Published in final edited form as:
J Allergy Clin Immunol. 2014 February ; 133(2): 603–604. doi:10.1016/j.jaci.2013.12.001.

Infection-induced wheezing in young children

Avraham Beigelman, MD, MSCI[a] and **Leonard B. Bacharier, MD**[a]

[a]Department of Pediatrics, Washington University and St. Louis Children's Hospital, St. Louis, MO

Clinical vignette

A previously healthy 4-month-old male infant presented to the emergency department (ED) during the month of January for evaluation of respiratory distress. His parents reported that his 6 year-old sister has had a "cold" for the preceding 7 days. Three days prior to the ED visit, the infant developed a runny nose and cough that had worsened over the previous 2 days. On the day of evaluation, the infant developed "difficulty breathing" and diminished oral intake.

The infant was born at full term after an uneventful pregnancy and delivery. He does not have history of eczema. His immunizations were up-to-date. Family history was notable for maternal asthma. His physical exam was remarkable for moderate respiratory distress with subcostal and intercostal retractions. His vital signs were: temperature of 38.3°C, heart rate of 150/min, respiratory rate of 75/min, room air oxygen saturation 89%. His weight and height were both at the 50th percentiles for his age. Crackles and expiratory wheezes were present in all lung fields, but the rest of the physical exam is unremarkable. Chest radiograph showed hyper-inflated lungs with peri-hilar infiltrates. Nasophyaryngeal swab (multiplex PCR for respiratory pathogens) was positive only for Respiratory Syncytial Virus (RSV). He was admitted for management of RSV bronchiolitis, which included: supplemental oxygen for 2 days until his oxygen saturation on room air was higher than 92% and intravenous fluids until his respiratory distress improved and he was able to resume oral feeding. Initially, he was treated with intermittent inhalation of albuterol via nebulization, but this was discontinued for lack of further clinical improvement after albuterol inhalations. His clinical status gradually improved and he was discharged home after 3 days with a recommendation to follow up with his primary care physician.

Over the ensuing year, he experienced 5 discrete episodes of respiratory distress accompanied by wheeze and cough, including one episode leading to emergency department care. These acute episodes lasted approximately a week, and were always in the context of

Corresponding Author: Leonard B. Bacharier, M.D. Division of Allergy, Immunology and Pulmonary Medicine, Department of Pediatrics, Washington University School of Medicine. 660 S. Euclid Ave. Campus Box 8116 St. Louis, MO 63110 Phone (314) 454-2694 Fax (314) 454-2515 bacharier_l@kids.wustl.edu.

viral respiratory tract illnesses (RTIs); he did not experience any respiratory symptoms outside of these episodes. Inhaled albuterol was given during these episodes and provided partial relief of symptoms; he was prescribed oral prednisolone during 3 of these episodes. The parents are asking for advice regarding the management of these acute wheezing episodes.

Review

Overview

Wheezing during early childhood is a common and heterogeneous clinical condition, with approximately 50% of children experiencing at least one wheezing episode before the age of 6 years[1], and with evidence of viral infection in 80-90% of these episodes[1]. In addition to serving as the most common trigger for wheezing episodes, viral RTIs early in life have been associated with the inception of recurrent wheezing and the eventual development of asthma[2]. The presentation of infection-induced wheezing in childhood is influenced by age, previous respiratory tract illnesses, genetic background, sensitization to aeroallergens, environmental factors, and interactions between these factors. Infection-induced wheezing in children represents a spectrum of clinical manifestations that often evolve over time: acute viral bronchiolitis is the prototypical initial manifestation of viral-induced wheezing which is a frequent antecedent to recurrent infection-induced wheezing episodes. Persistent or recurrent wheezing in the setting of viral respiratory tract infections may progress to asthma, which is often accompanied by infection-induced asthma exacerbations. In this review, we will summarize the significance of and treatment recommendations for initial and recurrent infection-induced wheezing presentations; the management of childhood asthma exacerbations has been discussed elsewhere [3].

