittent wheezing [3]. Prevention of viral infections, treating viral infections at the onset of illness with antivirals or inhibiting proinflammatory responses by viruses are potential future strategies for viral-induced wheeze [3]. A collection of studies have addressed the following questions. Do children with intermittent episodes benefit from asthma controller medications either administered regularly or only during illnesses? Which medication is the treatment of choice? What is the most effective time to start episodic treatment: prior to wheezing, at the onset of wheezing or after wheezing has progressed? Currently, there is uncertainty as to the

Curr Opin Allergy Clin Immunol 7:180–184. © 2007 Lippincott Williams & Wilkins.

Department of Pediatrics, Division of Allergy and Pulmonary Medicine, Washington University School of Medicine and St Louis Children's Hospital, St Louis, Missouri, USA

Correspondence to Leonard B. Bacharier, MD, Associate Professor of Pediatrics, Department of Pediatrics, Division of Allergy and Pulmonary Medicine, Washington University School of Medicine, St Louis Children's Hospital, One Children's Place, St Louis, MO 63110, USA
Tel: +1 314 454 2694; fax: +1 314 454 2515;
e-mail: Bacharier_L@kids.wustl.edu

Current Opinion in Allergy and Clinical Immunology 2007, 7:180–184

preferred approach to treatment of these wheezing episodes and whether these episodes can be prevented and/or modified with treatment. This review examines the current evidence addressing the various treatment options for intermittent wheezing in young children (summarized in Table 1).

Treatment with early initiation of oral corticosteroids

Although the use of OCSs is a common clinical practice for moderate/severe asthma exacerbations, there are few studies assessing the effect of early administration of OCSs on the severity of episodic wheezing in children.

Brunette *et al.* [4] examined the early use of OCSs on the progression of wheezing episodes. In a landmark study, 32 children aged 4 years or under at study entry who had four or more severe wheezing attacks induced by URIs per year with two or more hospitalizations were enrolled. In this unblinded, nonrandomized study, both study groups received theophylline and metaproteronol at the first signs of URI and OCSs after the onset of wheezing episodes during the first year. During the second year, 16 children received prednisone (1 mg/kg/day) at the first sign of an URI, which was continued throughout the illness and then tapered. Although the conventional therapy group had a similar number of episodes in both years, the prednisone group experienced significant reductions in the number of episodes (15.4 ± 3.5 vs. 6.8 ± 1.0) and fewer days with wheezing in year 2 (65 ± 12 vs. 23 ± 6). The prednisone group also had fewer emergency department visits (9.3 ± 0.9 vs. 3.6 ± 0.6) and hospitalizations (7.6 ± 2.5 vs. 0.7 ± 0.2) in year 2. This study, although small and unblinded, suggested beneficial effects of OCSs at URI onset in preschool children with viral wheezing. Consistent with these findings, the National Asthma Education and Prevention Program guidelines [5] recommend consideration of OCSs with viral respiratory infection if the patient has a history of severe exacerbations.

In 2003, Oomen *et al.* [6] addressed the role of OCSs in the treatment of episodic wheeze. In total, 217 children aged 1–5 years hospitalized for viral wheeze were stratified based on serum eosinophil cationic protein or eosinophil protein X levels. Participants were randomized to receive prednisolone 20 mg daily for 5 days or placebo ‘at the start of the next episode of viral wheeze’. Viral wheeze was defined as an acute episode of wheeze that arose within 2 days of coryzal upper respiratory symptoms. One hundred and twenty children experienced further episodes of wheeze. Symptom scores and albuterol use did not differ between control and prednisolone-treated groups. There was a trend towards

more frequent admissions in the prednisolone group. Eosinophil strata did not alter the outcomes. The interpretation of these findings is limited by a high dropout rate (more than 50% in the corticosteroid group), a high rate of noncompliance (68% of parents did not give study medication or complete diaries) and low symptom scores during episodes. Furthermore, the imprecise initiation time for treatment likely introduced a variety of treatment starting times, potentially contributing to the absence of a detectable effect.

Differing study designs and study-related limitations are the likely contributors to the contradictory findings in these trials [4,6]. Thus, further well-designed and controlled trials examining OCS use early in illnesses are necessary to fully determine if this currently recommended treatment strategy is effective.

