Advances in The Treatment of Respiratory Syncytial Virus Induced Bronchiolitis

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Target Audience

This CME activity is intended for physicians, medical students and nurse practitioners. Pediatric emergency department physicians, emergency physicians, pediatricians, and family practitioners will find this information especially useful.

Learning Objectives

After completion of this article, the reader will be able to:

1. *Identify risk factors for developing RSV bronchiolitis.*
2. *Recognize complications of RSV bronchiolitis.*
3. *Describe patterns of infections implicated in bronchiolitis.*
4. *Summarize conditions likely to be confused with the diagnosis of acute bronchiolitis.*
5. *Discuss bronchiolitis treatment and prevention options.*

***Editor's Note**: This is the third of four articles to be published in 2005 for which a total of up to 4 Category 1 CME credit hours can be earned. Instructions for how credit hours can be earned appear inside the front cover of the journal. Exam questions will appear after the article.*

Abstract

Bronchiolitis is a common, contagious, acute lower respiratory tract illness of infants and young children usually secondary to Respiratory Syncytial Virus (RSV) infection. Severe cases, particularly in children with underlying risk factors, may lead to significant morbidity and mortality. RSV infection results in the release of leukotrienes, which may contribute to inflammation and bronchial airway hyperresponsiveness. This review article presents current treatments available for acute bronchiolitis and its possible prevention. It highlights the use of Montelukast, a leukotriene receptor antagonist (LTRA) whose actions may ameliorate the reactivity of bronchial airways disease subsequent to RSV bronchiolitis. *Int Pediatr.2005;20(3):140-144.*

Key words: bronchiolitis, Respiratory Syncytial Virus, leukotriene receptor antagonists, monoclonal antibody

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Introduction

Bronchiolitis is a common, contagious, acute lower respiratory tract illness of infants and young children. Respiratory Syncytial Virus (RSV) infection has been implicated in nearly 75% of bronchiolitis cases. Fortunately, RSV infection usually results in only mild respiratory symptoms but may, in a subset of high-risk children, contribute to significant morbidity and even mortality. The hospitalization rate for bronchiolitis is increasing, with data demonstrating a 2.4-fold increase from 12.9 per 1000 in 1980 to 31.2 per 1000 in 1996 in the USA.[1] Despite new developments in the diagnosis and prevention of RSV infection, the treatment of moderate to severe bronchiolitis frequently remains a clinical challenge.

Characteristics of the RSV Infection

RSV is a seasonal virus, with peaks usually commencing in the winter months and extending into spring. The following are risk factors for developing RSV bronchiolitis: infants aged 3-6 months, not breast-fed, crowded living conditions, lower serum RSV antibody titers, maternal smoking, daycare attendance and born between April and September. Risk factors for severe disease, as gauged by the requirement for hospital admission include children aged 1 to 3 months,[2] with complex cardiac disease, chronic lung disease, and immunocompromised states.[3]

Interestingly, children from lower socioeconomic environments tend to be younger when they first acquire RSV-induced lower respiratory tract infections (LRTI). Furthermore, they are prone to a more intense clinical course with a 5-10 fold greater chance of hospitalization.[4] RSV-induced respiratory tract infections are usually localized to the upper respiratory tract and although repeated infections may continue throughout life, frequency and severity of illness decrease with age.

Despite the rapid clearance of the RSV virus from the respiratory tract of humans, significant pulmonary damage may occur as a consequence of the primary infection and the subsequent immune response. RSV is highly infectious, with infectious material being shed from the mucous membranes of the eyes, mouth, or nose. RSV-induced bronchiolitis is typically associated with profuse secretions, which facilitate viral spread through the inhalation of droplets generated by recurrent sneezing and coughing.

