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The Relationship Between Early Respiratory Viral Infections and Subsequent Wheezing and Asthma

Howard B. Panitch, MD

Introduction

Wheezing is a nonspecific sign of airway obstruction. Several factors have been shown to increase the risk of wheezing early in life, including preexisting low lung function,¹ prenatal and postnatal exposure to environmental tobacco smoke,² family history of atopy,³ and exposure to viral lower respiratory infections.⁴ In a comparative study, the relative risk of experiencing at least 2 wheezing illnesses in the first year of life was greatest among those infants with a history of a viral lower respiratory infection.⁵ Similarly, children who receive care in day care centers are more likely to acquire lower respiratory tract infections that result in hospitalization in the first 2 years of life than those children cared for at home,⁶ and day care attendance has been shown to be a risk factor for recurrent wheezing illnesses.⁷

Wheezing illnesses are common in infants and children. In a cohort of 826 unselected children followed up prospectively, 33.6% had at least 1 wheezing illness within the first 3 years of life.⁸ Among a group of 440 children who had at least 1 parent with a history of atopy, 50.7% reported at least 1 wheezing illness before age 3.⁹ Furthermore, among 188

low-income families in an urban area, at least 1 episode of wheezing in the first year of life occurred in as many as 80.3% of infants prospectively followed up.¹⁰

Asthma is a syndrome of recurrent episodes of airway obstruction that are at least partially reversible and that result from chronic inflammation of the airways. Asthma is manifested by bronchial hyperresponsiveness to a variety of stimuli and recurrent episodes of wheezing and cough. The most common chronic condition in children, asthma affected an estimated 6.2 million children younger than 18 years and 1.3 million children younger than 5 years in 2003.¹¹ Acute asthma exacerbations represent the third leading cause of hospitalization in children younger than 15 years.¹¹ Viral infections are important causes of wheezing among older children with a confirmed history of asthma as well. Viral infections were identified as the cause of 85% of acute exacerbations of wheezing in a longitudinal study of 108 children 9 to 11 years old with a history of asthma.¹²

Associations between viral illnesses in early infancy and subsequent airway dysfunction and asthma have long been made.¹³ Infection with certain viruses, such as respiratory syncytial virus (RSV), has been shown to be an important risk factor for the subsequent development of asthma.^{14,15} Other viral infections, especially rhinovirus illnesses, also have been associated with recurrent wheezing illnesses and asthma.^{16,17}

RSV and rhinovirus are both significant pathogens for infants. RSV is the most important pathogen to cause serious lower respiratory infection in infants, infecting almost two thirds within the first year of life and virtually all children by age 2.¹⁸ Upper respiratory illness develops in most of those infected; of

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these, 25% to 40% develop a mild-to-moderate lower respiratory illness, and only about 1% require hospitalization. Nevertheless, infection with RSV is a leading cause of infant morbidity, hospitalization, and death.¹⁹⁻²¹ Bronchiolitis is the most common wheezing illness in infancy, and RSV is the most common cause of bronchiolitis.²² Furthermore, the rates of serious lower respiratory tract infections from RSV and resulting hospitalization rates have increased significantly during the last 2 decades.^{23,24} Almost all hospitalizations for RSV infection in children occur in infants younger than 1 year.^{21,23}

Rhinovirus, in contrast, is often considered a cause of upper respiratory infection; however, a study published in 2003 that used sensitive viral detection techniques showed that rhinovirus also causes lower respiratory wheezing illnesses in infants.¹⁶ In this study, rhinovirus was more commonly detected in subjects older than 6 months and was the most prevalent respiratory virus isolated from subjects, 12 to 17 months old. Infants with rhinovirus who presented with wheezing illnesses also were more likely to have atopic dermatitis. In older children with asthma, rhinovirus infection has been found to be the most important cause of acute exacerbations.¹²

Although an association between early respiratory viral infection and subsequent recurrent wheezing illness and asthma has been made, causation has not been confirmed. The issue is one of intense investigation because of the tremendous implications for prevention and intervention. The purpose of this review is to examine the published evidence for an association between viral respiratory infections and subsequent wheezing and asthma and to explore new data on immunologic mechanisms of viral infection and how they relate to clinical findings. These findings will be placed in the context of current methods of prevention and future prophylaxis and treatment options.