Treatment with leukotriene modifiers

Given the risks and concerns regarding OCS use, alternative treatment strategies have been examined. Since leukotrienes have been identified as effectors in viral respiratory infections, leukotriene modifiers seem a logical treatment option for episodic viral-associated wheezing.

Bisgaard *et al.* [7] examined the efficacy of montelukast in 130 patients aged 3–36 months following hospitalization for acute respiratory syncytial virus bronchiolitis. Participants were randomized to daily montelukast vs. placebo for 28 days in this double-blind study. Patients with a history of asthma or asthma symptoms were excluded. The montelukast group experienced significantly more symptom-free days (22 vs. 4%) than the placebo group during the active treatment period, predominantly due to less daytime cough. Exacerbations, defined as withdrawal due to symptom severity, emergency department visit or hospitalization for respiratory symptoms, occurred in four montelukast patients and 10 placebo patients. Time to exacerbation, defined as study withdrawal or seeking emergency department care or hospitalization for wheezy symptoms, was significantly prolonged in the montelukast group (23 vs. 8 days). Thus, administration of montelukast in patients with acute respiratory syncytial virus infection increased symptom-free days and time to exacerbation over the ensuing month. While these findings suggest that strategies targeting leukotrienes are appropriate in the setting of viral-induced wheezing, the applicability of these findings to other episodic wheezing syndromes is unclear.

In 2005, Bisgaard *et al.* [8] examined the effect of daily montelukast in the PREVIA trial. Participants had a history of intermittent asthma symptoms resulting from URIs, and had absence of symptoms and β -agonist use in a typical week over the prior 3 months. In this multicenter,

Table 1 Summary of clinical trials in the management of intermittent wheezing in childhood

Citation	No. of participants	Age	Population	Intervention	Duration of follow-up	Outcomes
OCs at early signs of illness Brunette <i>et al.</i> [4]	32	≤4 years	≥4 severe wheezing attacks, ≥2 hospitalizations	Addition of prednisone (1 mg/kg/day) vs. conventional therapy at first signs of URI	2 years	↓ no. of wheezing episodes, ↓ days with wheezing
Oomen <i>et al.</i> [6]	217	1–5 years	Hospitalized for viral wheeze	Prednisone 20 mg daily vs. placebo for 5 days at start of next episode	1 year	↔ symptom scores, albuterol use and hospital admissions
Leukotriene receptor antagonists Bisgaard <i>et al.</i> [7]	130	3–36 months	Hospitalized with acute respiratory syncytial virus bronchiolitis	Montelukast vs. placebo for 28 days following hospitalization	28 days	↑ symptom-free days, ↑ time to exacerbation, ↔ ICS use
Bisgaard <i>et al.</i> [8]	549	2–5 years	Intermittent asthma symptoms with URI	Montelukast vs. placebo	48 weeks	↓ episodes/year, ↑ time to first exacerbation, ↓ ICS use, ↔ OCS use
Daily ICSs Wilson <i>et al.</i> [9]	40	8 months to 6 years	Wheezing with viral infections	Budesonide 200 µg b.i.d. vs. placebo	4 months	↔ symptoms, no. of episodes, symptom score and OCS use
Doull <i>et al.</i> [10]	104	7–9 years	Wheezing during URI	Beclomethasone 200 µg b.i.d. vs. placebo	6 months	↔ symptoms, frequency, severity and duration of episodes, ↑ FEV ₁ and PD ₂₀ , ↔ OCS use
Guilbert <i>et al.</i> [11••]	285	2 or 3 years	Recurrent wheeze, at high risk for asthma by modified asthma predictive index	Fluticasone 88 µg b.i.d. vs. placebo	2 years	↑ episode-free days, ↓ rate of exacerbations requiring OCS
ICSs during respiratory tract illnesses Wilson and Silverman [12]	24	1–5 years	Two or more episodes of wheeze in past 3 months	Beclomethasone 750 µg t.i.d. vs. placebo for 5 days at first signs of asthma attack	4 months	↓ symptoms first week, ↔ admissions, ↔ OCS use
Connett and Lenney [13]	25	1–5 years	Two or more episodes of wheeze in past 6 months	Budesonide 800 µg b.i.d. (older children with spacer) or 1600 µg b.i.d. (younger children with spacer and mask) vs. placebo from URI onset until asymptomatic	NA	↓ wheeze first week, ↔ no. treatment days, cough, bronchodilator use and OCS use
Svedmyr <i>et al.</i> [14]	22	3–10 years	Wheeze with URIs	Budesonide 200 µg q.i.d. vs. placebo for 3 days, 200 µg t.i.d. for 3 days, 200 µg b.i.d. for 3 days started at first sign of URI	NA	↑ PEF, ↔ symptom scores
Svedmyr <i>et al.</i> [15]	55	1–3 years	Three or more wheezing episodes with URI and asthma symptoms with last two airway infections	Budesonide 400 µg q.i.d. vs. placebo for 3 days, then 400 µg b.i.d. for 7 days started at first sign of URI	1 year	↓ symptom scores, ↔ emergency department visits, hospitalizations, and OCS use
Bisgaard <i>et al.</i> [16••]	301	1 month	Mothers with asthma; randomized at first wheezing episode	Budesonide 400 µg vs. placebo for 2 weeks initiated after third day of symptoms	3 years	↔ symptom-free days, rescue medication use, episode number, and open-label budesonide use