Pathophysiology

The typical abnormalities of the lower respiratory tract in RSV bronchiolitis are necrosis of the respiratory epithelium of the small airways, peribronchiolar mononuclear infiltration, plugging of the lumens, hyperinflation and atelectasis. In RSV pneumonia, the epithelial necrosis may extend to both the bronchi and the alveoli. This pathologic process involving the bronchioles and the production of chemical mediators results in serious alterations in gas exchange, with hypoxemia being a common complication of moderate to severe bronchiolitis.[5]

Clinical Spectrum of Disease

Mild bronchiolitis developing in children without risk factors requires only symptomatic management and assurance. It is, however, vital that those children at high risk for severe illness or apnea be identified.

Treatment

Despite the availability of different medications for the treatment of RSV-induced LRTIs, the mainstay of therapy remains supportive. Hospitalized patients commonly receive humidified oxygen to relieve hypoxemia and to reduce insensible water loss from tachypnea. Progressive hypercarbia, hypoxemia unresponsive to oxygen administration, and recurrent apnea are potential indications for endotracheal intubation and ventilation. Apnea may be the first presenting sign of RSV disease in childhood, and RSV, through the release of several neurotic mediators, may directly induce apnea.[6,7]

In the U.K. there is as yet, no national guidelines for the management of acute bronchiolitis.[8] It has been suggested that the current management of wheezing infants in the South Thames region are based more on anecdote rather than evidence. Current medications for the treatment of Bronchiolitis include:

Ribavirin

Large cohort studies[9-11] failed to prove unequivocal benefit from treatment with ribavirin. Given the concerns about benefit, cost, safety, and variable clinical efficacy, decisions about ribavirin aerosol therapy should be based on the particular clinical circumstances.[12]

Bronchodilators

Despite only modest short-term improvements in clinical features of mild to moderately severe bronchiolitis,[13] aerosolized β–2 agonists such as salbutamol, have been administered to many infants with bronchiolitis. The use of this therapy should only continue in the small subgroup that does indeed respond and should not be part of the routine management of all hospitalized infants.

Epinephrine

Results of a multicenter, randomized, double blind trial from Australia show no benefits to either short or long term outcomes when used to treat infants with acute bronchiolitis.[14] These findings are not in keeping with previous studies[15,16] which demonstrated that epinephrine, when compared with salbutamol, did reduce hospital admissions in cases of acute bronchiolitis.

Corticosteroids

Clinical trials provide little evidence to support the use of steroids for bronchiolitis caused by RSV, but many physicians continue to favor their use.[17]

Antibiotics

Given that secondary bacterial infection of the lower respiratory tract occurs in only 1.2% of children with infection caused by RSV,[18] routine use of antibiotics should be discouraged.

Prevention

Poor results and practical problems with active immunization and hyperimmune globulins respectively, have led to the development of alternative strategies in the prevention of acute bronchiolitis in high-risk children. Palivizumab, an immunoglobulin G monoclonal antibody against the F protein of RSV, has been shown to reduce RSV-related hospital admissions by more than 50% when used as monthly intramuscular injections in high-risk children.[19] Although Palivizumab is currently licensed for use in infants less than 6 months of age who were born prematurely (>35 weeks gestation), or infants with BPD aged less than 2 years, the widespread use of this treatment has been limited by cost.

Prognosis and Complications

Mortality rates reported among patients hospitalized with RSV infection or with bronchiolitis vary between 1% and 3% per year, depending largely on the prevalence of underlying risk factors in the population studied.[20] RSV has also been implicated in "cot death" and sudden infant death syndrome.[21] Some of these unexpected infant deaths associated with RSV may have resulted from apnea, a frequent presenting sign of RSV infection.[22]

Natural History

Infection with RSV in early infancy has long been implicated as a predisposing factor for the development of asthma and chronic lung disease.[23] The reasons for these sequelae appear to be multifactorial with a genetic, but not necessarily an atopic predisposition toward hyperreactivity of the lung having been suggested as a selective factor. Whether genetic airway over-responsiveness is the cause of chronic airway abnormalities, or whether the viral infection is synergistic or primary in causing these lung abnormalities in a previously normal host, is not clear.