Immunologic Mechanisms Linking Viral Infections to Recurrent Wheezing or Asthma

Does early viral infection predispose an infant to subsequent wheezing and the development of asthma, or does it merely uncover and make symptomatic at an early age those infants who are already at risk of developing wheezing illnesses? If viral respiratory

infections at an early age increase the likelihood of subsequent wheezing illnesses, a change in airway biology or the immune response to subsequent infections or irritants must occur.

Such changes have been demonstrated in a variety of animal models. Ferret kits infected with RSV within the first 10 days of life demonstrated altered neural control of airway smooth muscle, with enhanced cholinergic response to stimulation that was present at 4 and 8 weeks after infection but which resolved by 24 weeks.²⁵ In contrast, absent or markedly blunted relaxant responses mediated through the nonadrenergic–noncholinergic (NANC) inhibitory pathway (NANCi) persisted even 24 weeks after infection. The authors speculated that the viral-mediated airway injury during a period when normal mechanisms of airway control are developing could result in long-lasting changes.

The NANC system also has an excitatory pathway (NANCe) that causes bronchoconstriction and inflammation, largely through the actions of substance P.²⁶ Sensory nerve fibers located just below the respiratory epithelial surface can be stimulated by a variety of airborne irritants, causing the release of substance P and other tachykinins into the immediate submucosa and airway smooth muscle. Coupling of these neurotransmitters with their receptors, neurokinin 1 (NK1), NK2, and NK3, results in bronchoconstriction (NK2-mediated) and in vasodilation and exudative edema of the airway mucosa, leukocyte attraction, proliferation of T and B cells, mast cell degranulation, and release of several inflammatory mediators from macrophages and monocytes (NK1-mediated).²⁶ This neurogenic inflammation has been shown to be upregulated in both adult²⁷ and weanling rats²⁸ infected with RSV. In a series of elegant experiments, Peidimonte et al²⁶ demonstrated that RSV infection upregulates the production of the NK1 receptor, thus potentiating the effects of substance P–mediated neurogenic inflammation.²⁶

Furthermore, there is a maturational difference in the distribution of the NK1 receptor within the airways: the concentration of NK1 receptors is greater within the peripheral airways of weanling rats than in the central airways, and the opposite anatomic arrangement occurs by adulthood. Thus, RSV-mediated exaggeration of neurogenic inflammation is seen in the central but not peripheral airways of adult rats, whereas it occurs primarily in the peripheral but not the central airways of weanling

rats.²⁸ This maturational shift in neurodevelopment of the lung may be one reason that wheezing is more prevalent among infants who acquire an RSV infection than adults.

These same investigators also demonstrated that pretreatment of infected weanling or adult rats with palivizumab, a monoclonal antibody against the fusion (F) protein of RSV, ablated the RSV-mediated increase in NK1 receptor production.^{28,29} Other studies using antifusion or anti-G protein antibodies to RSV have also demonstrated a reduction in substance P-mediated neurogenic inflammation.^{30,31}

Other investigators have linked prolonged inflammation after acute viral infection with persistent heightened airway responsiveness. In a mouse model developed to study the acute and chronic changes that occur after RSV infection, Jafri et al³² showed that although RSV was cleared by the lungs by 7 days after inoculation, chronic inflammatory infiltrates of lymphocytes, macrophages, and plasma cells were present around vessels and airways up to 154 days after inoculation. Baseline measurements of airway obstruction remained elevated up to 42 days after acute infection in RSV-infected mice compared with controls. Furthermore, evidence of airway hyperreactivity to a single dose of methacholine was present consistently over those first 42 days and, intermittently, for as long as 154 days after infection.