ICS, inhaled corticosteroid; FEV₁, forced expired volume in 1 s; OCS, oral corticosteroid; PD₂₀, provocative dose of methacholine producing a 20% decline in FEV₁; PEF, peak expiratory flow; URI, upper respiratory infection; NA, not applicable.

double-blind study, 2- to 5-year-old children ($n=549$) were randomized to receive daily montelukast or placebo for 48 weeks. The montelukast group experienced a 31.9% reduction in exacerbations (1.6 vs. 2.3 exacerbations/year) and a 2-month increase in median time to first exacerbation. There was, however, no difference in OCS use between the two groups (0.53 courses/year in the montelukast group vs. 0.64 courses/year in the placebo group, $P=0.37$). A potential limitation of this study was the relatively mild nature of prior episodes (around 67% did not require OCSs in the past year), suggesting that this trial may have studied a population with a relatively low likelihood of response to therapy.

In aggregate, findings from these two studies [7,8] support further investigation of leukotriene receptor antagonists in the management of wheezing in the context of viral infections.

Treatment with daily inhaled corticosteroids

Daily administration of inhaled corticosteroids (ICSs) is the gold standard for treatment of persistent asthma. However, the efficacy of daily ICSs in the prevention of wheezing episodes in children without persistent symptoms is unclear. Clinicians frequently advocate this approach, especially if prior episodes were severe, but evidence supporting this strategy has been sparse.

In 1995, Wilson *et al.* [9] studied daily ICS therapy in patients with a history of wheezing with viral infections and absent or minimal symptoms between episodes. In this double-blind trial, 40 children aged 8 months to 6 years were randomized to budesonide 200 μg b.i.d. via metered dose inhalers or placebo for 4 months. There were no significant differences in symptoms, number of episodes, symptom score per episode, duration of episode or bronchodilator use between the budesonide and placebo groups. In 1997, Doull *et al.* [10] investigated daily ICS administration for episodic wheezing in school-age children. In this double-blind trial, 104 children aged 7–9 years with a history of wheezing during URIs were randomized to beclomethasone 200 μg b.i.d. via metered dose inhalers or placebo for 6 months. Despite an increase in forced expired volume in 1 s and decrease in airway hyperresponsiveness, there were no significant differences in symptoms, frequency, severity or duration of episodes. Limitations of these studies, however, include the small sample sizes and wide ranges of ages studied.