In a recently published epidemiological study, Martinez et al[24] observed a significantly higher total serum IgE level during the acute phase when compared with the convalescent phase of the LRTI in persistent wheezers. These persistent wheezers have an altered immune response with a rise in IgE levels during their first reported upper respiratory tract infection (URTI), but no reduction in eosinophil numbers during the acute phase of an URTI, in contrast to transient wheezers. These early transient wheezers have reduced airway function at birth; thus it is likely that their disease is at

least partly of a mechanical rather than purely of an immunologic nature. It is perhaps possible then that subjects who will continue to have persistent wheezing later in life may have had an altered immune response to viral infection during the acute phase of their first LRTI.[25]

Discussion

Of specific interest in the pathogenesis of RSV-induced bronchiolitis is the documented dominance of Leukotrienes LTC4[26,27] and eosinophil degranulation products[28] in the upper airway secretions. Rat and guinea pig models have shown that the leukotriene dominant inflammatory reaction induced by RSV bronchiolitis potentiates neurogenic inflammation. The process of neurogenic inflammation is largely mediated by growth factors such as nerve growth factors, which function as regulators of normal lung development during embryogenesis.[29] It is exactly these growth factors that researchers are presently trying to antagonize in-vitro, in an attempt to prevent the process of "airway remodeling." Rat models demonstrate that Montelukast, a leukotriene receptor antagonist (LTRA), abolishes albumin extravasation (as a marker of tissue damage) in the airways of those infected by RSV with a larger effect in the weanling rats than in the adult rats.[30] This age specific inflammatory response may assist in explaining marked age specific disease outcomes of RSV infected humans.

Considering that we have long known that RSV induces leukotriene release in the airways of patients with bronchiolitis, and that LTRA receptor antagonists are readily available, it is reassuring to see emerging clinical studies aiming to assess the efficacy of these antagonists in RSV-induced bronchiolitis. Bisgaard et al have been at the forefront of these studies which initially hypothesized that a LTRA receptor antagonist would ameliorate the reactive airway disease known to occur subsequent to RSV bronchiolitis. Their parallel comparison multicenter study included children (3-36 months of age) who were hospitalized with documented RSV bronchiolitis. Asthmatic children or those with known chronic diseases were excluded. Five-milligram tablets or matching placebo were commenced soon after admission and continued for 28 days, commencing within seven days of symptom onset. During treatment, diary card data recording symptom scores served as the primary outcome. Of the 130 children randomized, 116 provided completed diary cards (61 on active and 55 on placebo). Infants receiving Montelukast were free of symptoms on 6/28 days (22% of treatment period) as compared to 1/28 days (4% of the treatment period) in children on placebo ($p=0.015$). Exacerbations occurred in 4 infants on Montelukast and 10 on placebo. Time to exacerbation was 8 days in the placebo group and 23 days in the Montelukast treated group ($p=0.44$).[31] Although this appears promising, Montelukast tablets are only approved for children older than 2 years of age with both safety and efficacy data required for younger children for whom RSV bronchiolitis presents the greatest threat. It also remains to be seen if the LTRA receptor antagonists can reduce symptoms in the acute stage of the illness. Reassuringly, extensive experience has now been gained with the use of LTRAs in asthmatic children where their use has shown to be well tolerated and safe. In the United Kingdom, LTRA are licensed and indicated when there is no response to a long-acting β-agonist or if there is persistent poor control on moderate doses of inhaled steroid and long-acting β–agonist.[32]

Conclusion

To conclude, although the majority of infants and older children infected by RSV have mild disease and do not require any therapeutic interventions, a subgroup of patients does develop moderate to severe disease. For children at high risk of developing severe RSV infection, passive immunization may reduce morbidity and mortality. Active management

of moderate-severe bronchiolitis includes the use of oxygen therapy, hydration, and ventilatory support if needed. The use of bronchodilators may be used as a therapeutic trial. With a better understanding of the pathogenesis of RSV-bronchiolitis, there does indeed seem to be some scientific rationale behind the use of LTRAs in this condition. This is however still under investigation, and none of the LTRAs are presently licensed for this use. Finally, as with most infectious diseases, a safe and effective vaccine is desperately needed to reduce hospitalizations for the treatment of bronchiolitis.