Cellular responses to viral infection also have been shown to be age-dependent. The immune system matures postnatally, and it has been postulated that certain infections that occur during this maturation process can drive the immune system toward allergic (T-helper cell type 2 [Th2]) or nonallergic (Th1) responses upon subsequent antigen rechallenge.³³ Thus, not only the type of infection but also the timing of infection with particular organisms could have important and long-lasting implications. Supporting this notion is the finding that mice infected with RSV as neonates (1 or 7 days old) demonstrated a marked Th2 response when reinfected with RSV at 12 weeks of age, whereas those initially infected as young mice (4 weeks old) or as young adults (8 weeks old) did not show a Th2-biased response upon rechallenge.³⁴

Dakhama et al³⁵ extended these observations in the murine model by assessing both lung histology and airway responsiveness in addition to cytokine production after primary and secondary RSV infections.

Mice inoculated during the neonatal period (<1 week) demonstrated more mucus-producing cells, less interferon- γ (IFN- γ), greater amounts of interleukin-13 (IL-13), and mild, but significantly more, airway eosinophilia compared with mice experiencing their first RSV infection during the weanling period (3 weeks of age). In this and other studies, IL-13 has been shown to be necessary for the development of mucus hypersecretion and airway hyperresponsiveness in murine models of allergic inflammation.³⁶ Both groups had similar elevated responses to graded doses of methacholine, which subsequently resolved.

Upon reinfection several weeks later, however, divergent immunologic and functional responses occurred: the neonatal group demonstrated markedly enhanced mucus production and prominent pulmonary eosinophilia, as well as elevated IL-13 levels and marked airway hyperresponsiveness. In contrast, the weanling mice did not have an exaggerated mucus-producing response, pulmonary eosinophilia, or elevated IL-13 levels. In fact, IFN- γ levels were increased, and there was no evidence of airway hyperresponsiveness. Thus, the later age at the initial infection appeared to be protective against an asthma-like response to secondary RSV reinfection.

In children with a family history of atopy or asthma, IL-13 responses to *in vitro* stimulation of mononuclear cells from those who wheezed during RSV infection did not change or increase during the first year of life, whereas those who did not experience wheezing after viral infection showed a reduction in IL-13 responses at 1 year.³⁷ In addition, those infants who had detectable RSV-induced IFN- γ at birth were less likely to wheeze during the first year of life.³⁷ Together, these results suggest that RSV infection produces a T-cell memory that affects subsequent response to reinfection and perhaps to other viruses or irritants.³⁸

A similar age dependence in cytokine production has been suggested in human infants after viral infection. Infants 3 months or younger hospitalized with RSV, parainfluenza, or influenza infection had elevated levels of IL-4 (a Th2 cytokine) in nasopharyngeal secretions, compared with infants, aged 3 through 7 months, infected with RSV and age-matched controls.³⁹ The authors interpreted this finding as evidence that younger infants respond to severe viral infection with a predominantly Th2 response. All infected infants also had elevated levels of macrophage inflammatory protein 1 β (a CD4+ chemokine attractant)

and eosinophil cationic protein in their nasopharyngeal secretions compared with age-matched healthy control infants. Thus, all infected infants who were 7 months old or younger at the time of their severe viral infections had evidence of infiltration of Th2 cells associated with the influx and activation of eosinophils.³⁹

In the 2 murine studies cited, mice infected with RSV during the neonatal period produced less IFN- γ (a Th1 cytokine) at the time of primary infection compared with those infected at 3 or 8 weeks of age.^{34,35} If stimulation of IFN- γ production was experimentally prevented from occurring, a Th2-cytokine profile persisted and led to lung eosinophilia.⁴⁰ Similarly, those mice infected with RSV as neonates (younger than 1 week), who were then reinfected at 5 weeks of age, demonstrated both airway hyperresponsiveness and significant airway eosinophilia.³⁵

Although the major inflammatory cells recovered from the lungs of infants with acute RSV bronchiolitis are neutrophils,⁴¹ a subset of children with acute bronchiolitis have elevated numbers of eosinophils in bronchoalveolar lavage (BAL) fluid at the time of acute infection, similar in number to eosinophils found in the BAL fluid of children with acute asthma exacerbations.⁴² Those infants with RSV bronchiolitis and elevated pulmonary eosinophils also had significantly higher levels of IL-5 and ratios of IL-5/IFN- γ compared with controls, but infants who did not have pulmonary eosinophilia at the time of RSV bronchiolitis did not have such cytokine responses.⁴² It is not known why some infants responded with an eosinophilic response to RSV infection while others did not, and those subjects were not followed up prospectively to determine if the infants with pulmonary eosinophilia during acute RSV infection were more likely to experience recurrent wheezing or asthma.