In 2006, the Prevention of Early Asthma in Kids trial [11^{••}] examined the effect of daily ICSs on episode-free days during treatment as a secondary outcome. This large randomized, multicenter, double-blind, parallel-group, placebo-controlled trial enrolled 285 children aged 2–3 years at high risk for asthma based on a positive modified asthma predictive index (includes at least four episodes of

wheezing in the prior year). During the 4-week run-in phase, participants were excluded if they experienced asthma symptoms an average of 4 days or more per week. Participants received fluticasone 88 μg twice daily or placebo for 2 years. All patients were then taken off study medication and observed for year 3. The primary outcome was episode-free days during the observation year. During the 2-year treatment period, the proportion of episode-free days was significantly higher in the fluticasone group than in the placebo group (93.2 vs. 88.4%, $P=0.006$). The fluticasone group experienced a significantly lower rate of exacerbations requiring OCSs than the placebo group (57.4 vs. 89.4 per 100 child-years, $P<0.001$), while there were no significant differences in unscheduled visits to a physician, bronchodilator use or time to first course of systemic corticosteroids. This study provides evidence that daily administration of ICSs to preschool children with frequent wheezing at high risk for asthma, but without evidence of active uncontrolled asthma, can reduce exacerbations requiring OCSs.

Treatment with episodic use of inhaled corticosteroids during respiratory tract illnesses

Given the resistance from parents and physicians to administer ICSs daily to children who appear well the great majority of the time, numerous studies have attempted to address the efficacy of intermittent use of ICSs with mixed results.

Several studies in the 1990s addressed the use of ICSs only with episodes of wheeze [12–15]. These randomized, double-blind, placebo-controlled trials initiated ICSs at the first sign of an acute asthma episode or at the first sign of a URI and continued treatment for 5–10 days. Three studies showed decreased symptom scores in the ICS groups [12,13,15], while a fourth demonstrated increased peak expiratory flow with no difference in symptoms [14]. Two studies showed no difference in hospital admissions or OCS use [12,15]. All of these studies had relatively small sample sizes and were likely inadequately powered to detect an effect on infrequent outcomes, such as OCS use and healthcare utilization. The trends toward symptomatic improvement, however, demonstrated in these studies have prompted further studies investigating this treatment strategy.

More recently, Bisgaard *et al.* [16^{••}] studied 411 infants enrolled at 1 month of age with maternal histories of physician-diagnosed asthma. In total, 301 patients were randomized at the first episode of wheezing to receive either budesonide 400 μg daily via metered dose inhalers and spacer or placebo for 2 weeks during each subsequent wheezing episode. Treatment was initiated after the third day of symptoms. Episodes of wheezing were defined as 3 consecutive days of wheezing symptoms,

which included noisy breathing, breathlessness, shortness of breath and persistent coughing. Daily symptoms and β -agonist use were recorded for 3 years. The proportion of symptom-free days, days without rescue medication, numbers of episodes and treatments with open-label budesonide were similar in the two groups. Respiratory symptoms during episodes were also similar between groups and episodes lasted an average of 10 days in both groups. Atopic dermatitis status did not affect treatment response. The negative findings in this study may be due to failure of treatment initiation in one-third of the retrospectively identified episodes retrieved from diaries and/or initiation of ICSs too late into the episode to influence the course of the episode.

Integrating the literature in this area is difficult, as most of these studies had relatively small study populations, raising the concern that the early studies may have been underpowered and, therefore, at substantial risk for a type II error. Episodic ICS use, however, produces a modest effect on symptoms in many of these studies. A meta-analysis of randomized controlled trials employing ICSs for episodic viral wheeze also concluded that high-dose ICSs used with mild episodes is a partially effective strategy [17]. Timing of initiation, dosage and delivery systems may also influence outcomes of these interventions.

Conclusion

Consensus on a treatment modality for intermittent wheezing remains elusive. In reviewing the current literature, a short course of OCSs added at the first sign of a URI may decrease the number of wheezing episodes, but a recent controlled trial failed to demonstrate efficacy of this strategy. The possible role of leukotriene antagonism is supported by a decrease in symptoms following hospitalization for respiratory syncytial virus and reduction in exacerbations, but not in OCS use, in children with intermittent asthma. While two older studies did not show significant differences in symptoms, frequency, severity, or duration of episodes with daily ICS use, the Prevention of Early Asthma in Kids trial demonstrated that daily ICS reduces symptoms and exacerbations requiring OCSs in young children with recurrent wheeze and risk factors for the persistence of asthma symptoms. Finally, studies of episodic ICS use provide evidence suggesting that this approach may reduce symptoms associated with wheezing episodes.