The inception of recurrent wheezing and asthma: the role of viral bronchiolitis

The term viral bronchiolitis describes the initial episode of viral-induced lower respiratory tract illness (LRTI) in a child younger than 1-2 years. The 2 major respiratory viruses associated with viral bronchiolitis are RSV and human rhinovirus (HRV); however, other viruses including human metapneumovirus and parainfluenza virus have been reported as causative pathogens[2]. RSV bronchiolitis is the leading cause for hospitalization during the winter months among young children in the US, and has a major role in the inception of wheezing and asthma as up to 50% of the children hospitalized for RSV bronchiolitis are diagnosed with asthma during the first 6 years of life[4]. The likelihood of recurrent wheezing or asthma following bronchiolitis is directly associated with the severity of the initial illness, as children who require hospitalization are more likely to have these long-term outcomes compared to children who experience milder cases of bronchiolitis[5, 6]. Moreover, RSV bronchiolitis requiring hospitalization remains a risk factor for asthma at least until the age of 18 years, while the risk following non-hospitalized RSV bronchiolitis may abate by the age of 13 years[2].

Advances in viral detection methodologies have led to the identification of HRV and other viruses as important triggers for acute wheezing illnesses in early life and as antecedents for future asthma. The COAST birth cohort [7] of infants at high risk for allergic diseases and/or

asthma demonstrated that outpatient wheezing illnesses associated with HRV infection during the first 3 years of life was the most significant predictor of asthma at age 6 years. Thus, while RSV and HRV infections early in life are both associated with future asthma, these 2 pathogens may exert their effects on subsequent respiratory tract disease through different pathways which may differ in terms of the severity of the initial illness (hospitalized RSV bronchiolitis vs outpatient HRV-associated wheezing) and/or genetic predispositions (for atopy and/or susceptibility to specific viral infections)[2].

It remains uncertain if severe early life bronchiolitis represents the cause of future asthma by serving as the initial event ('the first hit') in creating airway allergic inflammation, or if it serves as a marker for asthma susceptibility in children with a predisposition for asthma[2]. Two recent reports provide enhanced understanding of this complex relationship. Treatment of late preterm infants with the anti-RSV monoclonal antibody palivizumab during the RSV season resulted in a significant reduction of wheezing days during the first year of life, with effects that persisted following the end of the treatment period, suggesting that the occurrence of RSV bronchiolitis has a major causative role in the pathogenesis of recurrent wheezing[8]. Secondly, among participants of the COAST cohort, sensitization to aeroallergens preceded and served as a significant risk factor for HRV-associated wheezing. In contrast, having HRV-associated wheeze did not increase the risk of developing allergic sensitization, suggesting that at least in this high risk cohort, HRV-induced wheezing was a consequence rather than the cause of atopic tendency[9]. The progression from a single episode of early life viral-induced wheeze to recurrent wheeze is also related to interactions between host genetic background and the virus, since among the COAST cohort, genetic variants in an asthma-associated gene locus on chromosome 17 (17q21) were associated with future asthma diagnosis, but only among children who experienced HRV wheezing in early life [10].

The first episode of infection-induced wheezing in young children: acute management

Despite the conduct of numerous studies examining the efficacy of various asthma-related therapies in acute bronchiolitis, recent evidence-based recommendations favor supportive therapy for viral bronchiolitis, since inhaled bronchodilators, corticosteroids (systemic or inhaled), montelukast, and antibiotics have failed to show consistent and meaningful clinical benefits[11, 12].

Recently, two interventions have been demonstrated to provide clinical benefit among patients with severe bronchiolitis and may become considerations for incorporation into clinical guidelines. The combination of nebulized epinephrine with oral dexamethasone administered in the ED was superior to placebo in preventing hospital admission[13]. However, there was no clinical benefit for either medication given alone, and the effect of the combined intervention became non-statistically significant after adjustment for multiple comparisons, suggesting that the potential benefit of this combination must be confirmed in additional studies before it is recommended for patient care. A recent systematic review concluded that nebulized 3% saline significantly reduced the duration of hospitalization among infants hospitalized with viral bronchiolitis, but was not associated with a reduction in the rate of hospitalization when given in the ED setting [14].

Prevention of subsequent wheezing following an initial episode of infection-induced wheezing in young children

While recurrent wheezing and asthma are frequent sequelae to bronchiolitis, treatment with asthma controller therapy (including corticosteroids and montelukast) during or following bronchiolitis has not been found to be effective in altering the natural history of post-viral bronchiolitis wheezing. One potential exception to this conclusion is a finding derived from a *post hoc* analysis of a study that originally investigated the effect of oral corticosteroid therapy during acute viral bronchiolitis. While OCS treatment was not associated with a protective effect for the development of recurrent wheezing among the study group as a whole, it was associated with a lower likelihood to develop recurrent wheezing over the following year in the subgroup of children hospitalized with HRV, but not RSV, bronchiolitis[15]. This finding must be confirmed in prospective studies before systemic corticosteroids should be recommended as a preventative approach for post-HRV wheezing.