A separate study, however, showed that infants who demonstrated eosinophilia in peripheral blood samples at the time of RSV bronchiolitis were more likely to experience recurrent episodes of wheezing that persisted into school age.⁴³ In fact, the presence of peripheral blood eosinophilia was the only factor that predicted wheezing at age 7, whereas family history of asthma, gender, and exposure to environmental tobacco smoke did not.⁴³

A prominent component of the asthmatic phenotype is elevated immunoglobulin E (IgE) levels. Respiratory syncytial virus-specific IgE has been found in nasopharyngeal secretions of infants during acute RSV infections,⁴⁴ and higher levels were

shown to correlate with recurrent wheezing following acute infection.⁴⁵

In a murine model, RSV infection resulted in production of RSV-specific IgE.⁴⁶ In vitro studies showed that RSV caused mast cell degranulation if the mast cells were sensitized with RSV-specific IgE. In addition, when mice were passively sensitized with virus-specific IgE antibodies, exaggerated airway hyperresponsiveness to methacholine developed after RSV infection compared with infected mice that were not sensitized.⁴⁶

Production of IgE is not unique to RSV infections and can occur with other viral illnesses.⁴⁷ Thus, the production of virus-specific IgE might contribute to postbronchiolitis recurrent wheezing in humans when they are rechallenged with the virus during subsequent infection.

Clinical Findings

Infants who required hospitalization for acute bronchiolitis have been reported to have high rates of recurrent wheezing and asthma that decrease over time. Henry et al⁴⁸ monitored 55 children for 2 years after hospitalization and found that 82% had protracted lower respiratory illness, wheezing episodes, or both during that interval. In a 3.5-year study, the same group observed 81 children who had been hospitalized with acute viral bronchiolitis after acute infection and found that 69% had lower respiratory symptoms that occurred in the previous year.⁴⁹ Another prospective study of infants hospitalized with proven RSV bronchiolitis and followed up for 6 to 8 years after the initial infection showed that 31% had recurrent lower respiratory tract disease or recurrent wheezing.⁵⁰

More recently, a cohort of 47 children who were hospitalized within the first year of life with documented RSV bronchiolitis were followed up at ages 1, 3, 7.5, and 13 years, and their courses were compared with those of 93 controls carefully matched for age and gender.^{14,15,51} At each age studied, those children hospitalized with RSV bronchiolitis in infancy had a higher incidence of asthma (at least 3 episodes of physician-diagnosed wheezing) or any wheezing compared with the controls. In addition, the history of RSV bronchiolitis in infancy was the most important predictor for subsequent wheezing illness, even when family history of atopy or exposure to environmental tobacco smoke was considered. In

an intriguing finding, Sigurs et al⁵¹ also noted a higher rate of allergic sensitization among the children with a history of RSV infection, but the control subjects had a rate of atopic disease generally considered lower than that found in the general population.

Of importance is that several other studies failed to demonstrate an increase in allergic sensitization several years after RSV infection in early childhood.⁵²⁻⁵⁵ Possible reasons for the discrepancy could include the age at initial infection, since earlier infection (<1 year) might affect the developing immune system differently from an infection in older infants (<2 years); burden of allergic sensitization in the community, as already mentioned; or the severity of the initial infection.

Some experts have questioned whether hospitalization for bronchiolitis in infancy, connoting severe disease, is a marker for preexisting airway dysfunction or risk of subsequent wheezing illness. Others, however, have shown that even children with mild disease that did not require hospitalization can be predisposed toward recurrent episodes of airway dysfunction. Tepper et al⁵⁶ demonstrated exaggerated responses to methacholine in 18 infants with acute bronchiolitis compared with 24 healthy controls 10 months after their acute infection. Half of the infants with bronchiolitis were treated as outpatients for their acute illness. Stein et al⁵² observed a cohort of 888 healthy children through the first 3 years of life and obtained viral respiratory cultures during acute lower respiratory tract illnesses. All of the 207 children who acquired an acute RSV illness were considered to have a mild case (ie, none required hospitalization). Those children with a history of RSV lower respiratory tract illness before age 3 demonstrated a significantly greater risk of subsequent wheezing illnesses during the first 10 years of life. This risk of wheezing was self-limited, however, and no significant difference was seen in the frequency of wheezing illnesses by age 13.