Clearly, further well-designed and adequately powered studies examining treatment options will be necessary to clarify these important treatment issues. Future trials must incorporate recognition of several key factors, including the possibility that the heterogeneity of different wheezing phenotypes may lead to differential responses to interventions. The duration of treatment,

as well as the timing of treatment initiation, is also likely to be an important factor. The choice of drug and delivery system are integral as well. The mechanisms of episodic wheezing are not well elucidated and current treatments may not effectively target or affect these mechanisms. Further definition of the phenotypes and genotypes, leading to individualized treatment approaches, would likely improve therapy. Ultimately, the definition of different categories of episodic wheezing may help select treatments for individual patterns.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 220).

- 1 Martinez FD. What have we learned from the Tucson Children's Respiratory Study? *Paediatr Respir Rev* 2002; 3:193–197.
 - 2 Wilson NM. Virus infections, wheeze and asthma. *Paediatr Respir Rev* 2003; 4:184–192.
 - 3 Gern JE, Busse WW. Relationship of viral infections to wheezing illnesses and asthma. *Nat Rev Immunol* 2002; 2:132–138.
 - 4 Brunette MG, Lands L, Thibodeau LP. Childhood asthma: prevention of attacks with short-term corticosteroid treatment of upper respiratory tract infection. *Pediatrics* 1988; 81:624–629.
 - 5 National Asthma Education and Prevention Program. Expert panel report 2: guidelines for the diagnosis and management of asthma (publication 97-4051). Bethesda: National Institutes of Health, 1997.
 - 6 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; 362:1433–1438.
 - 7 Bisgaard H. A randomized trial of montelukast in respiratory syncytial virus postbronchiolitis. *Am J Respir Crit Care Med* 2003; 167:379–383.
 - 8 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; 171:315–322.
 - 9 Wilson N, Sloper K, Silverman M. Effect of continuous treatment with topical corticosteroid on episodic viral wheeze in preschool children. *Arch Dis Child* 1995; 72:317–320.
 - 10 Doull IJM, Lampe FC, Smith S, *et al*. Effect of inhaled corticosteroids on episodes of wheezing associated with viral infection in school age children: randomised double blind placebo controlled trial. *BMJ* 1997; 315:858–862.
 - 11 Guilbert TW, Morgan WJ, Zeiger RS, *et al*. Long-term inhaled corticosteroids •• in preschool children at high risk for asthma. *N Engl J Med* 2006; 354:1985–1997.
- This study is a large, multicenter trial that provides evidence for the daily use of ICSs in children with intermittent wheezing at high risk of persistence of asthma symptoms. The proportion of episode-free days was significantly higher and of exacerbations requiring OCSs was significantly lower with ICSs relative to placebo.
- 12 Wilson NM, Silverman M. Treatment of acute, episodic asthma in preschool children using intermittent high dose inhaled steroids at home. *Arch Dis Child* 1990; 65:407–410.
 - 13 Connett G, Lenney W. Prevention of viral induced asthma attacks using inhaled budesonide. *Arch Dis Child* 1993; 68:85–87.
 - 14 Svedmyr J, Nyberg E, Asbrink-Nilsson E, Hedlin G. Intermittent treatment with inhaled steroids for deterioration of asthma due to upper respiratory tract infections. *Acta Paediatr* 1995; 84:884–888.
 - 15 Svedmyr J, Nyberg E, Thunqvist P, *et al*. Prophylactic intermittent treatment with inhaled corticosteroids of asthma exacerbations due to airway infections in toddlers. *Acta Paediatr* 1999; 88:42–47.
 - 16 Bisgaard H, Hermansen MN, Loland L, *et al*. Intermittent inhaled corticosteroids •• in infants with episodic wheezing. *N Engl J Med* 2006; 354:1998–2005.
- This study is a recent study on the use of episodic ICSs for intermittent wheezing showing that treatment with intermittent budesonide following 3 days of wheezing symptoms did not influence symptoms during acute episodes.
- 17 McKean M, Ducharme F. Inhaled steroids for episodic viral wheeze of childhood. *Cochrane Database Syst Rev* 2000; 2:CD001107.