Viral-induced recurrent wheezing in early childhood

Recurrent wheezing among preschool children is a heterogeneous disorder with multiple phenotypes, and identification of these phenotypes might assist in predicting the progression to asthma in childhood, and potentially in predicting treatment response. Commonly, preschool children experience the majority of their wheezing activity during acute episodes triggered by viral URI (typically HRV) while experiencing minimal-to-no symptoms between these episodes[1]. The terms episodic viral wheeze and severe intermittent wheezing have been proposed to describe the phenotype of children who wheeze exclusively during viral infections. In contrast, the term multiple-trigger wheeze has been suggested for children who wheeze when exposed to multiple triggers (including allergens, exercise, and viruses) rather than with viral infections only. However, the classification of episodic and multiple-trigger wheeze appear to be unstable over time, since many children will commonly switch between these two categories[3]. Most of the children who wheeze during early life do not continue to wheeze at school age[3] . Models which include indicators of subsequent asthma risk have been developed to help the clinician identify children at greatest risk for continued wheezing (and presumably asthma) into older childhood. One of these models is the modified Asthma Predictive Index (mAPI) that includes a combination of risk factors in addition to recurrent wheezing: parental history of asthma, personal history of atopic dermatitis, allergic sensitization to inhalant or food allergens, peripheral blood eosinophilia, and wheezing not related to a cold. The clinical utility of identifying children at high risk for recurrent wheezing using the mAPI is supported by a study demonstrating significantly fewer wheezing exacerbations requiring oral corticosteroids among children with positive mAPIs receiving daily low dose ICS compared to placebo[3]. A detailed assessment of the relative benefits of daily controller therapy regimens (which may include ICS and/or montelukast) for the prevention of recurrent wheezing episodes is beyond the scope of this review and is discussed elsewhere [3]

Acute management of recurrent viral-induced wheezing episodes in children

As in bronchiolitis, the management of acute viral-associated wheezing illnesses in young children has traditionally consisted of asthma medications as inhaled bronchodilators,

corticosteroids (systemic or inhaled), and/or montelukast[1]. Inhaled β2-agonists are recommended for short-term relief of acute wheezing symptoms [16], although the efficacy of this approach during confirmed viral-induced wheezing episodes has not been studied outside of the context of viral bronchiolitis. Intermittent montelukast given at the first sign of URI has not been effective in preventing the progression to severe exacerbation requiring OCS[17] but has been associated with attenuation of clinical severity of the acute episodes measured by symptom severity[17] and heath care utilization[18], and is a recommended approach by the ERS for episodic viral wheeze[16]. The beneficial effects of intermittent montelukast on symptomatology during acute RTIs in this wheezing phenotype have been demonstrated among children with positive modified-APIs[17], further emphasizing the need to customize treatment according to disease phenotype.

Given the episodic nature of this condition, the role of intermittent high dose ICS therapy among children with recurrent, but not persistent, wheezing has been a topic of recent research. Intermittent high dose fluticasone propionate (750 mcg BID) beginning at the onset of an URI among preschool children with histories of recurrent wheezing triggered by viral infections was associated with a 50% reduction in the rate of exacerbations requiring OCS[19]. However, the clinical applicability of this specific approach was limited by significantly smaller gains in height and weight among patients treated with this specific high dose ICS regimen[19]. In preschool children with episodic wheeze and positive modified-API, intermittent high dose ICS treatment (budesonide 1mg BID for 7 days), when started at the earliest signs of an RTI was comparable to daily low dose ICS (budesonide 0.5mg once daily) in prevention of progression from early RTI symptoms to severe exacerbation requiring OCS[20]. Taken together, these studies suggest that intermittent treatment with high dose ICS or montelukast may have a role early in the manifestations during acute wheezing episodes in preschool children, particular those with asthma risk factors (i.e. positive mAPI). However, additional studies are required to maximize the efficacy of these treatments, to prevent side effects, and to identify the children who will benefit the most from these treatments.