Other studies have not shown a relationship between early RSV infection and asthma in older children and young adults. Korppi et al⁵³ observed a cohort of children hospitalized with either RSV bronchiolitis or pneumonia and a cohort of healthy subjects until 18 to 20 years of age. Although the subjects with a history of RSV hospitalization before age 2 had a higher than normal prevalence of asthma at age 5 to 6 years, no relationship existed between early RSV infection and asthma by young adulthood. In contrast, early RSV infection was

associated with some persistent abnormalities of lung function as detected by spirometry. A recent meta-analysis also failed to demonstrate a relationship between early RSV infection and recent recurrent wheezing in children older than 5 years, although such a relationship clearly was present in children younger than 5 years.⁵⁴

Respiratory syncytial virus is not the only agent that has been associated with persistent or recurrent lower respiratory tract symptoms in children who experience infection in early life.⁵² Other early viral infections—most notably with rhinovirus, human metapneumovirus, parainfluenza, and influenza A—have all been associated with increased risk of subsequent chronic lower respiratory tract symptoms.^{17,57,58} The most common infection associated with bronchiolitis and subsequent recurrent wheezing is caused by RSV, however, so most studies have concentrated on host responses to that virus. Similar studies are required to determine the effects of other viruses on immune responses and subsequent airway function.

Treatment and Prevention

A common theme of the studies that have been cited is the sense that the timing of viral respiratory infections may be critical in determining a child's subsequent response to other infections or presentation of aeroallergens, and that delaying the onset of viral respiratory infection until the infant is older might promote a nonallergic response to subsequent challenges. Although prevention or avoidance of infection during early infancy is clearly the most desirable way to achieve this goal, it is not a practical strategy given the widespread presence of viruses and the limited means of many families to keep young infants segregated. If a causal relationship exists between early viral infection and subsequent wheezing illness, then both antiviral and preventative therapies could be important tools that could not only ameliorate the acute infection but possibly also reduce the long-term effects of early viral illnesses.

Ribavirin is an agent with broad antiviral activity against RSV, measles, influenza, parainfluenza, and other viruses.⁵⁹ Despite its widespread use in the 1980s, ribavirin did not appreciably alter the duration or severity of illness in infants with RSV bronchiolitis who did not require mechanical ventilation.⁶⁰ One of the possible benefits of ribavirin use, however, was

that it inhibited the production of RSV-specific IgE.⁶¹ One could therefore speculate that although ribavirin use during acute RSV bronchiolitis might not alter the acute course, it could ameliorate subsequent airway obstructive symptoms. Most of the studies that have assessed pulmonary symptoms years later in children who received ribavirin for treatment of RSV bronchiolitis in infancy have not, unfortunately, demonstrated any difference in frequency of reactive airways disease or pulmonary symptoms compared with those who were not treated with ribavirin.⁶²

No licensed vaccines are currently available to prevent RSV infection in infants. Significant progress in vaccine development has been made, but the obstacles to providing active immunization to young infants are considerable.⁶³⁻⁶⁵ In contrast, passive immunoprophylaxis against severe RSV lower respiratory tract infections has been available for more than 10 years. Initially, RSV-immune globulin (RSV-IVIG), a polyclonal antibody,⁶⁶ and later palivizumab, a humanized monoclonal antibody against the F (fusion) protein of RSV,⁶⁷ were shown to decrease hospitalization for RSV lower respiratory tract infection in premature infants with and without bronchopulmonary dysplasia.

As noted, palivizumab administration in both adult and weanling rats was shown to prevent neurogenic inflammation after RSV inoculation.^{28,29} Pretreatment of adult rats with RSV-IVIG before inoculation with RSV also reduced neurogenic inflammation, but to a lesser extent than did palivizumab.²⁹ If these prophylaxis agents can alter the immune response to the acute viral infection, then they might also modulate the subsequent course of airway dysfunction.