References

1. Kimpen JL. Prevention and treatment of respiratory syncytial virus bronchiolitis and postbronchiolitic wheezing. *Respir Res* 2002;3(Suppl 1):S40-S45.
2. Shay DK, Holman RC, Newman RD, et al. Bronchiolitis-associated hospitalizations among US children, 1980-1996. *JAMA* 1999;282:1440-6.
3. Panitch HB, Callahan CW Jr, Schidlow DV. Bronchiolitis in children. *Clin Chest Med* 1993;14:715-31.
4. Hall CB. Respiratory syncytial virus. In: Feigin RD, Cherry JD, eds. *Textbook of Pediatric Infectious Diseases*. 4th ed. Philadelphia: WB Saunders Co;1998:2084-2102.
5. Wohl MEB. Bronchiolitis. In: Chernick V, Boat TF, eds. *Kendig's Disorders of the Respiratory Tract in Children*. Philadelphia: WB Saunders Co;1998:473-476.
6. Kneyber MC, Brandenburg AH, de Groot R, et al. Risk factors for respiratory syncytial virus associated apnoea. *Eur J Pediatr* 1998;157:331-5.
7. Ng YT, Cox C, Atkins J, Butler IJ. Encephalopathy associated with respiratory syncytial virus bronchiolitis. *J Child Neurol* 2001;16:105-8.
8. Chavasse RJ, Bastian-Lee Y, Seddon P. How do we treat wheezing infants? Evidence or anecdote. *Arch Dis Child* 2002;87:546-7.
9. Wheeler JG, Wofford J, Turner RB. Historical cohort evaluation of ribavirin efficacy in respiratory syncytial virus infection. *Pediatr Infect Dis J* 1993;12:209-13.
10. Moler FW, Steinhart CM, Ohmit SE, et al. Effectiveness of ribavirin in otherwise well infants with respiratory syncytial virus-associated respiratory failure. *J Pediatr* 1996;128:422-8.
11. Randolph A, Wang E. Ribavirin for respiratory syncytial virus infection of the lower respiratory tract. *Cochrane Database Syst Rev* 2000;(2):CD000181.
12. Pickering LK, ed. *Report of the Committee on Infectious Diseases.* American Academy of Pediatrics;2000:485.
13. Kellner JD, Ohlsson A, Gadomski AM, et al. Efficacy of bronchodilator therapy in bronchiolitis: a meta-analysis. *Arch Pediatr Adolesc Med* 1996;150:116-7.
14. Wainwright C, Altamirano L, Cheney M, et al. A multicenter, randomized, double-blind, controlled trial of nebulized epinephrine in infants with acute bronchiolitis. *N Engl J Med* 2003;349:27-35.
15. Menon K, Sutcliffe T, Klassen T. A randomized trial comparing the efficacy of epinephrine with salbutamol in the treatment of acute bronchiolitis. *J Pediatr* 1995;126:1004-7.
16. Ray MS, Singh V. Comparison of nebulized adrenaline versus salbutamol in wheeze associated respiratory tract infections in infants. *Indian Pediatr* 2002;39:12-22.
17. Springer C, Bar-Yishay E, Uwayyed K, et al. Corticosteroids do not affect the clinical or physiological status of infants with bronchiolitis. *Pediatr Pulmonol* 1990;9:181-5.
18. Hall CB, Powell KR, Schnabel KC, et al. Risk of secondary bacterial infection in infants hospitalized with respiratory syncytial viral infection. *J Pediatr* 1988;113:266-71.
19. The Impact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics* 1998;102:531-7.
20. Wang EEL, Law BJ, Stephens D. Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) prospective study of risk factors and outcomes in patients hospitalized with respiratory syncytial viral lower respiratory tract infection. *J Pediatr* 1995;126:212-9.
21. Williams AL, Ureh EC, Bretherton L. Respiratory viruses and sudden infant death. *BMJ* 1984;288:1491-3.
22. Church NR, Anas NG, Hall CB, et al. Respiratory syncytial virus-related apnea in infants: demographics and outcome. *Am J Dis Child* 1984;138:247-50.
23. Gern JE. Viral respiratory infection and the link to asthma. *Pediatr Infect Dis J* 2004;23:S78-S86.
24. Martinez FD, Stern DA, Taussig LM, et al. Differential immune responses to acute lower respiratory illness in early life and subsequent development of persistent wheezing and asthma. *J Allergy Clin Immunol* 1998;102:915-20.
25. Papadopoulas NG, Johnston S. The role of Viruses in the induction and progression of Asthma. *Curr Allergy Asthma Rep* 2001;1:144-52.
26. Volovitz B, Welliver RC, De Castro G, et al. The release of leukotrienes in the respiratory tract during infection with respiratory syncytial virus: role in obstructive airway disease. *Pediatr Res* 1988;24:504-7.
27. Van Schaik SM, Tristan DA, Nagpal IS, et al. Increased production of IFN-gamma and cysteinyl leukotrienes in virus-induced wheezing. *J Allergy Clin Immunol* 1999;103:630-6.
28. Garofalo R, Kimpen JL, Welliver RC, et al. Eosinophil degranulation in the respiratory tract during naturally acquired respiratory syncytial virus infection. *J Pediatr* 1992;120:28-32.
29. Hu C, Wedde-Beer K, Auais A, et al. Nerve Growth factor and nerve growth factor receptors in RSV-infected lungs. *Am J Physiol Lung Cell Mol Physiol* 2002;283:L494-502.
30. Wedde-Beer K, Rodriguez MM, Piedimonte G. Leukotrienes mediate neurogenic inflammation in lungs of young rats infected with RSV. *Am J Physiol Cell Mol Physiol* 2002;282:L1143-50.
31. Bisgaard H, Hermansen M, Andersen EA, et al. A randomized trial of a Leukotriene Receptor Antagonist in Respiratory Syncytial Virus Post Bronchiolitis. *Am J Respir Crit Care Med* 2003;167:379-83.
32. BTS/SIGN. British guidelines on the management of asthma. *Thorax* 2003;58(suppl 1):i1-94.