OCS are recommended as a treatment for acute asthma exacerbations by asthma guidelines[21]. However, despite the substantial body of evidence supporting the efficacy of this treatment for asthma exacerbations among school-aged children and adolescents, evidence supporting the benefits of OCS for viral-induce wheeze among preschool-aged children is very limited[22]. A recent large placebo controlled clinical trial investigated the efficacy of OCS among 700 preschool children hospitalized with clinically suspected (but not confirmed) viral-induced wheeze[23]. This study did not show a significant difference in the duration of hospitalization or in the rate of symptom resolution following discharge among children treated with OCS vs placebo[23], nor was there a difference in OCS response among those with asthma risk factors. A recent *post-hoc* analysis in two independent outpatient cohorts of preschool children with episodic wheeze, including more than 1500 RTIs, also revealed that OCS did not reduce symptom severity during these episodes[24]. The lack of OCS response among preschool children with viral-induced wheezing might be related the heterogeneity of wheezing phenotypes in early life and/or a lesser extent of eosinophilic airway inflammation, which is steroid responsive, among most of these young

children. These studies and accompanying editorials suggest reconsideration of OCS use in preschool viral-associated wheeze, with added consideration of avoidance using OCS for outpatient wheezing illnesses while reserving this treatment to the seriously ill hospitalized children[22, 25]. Additional prospective randomized controlled trials are required in confirm this finding in outpatient episodes before abandoning this longstanding therapy.

The Case Revisited

The patient has history of severe RSV bronchiolitis in infancy, which is a known independent risk factor for subsequent wheezing episodes and eventually asthma. Indeed, over the year following the initial RSV bronchiolitis the patient experienced multiple discrete episodes of respiratory distress accompanied by wheeze and cough that were triggered by viral illness. Although the patient experienced significant morbidity during these LRTI, he did not have respiratory symptoms outside of these episodes. The parents were advised that inhaled albuterol should be provided for short-term relief of these acute respiratory symptoms. In addition, early intermittent treatment with high dose ICS or oral montelukast could be given to reduce clinical symptoms during these acute illnesses given the patient's high likelihood of response to this approach based on his positive modified-API index (maternal history of asthma). The parents were informed that recent studies and expert opinions questioned the beneficial effects of oral corticosteroids. Based upon this uncertainty, the decision whether to start OCS treatment should be determined by the severity of symptoms during future episodes, as well as considering not using OCS during milder episodes that do not require inpatient care. The current data and recommendations regarding the acute management of infection induced wheezing in young children are summarized in Table 1.

This case highlights many of aspects associated with the complex interaction between respiratory viral infections early in life and asthma. Viral infections are the dominant trigger of wheezing illnesses during early childhood. Despite the remarkably high prevalence of these illnesses and their attendant morbidity, the optimal treatment strategies remain undefined for management of acute episodes and prevention of recurrent episodes. Future research should focus on expanding the currently limited evidence base for decision-making in these clinical situations.

Acknowledgments

Source of funding: Supported in part by the Washington University Institute of Clinical and Translational Sciences grant UL1 TR000448 from the National Center for Advancing Translational Sciences- sub award KL2 TR000450

References

1. Bacharier LB. Viral-induced wheezing episodes in preschool children: approaches to therapy. Curr Opin Pulm Med. 2010; 16:31–5. [PubMed: 19816178]
2. Beigelman A, Bacharier LB. The role of early life viral bronchiolitis in the inception of asthma. Curr Opin Allergy Clin Immunol. 2013; 13:211–6. [PubMed: 23385289]
3. Bacharier LB, Guilbert TW. Diagnosis and management of early asthma in preschool-aged children. J Allergy Clin Immunol. 2012; 130:287–96. quiz 97-8. [PubMed: 22664162]