Wenzel et al⁶⁸ assessed the pulmonary and allergic outcomes of 13 children, who received RSV-IVIG in early life, 7 to 10 years after they received immunoprophylaxis and compared them with 26 children matched for chronologic and gestational age who were considered high-risk infants but who did not receive immunoprophylaxis. The children who had received immunoprophylaxis had a lower frequency of RSV lower respiratory infection than the control group. The treated children also had better lung function, less atopy, fewer school absences, and were less likely to have had an asthma attack at the time of follow-up. These data suggest that there may be long-term benefits in respiratory and allergic outcomes from immunoprophylaxis against RSV in high-risk infants.

Preliminary data also have been reported on the effects of palivizumab on subsequent pulmonary symptoms. In a multicenter, prospective case-cohort

study, pulmonary outcomes of 193 preterm infants who received palivizumab in their first RSV season were compared with a cohort of 231 preterm infants who did not receive palivizumab.⁶⁹ The treated group had a lower risk of recurrent wheezing (6.8% versus 19.1%, or a 64% risk reduction) at the 12-month follow-up. The treated group also had fewer siblings or adults in the home and fewer siblings in day care, and the risk of respiratory-related hospitalization was related both to palivizumab use and fewer adults in the home. Clearly, larger studies are needed to determine the impact of RSV immunoprophylaxis on the risk of subsequent wheezing illnesses and the development of asthma.

Future Directions

Alteration of the initial immune response appears to be the most promising approach to the prevention of recurrent respiratory symptoms beyond complete avoidance of infection in early infancy. A new monoclonal antibody with enhanced neutralizing activity against RSV (MEDI-524) has been developed and is undergoing clinical testing. In the murine model of acute RSV infection, pretreatment with MEDI-524 was found to be more effective than pretreatment with palivizumab at 4 and 8 weeks after inoculation in reducing lung inflammation in the acute and chronic phases of the disease, in preventing signs of airway obstruction, and in preventing airway hyper-responsiveness.⁷⁰

Significant progress continues in the development of active vaccines against RSV, including subunit (against particular proteins of the virus) vaccines, live attenuated vaccines, and recombinant virus vaccines.⁷¹ No such interventions are currently available for important pathogens such as rhinovirus,⁷² and the long-term effects of antiviral therapy or early vaccination for influenza on subsequent pulmonary function in children have not yet been described. Once such approaches become viable for protection of young infants, important observations about the association of early viral respiratory infection and long-term pulmonary outcomes can be elucidated.

Conclusions

There has been longstanding recognition that viral respiratory infections in early infancy are associated with recurrent wheezing illnesses in childhood.

Whether such infections cause subsequent respiratory morbidity or merely unmask those subjects who are already destined to have recurrent or chronic respiratory problems remains a topic of intense investigation. Clearly, if a causal relationship between early viral respiratory infection and recurrent wheezing and asthma exists, then preventing infection or altering the immune response toward more of a Th1-type response would have important long-term health consequences.

Animal and human studies continue to examine the mechanisms by which viruses cause both acute wheezing and possibly long-term alterations in airway and immune function that lead to asthma and recurrent wheezing illnesses. As a model, immunoprophylaxis against RSV reduces subsequent wheezing in humans and modifies the immune response in animal models. As such, similar approaches for other viruses can help to clarify the role that early viral infections play in the development of asthma and potentially improve the long-term respiratory outcomes of children.