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Du Toit G, Fox AT, Royed C. *Int Pediatr* 2005;20(3)140-144.

QUESTIONS

1. Which of the following is a risk factor for developing RSV bronchiolitis?
a. Age over 1 year
b. High socio-economic status
c. Maternal alcohol ingestion
d. Daycare attendance
e. Breast-feeding

2. Which of the following is not a complication of RSV bronchiolitis?
a. Atelectasis
b. Secondary bacterial infection
c. Pneumatoceles
d. Apnea
e. An association with asthma

3. Which pattern of infection is most commonly implicated in bronchiolitis?
a. Parainfluenza virus type 3 in winter months
b. Adenovirus all year round
c. Respiratory Syncytial virus in winter months
d. Respiratory Syncytial virus in late spring
e. Adenovirus in summer months

4. Which of the following is UNLIKELY to be confused with the diagnosis of acute bronchiolitis?
a. Whooping cough in a previously immunized patient
b. Organophosphate poisoning
c. Epiglottitis
d. Foreign body in trachea
e. All of the above

5. There are large randomized controlled trials showing clear evidence of benefit in acute bronchiolitis for which of the following treatments:
a. Nebulized salbutamol
b. Nebulized ribavirin
c. Nebulized ipratropium bromide
d. Nebulized steroids
e. None of the above

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