4. Bacharier LB, Cohen R, Schweiger T, Yin-Declue H, Christie C, Zheng J, et al. Determinants of asthma after severe respiratory syncytial virus bronchiolitis. J Allergy Clin Immunol. 2012; 130:91–100. e3. [PubMed: 22444510]
5. Escobar GJ, Masaquel AS, Li SX, Walsh EM, Kipnis P. Persistent recurring wheezing in the fifth year of life after laboratory-confirmed, medically attended respiratory syncytial virus infection in infancy. BMC Pediatr. 2013; 13:97. [PubMed: 23782528]
6. Carroll KN, Wu P, Gebretsadik T, Griffin MR, Dupont WD, Mitchel EF, et al. The severity-dependent relationship of infant bronchiolitis on the risk and morbidity of early childhood asthma. J Allergy Clin Immunol. 2009; 123:1055–61. 61, e1. [PubMed: 19361850]
7. Lemanske RF Jr. The childhood origins of asthma (COAST) study. Pediatr Allergy Immunol. 2002; 13(Suppl 15):38–43. [PubMed: 12688623]
8. Blanken MO, Rovers MM, Molenaar JM, Winkler-Seinstra PL, Meijer A, Kimpen JL, et al. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. N Engl J Med. 2013; 368:1791–9. [PubMed: 23656644]
9. Jackson DJ, Evans MD, Gangnon RE, Tisler CJ, Pappas TE, Lee WM, et al. Evidence for a causal relationship between allergic sensitization and rhinovirus wheezing in early life. Am J Respir Crit Care Med. 2012; 185:281–5. [PubMed: 21960534]
10. Caliskan M, Bochkov YA, Kreiner-Moller E, Bonnelykke K, Stein MM, Du G, et al. Rhinovirus wheezing illness and genetic risk of childhood-onset asthma. N Engl J Med. 2013; 368:1398–407. [PubMed: 23534543]
11. Diagnosis and management of bronchiolitis. Pediatrics. 2006; 118:1774–93. [PubMed: 17015575]
12. Wainwright C. Acute viral bronchiolitis in children- a very common condition with few therapeutic options. Paediatr Respir Rev. 2010; 11:39–45. quiz. [PubMed: 20113991]
13. Plint AC, Johnson DW, Patel H, Wiebe N, Correll R, Brant R, et al. Epinephrine and dexamethasone in children with bronchiolitis. N Engl J Med. 2009; 360:2079–89. [PubMed: 19439742]
14. Zhang L, Mendoza-Sassi RA, Wainwright C, Klassen TP. Nebulised hypertonic saline solution for acute bronchiolitis in infants. Cochrane Database Syst Rev. 2013; 7:CD006458. [PubMed: 23900970]
15. Lehtinen P, Ruohola A, Vanto T, Vuorinen T, Ruuskanen O, Jartti T. Prednisolone reduces recurrent wheezing after a first wheezing episode associated with rhinovirus infection or eczema. J Allergy Clin Immunol. 2007; 119:570–5. [PubMed: 17196244]
16. Brand PL, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A, et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. Eur Respir J. 2008; 32:1096–110. [PubMed: 18827155]
17. Bacharier LB, Phillips BR, Zeiger RS, Szefler SJ, Martinez FD, Lemanske RF Jr. 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; 122:1127–35. e8. [PubMed: 18973936]
18. Robertson CF, Price D, Henry R, Mellis C, Glasgow N, Fitzgerald D, et al. Short Course Montelukast for Intermittent Asthma in Children: a Randomised Controlled Trial. Am J Respir Crit Care Med. 2007; 175:323–9. [PubMed: 17110643]
19. Ducharme FM, Lemire C, Noya FJ, Davis GM, Alos N, Leblond H, et al. Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. N Engl J Med. 2009; 360:339–53. [PubMed: 19164187]
20. Zeiger RS, Mauger D, Bacharier LB, Guilbert TW, Martinez FD, Lemanske RF Jr. et al. Daily or intermittent budesonide in preschool children with recurrent wheezing. N Engl J Med. 2011; 365:1990–2001. [PubMed: 22111718]
21. National Asthma Education and Prevention Program. Expert Panel Report III: Guidelines for the diagnosis and management of asthma. US Department of Health and Human Services; Bethesda, MD: 2007.
22. Grigg J. Role of systemic steroids in acute preschool wheeze. Arch Dis Child. 2010; 95:491–2. [PubMed: 20371589]