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References

- Martinez FD, Morgan WJ, Wright AL, Holberg CJ, Taussig LM. Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. *N Engl J Med*. 1988;319:1112-1117.
- DiFranza JR, Aligne CA, Weitzman M. Prenatal and postnatal environmental tobacco smoke exposure and children's health. *Pediatrics*. 2004;113(4 suppl):1007-1015.
- Arshad SH, Kurukulaaratchy RJ, Fenn M, Matthews S. Early life risk factors for current wheeze, asthma, and bronchial hyperresponsiveness at 10 years of age. *Chest*. 2005;127:502-508.
- Gold DR, Tager IB, Weiss ST, Tosteson TD, Speizer FE. Acute lower respiratory illness in childhood as a predictor of lung function and chronic respiratory symptoms. *Am Rev Respir Dis*. 1989;140:877-884.
- Gold DR, Burge HA, Carey V, Milton DK, Platts-Mills T, Weiss ST. Predictors of repeated wheeze in the first year of life: the relative roles of cockroach, birth weight, acute lower respiratory illness, and maternal smoking. *Am J Respir Crit Care Med*. 1999;160:227-236.
- Anderson LJ, Parker RA, Strikas RA, et al. Day-care center attendance and hospitalization for lower respiratory tract illness. *Pediatrics*. 1988;82:300-308.
- Marbury MC, Maldonado G, Waller L. Lower respiratory illness, recurrent wheezing, and day care attendance. *Am J Respir Crit Care Med*. 1997;155:156-161.
- Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ, for the Group Health Medical Associates. Asthma and wheezing in the first six years of life. *N Engl J Med*. 1995;332:133-138.
- Ly NP, Gold DR, Weiss ST, Celedon JC. Recurrent wheeze in early childhood and asthma among children at risk for atopy. *Pediatrics*. 2006;117:e1132-e1138.
- Mallol J, Andrade R, Auger F, Rodriguez J, Alvarado R, Figueroa L. Wheezing during the first year of life in infants from low-income population: a descriptive study. *Allergol Immunopathol (Madr)*. 2005;33:257-263.
- American Lung Association. *Lung Disease Data: 2006*. Available at: <http://www.lungusa.org/site/apps/s/content.asp?c=dvLUK900E&b=34706&ct=67648>. Accessed September 14, 2006.
- Johnston SL, Pattermore PK, Sanderson G, et al. Community study of role of viral infections in exacerbations of asthma in 9-11 year old children. *BMJ*. 1995;310:1225-1229.
- Pullan CR, Hey EN. Wheezing, asthma, and pulmonary dysfunction 10 years after infection with respiratory syncytial virus in infancy. *Br Med J (Clin Res Ed)*. 1982;284:1665-1669.
- Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B, Björkstén B. Asthma and immunoglobulin E antibodies after respiratory syncytial virus bronchiolitis: a prospective cohort study with matched controls. *Pediatrics*. 1995;95:500-505.
- Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. *Am J Respir Crit Care Med*. 2000;161:1501-1507.
- Kotaniemi-Syrjänen A, Vainionpää R, Reijonen TM, Waris M, Korhonen K, Korppi M. Rhinovirus-induced wheezing in infancy—the first sign of childhood asthma? *J Allergy Clin Immunol*. 2003;111:66-71.
- Lemanske RF Jr, Jackson DJ, Gangnon RE, et al. Rhinovirus illnesses during infancy predict subsequent childhood wheezing. *J Allergy Clin Immunol*. 2005;116:571-577.
- Glezen WP, Taber LH, Frank AL, Kasel JA. Risk of primary infection and reinfection with respiratory syncytial virus. *Am J Dis Child*. 1986;140:543-546.
- Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA*. 2003;289:179-186.
- Shay DK, Holman RC, Roosevelt GE, Clarke MJ, Anderson LJ. Bronchiolitis-associated mortality and estimates of respiratory syncytial virus-associated deaths among US children, 1979-1997. *J Infect Dis*. 2001;183:16-22.