23. Panickar J, Lakhanpaul M, Lambert PC, Kenia P, Stephenson T, Smyth A, et al. Oral prednisolone for preschool children with acute virus-induced wheezing. N Engl J Med. 2009; 360:329–38. [PubMed: 19164186]
24. Beigelman A, King TS, Mauger D, Zeiger RS, Strunk RC, Kelly HW, 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; 131:1518–25. [PubMed: 23498594]
25. Bush A. Practice imperfect--treatment for wheezing in preschoolers. N Engl J Med. 2009; 360:409–10. [PubMed: 19164192]
26. Bush A, Thomson AH. Acute bronchiolitis. BMJ. 2007; 335:1037–41. [PubMed: 18007004]
27. Gadomski AM, Brower M. Bronchodilators for bronchiolitis. Cochrane Database Syst Rev. 2010:CD001266. [PubMed: 21154348]
28. Corneli HM, Zorc JJ, Mahajan P, Shaw KN, Holubkov R, Reeves SD, et al. A multicenter, randomized, controlled trial of dexamethasone for bronchiolitis. N Engl J Med. 2007; 357:331–9. [PubMed: 17652648]

References

1. Beigelman A, Bacharier LB. The role of early life viral bronchiolitis in the inception of asthma. Curr Opin Allergy Clin Immunol. 2013; 13:211–6. [PubMed: 23385289]
2. Diagnosis and management of bronchiolitis. Pediatrics. 2006; 118:1774–93. [PubMed: 17015575]
3. Wainwright C. Acute viral bronchiolitis in children- a very common condition with few therapeutic options. Paediatr Respir Rev. 2010; 11:39–45. quiz. [PubMed: 20113991]
4. Bacharier LB, Phillips BR, Zeiger RS, Szefler SJ, Martinez FD, Lemanske RF Jr. 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; 122:1127–35. e8. [PubMed: 18973936]
5. Robertson CF, Price D, Henry R, Mellis C, Glasgow N, Fitzgerald D, et al. Short Course Montelukast for Intermittent Asthma in Children: a Randomised Controlled Trial. Am J Respir Crit Care Med. 2007; 175:323–9. [PubMed: 17110643]
6. Brand PL, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A, et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. Eur Respir J. 2008; 32:1096–110. [PubMed: 18827155]
7. Ducharme FM, Lemire C, Noya FJ, Davis GM, Alos N, Leblond H, et al. Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. N Engl J Med. 2009; 360:339–53. [PubMed: 19164187]
8. Zeiger RS, Mauger D, Bacharier LB, Guilbert TW, Martinez FD, Lemanske RF Jr. et al. Daily or intermittent budesonide in preschool children with recurrent wheezing. N Engl J Med. 2011; 365:1990–2001. [PubMed: 22111718]
9. Global Initiative for Asthma (GINA). 2011. Available from http://www.ginasthma.org
10. National Asthma Education and Prevention Program. Expert Panel Report III: Guidelines for the diagnosis and management of asthma. US Department of Health and Human Services; Bethesda, MD: 2007.
11. Rowe BH, Spooner C, Ducharme FM, Bretzlaff JA, Bota GW. Early emergency department treatment of acute asthma with systemic corticosteroids. Cochrane database of systematic reviews. 2001:CD002178. [PubMed: 11279756]
12. Rowe BH, Edmonds ML, Spooner CH, Diner B, Camargo CA Jr. Corticosteroid therapy for acute asthma. Respiratory medicine. 2004; 98:275–84. [PubMed: 15072167]
13. Rachelefsky G. Treating exacerbations of asthma in children: the role of systemic corticosteroids. Pediatrics. 2003; 112:382–97. [PubMed: 12897291]
14. Rowe BH, Spooner CH, Ducharme FM, Bretzlaff JA, Bota GW. Corticosteroids for preventing relapse following acute exacerbations of asthma. Cochrane Database Syst Rev. 2007:CD000195. [PubMed: 17636617]
15. Tal A, Levy N, Bearman JE. Methylprednisolone therapy for acute asthma in infants and toddlers: a controlled clinical trial. Pediatrics. 1990; 86:350–6. [PubMed: 2201941]

16. Panickar J, Lakhanpaul M, Lambert PC, Kenia P, Stephenson T, Smyth A, et al. Oral prednisolone for preschool children with acute virus-induced wheezing. N Engl J Med. 2009; 360:329–38. [PubMed: 19164186]

17. Beigelman A, King TS, Mauger D, Zeiger RS, Strunk RC, Kelly HW, 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; 131:1518–25. [PubMed: 23498594]

18. Bush A. Practice imperfect--treatment for wheezing in preschoolers. N Engl J Med. 2009; 360:409–10. [PubMed: 19164192]

19. Grigg J. Role of systemic steroids in acute preschool wheeze. Arch Dis Child. 2010; 95:491–2. [PubMed: 20371589]

Question 1

Which of the following statements best describes the role of early life viral bronchiolitis in the inception of recurrent wheezing and childhood asthma?

1. Early life viral bronchiolitis is rarely followed by a diagnosis of asthma
2. Early life viral bronchiolitis is associated with an increased risk for the development of future childhood asthma, but it is not clear if it is the direct cause of asthma
3. All children who have early life viral bronchiolitis will be subsequently diagnosed with asthma
4. Early life viral bronchiolitis is not associated with subsequent recurrent wheezing

Early life viral wheeze is a risk factor for subsequent recurrent wheezing and childhood asthma. However, it remains uncertain if early life viral wheeze represents the cause of future asthma by serving as the initial event (‘the first hit’) in creating a pattern of airway allergic inflammation, or if it serves as a marker for asthma susceptibility in children with a predisposition for asthma. Both basic science and epidemiological research support both of these possibilities, which are not likely to be mutually exclusive[1].

Questions 2

Which of the following viruses are most commonly associated with viral induced wheeze in early childhood:

1. Parainfluenza and Respiratory Syncytial virus
2. Respiratory Syncytial Virus and human rhinovirus
3. Parainfluenza and human rhinovirus
4. Metapneumovirus and Parainfluenza

The 2 major respiratory viruses associated with viral wheeze in early childhood are Respiratory Syncytial virus and human rhinovirus; however, other viruses including human metapneumovirus and parainfluenza virus have been reported as causative pathogens[1].

Question 3

Which one of the following treatments is the most appropriate evidence based recommendation for treatment of an infant hospitalized with viral bronchiolitis?

1. High dose inhaled corticosteroids
2. Systemic corticosteroids
3. Oral montelukast
4. Supportive therapy

Despite the conduct of numerous studies examining the efficacy of various asthma-related therapies in acute bronchiolitis, recent evidence-based recommendations favor supportive therapy for viral bronchiolitis, since inhaled bronchodilators, corticosteroids (systemic or inhaled), montelukast, and antibiotics have failed to show consistent and meaningful clinical benefits[2, 3].

Question 4

Which of the following statements best describes the evidence of efficacy of intermittent montelukast therapy and/or intermittent high dose inhaled corticosteroids (ICS) therapy when given at the first sign of URI in children with history of recurrent viral-induced wheeze?

1. Studies have revealed benefits for intermittent montelukast treatment, but not for high dose intermittent ICS treatment
2. Daily low dose ICS is superior to intermittent high dose ICS treatment at the earliest signs of an RTI for the prevention severe exacerbations requiring oral corticosteroids
3. Neither one of these approaches has been proven as an effective therapy in this clinical scenario
4. Both of these approaches have been shown to provide clinical benefit in terms of episode severity

Intermittent montelukast given at the first sign of URI has not been effective in preventing the progression to severe exacerbation requiring OCS[4] but has been associated with a modest attenuation of clinical severity of the acute episodes[4] and heath care utilization[5], and is a recommended approach by the ERS for episodic viral wheeze[6]. Intermittent high dose fluticasone propionate (750 mcg BID) beginning at the onset of an URI among preschool children with histories of recurrent wheezing triggered by viral infections was associated with a 50% reduction in the rate of exacerbations requiring OCS[7]. However, the clinical applicability of this specific approach and dosing was limited by significantly smaller gains in height and weight among patients treated with this specific high dose ICS regimen[7]. In preschool children with episodic wheeze and positive modified-API, intermittent high dose ICS treatment (budesonide 1mg BID for 7 days), when started at the earliest signs of an RTI was comparable to daily low dose ICS (budesonide 0.5mg once daily) in prevention of progression from early RTI symptoms to severe exacerbation requiring OCS, and both approaches had a similar safety profile[8]. In addition, intermittent montelukast and high dose ICS treatment, when given at the first sign of respiratory tract illness symptoms, have been shown to attenuate respiratory symptoms, most notably among children with positive mAPIs[4].

Question #5

Which of the following statements describe the role of oral corticosteroids (OCS) for the acute management of viral-induce wheezing episodes?

1. There is limited high-quality evidence for the benefits of OCS treatment for viral-induced wheeze among preschool-aged children.
2. Multiple studies have revealed consistent efficacy of OCS treatment for viral-induced wheeze among preschool-aged children.
3. Studies among preschool children hospitalized with viral wheeze showed that OCS treatment compared to placebo resulted in a shorter duration of hospitalization.
4. Oral corticosteroids given to preschool children with outpatient wheezing episodes significantly reduce the duration of illness and risk for hospitalization.

OCS are recommended as a treatment for acute asthma exacerbations by asthma guidelines [9, 10]. Despite substantial evidence for the efficacy of OCS in asthma exacerbations in school-aged children and adolescents [11-14], evidence supporting the efficacy of OCS among in non-hospitalized preschool aged children is limited[15]. Furthermore, a large trial among hospitalized children with presumed viral-induced wheezing failed to demonstrate a reduction in duration of hospitalization among those treated with OCS[16], and a recent post-hoc analysis of two independent outpatient cohorts of preschool children with episodic wheeze, also revealed that OCS did not reduce symptom severity during these episodes[17]. Recent data on the potential lack of efficacy of this traditional intervention have led several authors question the benefit of OCS for wheezing illnesses in this age group[18, 19].

Learning objectives

1. To learn about the significance of viral infections in the inception of wheezing episodes and asthma
2. To review treatment recommendations for the initial episode of viral-induced wheeze in children
3. To review the acute management of recurrent viral-induced wheeze in children

J Allergy Clin Immunol. Author manuscript; available in PMC 2015 February 01.

Table 1

Management of infection induced wheezing in young children

Setting of the wheezing episode	Intervention	Current evidence on the efficacy of the intervention and/or whether the intervention is recommended by clinical guidelines
The first episode of viral-induced wheezing: "viral bronchiolitis"	Supportive treatment including supplemental oxygen	Recommended as a treatment for viral bronchiolitis[11, 26]
	Bronchodilators	Produce small short-term improvements in clinical scores among some children[27]
		Have not shown to affect major clinical outcome as the rate of hospital admission or the duration of hospitalization[27]
		Could be given as a trial in order to evaluate treatment response, but should not be used routinely in the management of bronchiolitis[11, 26]
	Corticosteroids	Corticosteroids (oral or inhaled) do not effect bronchiolitis clinical outcomes[28] and are not recommended in the management of acute bronchiolitis[11, 26]
	Nebulized 3% saline	Modest reduction in the duration of hospitalization, but not associated with a reduction in the rate of hospitalization when given in the ED setting [14]
Recurrent viral-induced wheezing episodes	Inhaled β2-agonists	Recommended for short-term relief of acute wheezing symptoms [16]
	Intermittent montelukast	Given at the first sign of URI, intermittent montelukast has been associated with attenuation of clinical severity of the acute wheezing episodes measured by symptom severity[17] and heath care utilization[18]
		A recommended approach by the ERS for episodic viral wheeze[16]
	Intermittent high dose inhaled corticosteroids (ICS)	Treatment at the onset of an URI has been associated with a reduction in the rate of exacerbations requiring OCS [19]
		The specifics of intermittent high dose ICS treatment still need to be determined to avoid potential side effects that have been shown in one study[19]
		In preschool children with episodic wheeze and positive modified-API, intermittent high dose ICS treatment at the earliest signs of an RTI was comparable to daily low dose ICS in prevention of progression from early RTI symptoms to severe exacerbation requiring OCS[20]
	Oral corticosteroids (OCS)	Recommended treatment for acute asthma exacerbations by asthma guidelines[21]
		OCS treatment compared to placebo, among preschool children hospitalized with clinical viral-induced wheeze, did not result in a significant difference in the duration of hospitalization or in the rate of symptom resolution following discharge[23]
		Recent *post-hoc* analysis in two independent outpatient cohorts of preschool children with episodic wheeze concluded that OCS did not reduce symptom severity during these episodes[24]

Setting of the wheezing episode	Intervention	Current evidence on the efficacy of the intervention and/or whether the intervention is recommended by clinical guidelines
		Recent editorials suggest reconsideration of OCS use in preschool viral-associated wheeze, with added consideration of avoidance using OCS for outpatient wheezing illnesses while reserving this treatment to the seriously ill hospitalized children[22, 25]

ERS: European respiratory society; ICS: Inhaled Corticosteroids; mAPI: modified Asthma Predictive Index; OCS: Oral corticosteroids; RTI: Respiratory tract illness; URI: Upper respiratory tract infection