21. Leader S, Kohlhasse K. Recent trends in severe respiratory syncytial virus (RSV) among US infants, 1997 to 2000. *J Pediatr*. 2003;143(5 suppl):S127-S132.
22. Hall CB. Respiratory syncytial virus. In: Feigin RD, Cherry JD, eds. *Textbook of Pediatric Infectious Diseases*. Philadelphia, Pa: WB Saunders Co; 1998:2087.
23. Shay DK, Holman RC, Newman RD, Liu LL, Stout JW, Anderson LJ. Bronchiolitis-associated hospitalizations among US children, 1980-1996. *JAMA*. 1999;282:1440-1446.
24. Langley JM, LeBlanc JC, Smith B, Wang EE. Increasing incidence of hospitalization for bronchiolitis among Canadian children, 1980-2000. *J Infect Dis*. 2003;188:1764-1767.
25. Colasurdo GN, Hemming VG, Prince GA, Gelfand AS, Loader JE, Larsen GL. Human respiratory syncytial virus produces prolonged alterations of neural control in airways of developing ferrets. *Am J Respir Crit Care Med*. 1998;157:1506-1511.
26. Piedimonte G. Contribution of neuroimmune mechanisms to airway inflammation and remodeling during and after respiratory syncytial virus infection. *Pediatr Infect Dis J*. 2003;22(2 suppl):S66-S74; discussion S74-S75.
27. Piedimonte G, Rodriguez MM, King KA, McLean S, Jiang X. Respiratory syncytial virus upregulates expression of the substance P receptor in rat lungs. *Am J Physiol*. 1999;277:L831-L840.
28. King KA, Hu C, Rodriguez MM, Romaguera R, Jiang X, Piedimonte G. Exaggerated neurogenic inflammation and substance P receptor upregulation in RSV-infected weanling rats. *Am J Respir Cell Mol Biol*. 2001;24:101-107.
29. Piedimonte G, King KA, Holmgren NL, Bertrand PJ, Rodriguez MM, Hirsch RL. A humanized monoclonal antibody against respiratory syncytial virus (palivizumab) inhibits RSV-induced neurogenic-mediated inflammation in rat airways. *Pediatr Res*. 2000;47:351-356.
30. Tripp RA, Moore D, Winter J, Anderson LJ. Respiratory syncytial virus infection and G and/or SH protein expression contribute to substance P, which mediates inflammation and enhanced pulmonary disease in BALB/c mice. *J Virol*. 2000;74:1614-1622.
31. Tripp RA, Barskey A, Goss L, Anderson LJ. Substance P receptor expression on lymphocytes is associated with the immune response to respiratory syncytial virus infection. *J Neuroimmunol*. 2002;129:141-153.
32. Jafri HS, Chávez-Bueno S, Mejías A, et al. Respiratory syncytial virus induces pneumonia, cytokine response, airway obstruction, and chronic inflammatory infiltrates associated with long-term airway hyperresponsiveness in mice. *J Infect Dis*. 2004;189:1856-1865.
33. Openshaw PJM, Yamaguchi Y, Tregoning JS. Childhood infections, the developing immune system, and the origins of asthma. *J Allergy Clin Immunol*. 2004;114:1275-1277.
34. Culley FJ, Pollott J, Openshaw PJM. Age at first viral infection determines the pattern of T cell-mediated disease during reinfection in adulthood. *J Exp Med*. 2002;196:1381-1386.
35. Dakhama A, Park JW, Taube C, et al. The enhancement or prevention of airway hyperresponsiveness during reinfection with respiratory syncytial virus is critically dependent on the age at first infection and IL-13 production. *J Immunol*. 2005;175:1876-1883.
36. Dakhama A, Lee YM, Gelfand EW. Virus-induced airway dysfunction: pathogenesis and biomechanisms. *Pediatr Infect Dis J*. 2005;24(11 suppl):S159-S169, discussion S166-S167.
37. Gern JE, Brooks GD, Meyer P, et al. Bidirectional interactions between viral respiratory illnesses and cytokine responses in the first year of life. *J Allergy Clin Immunol*. 2006;117:72-78.
38. O'Donnell DR, Openshaw PJ. Anaphylactic sensitization to aeroantigen during respiratory virus infection. *Clin Exp Allergy*. 1998;28:1501-1508.
39. Kristjansson S, Bjarnarson SP, Wennergren G, et al. Respiratory syncytial virus and other respiratory viruses during the first 3 months of life promote a local TH2-like response. *J Allergy Clin Immunol*. 2005;116:805-811.
40. Openshaw PJ. Potential therapeutic implications of new insights into respiratory syncytial virus disease. *Respir Res*. 2002;3(suppl 1):S15-S20.
41. Kim CK, Chung CY, Choi SJ, Kim DK, Park Y, Koh YY. Bronchoalveolar lavage cellular composition in acute asthma and acute bronchiolitis. *J Pediatr*. 2000;137:517-522.
42. Kim CK, Kim SW, Park CS, Kim BI, Kang H, Koh YY. Bronchoalveolar lavage cytokine profiles in acute asthma and acute bronchiolitis. *J Allergy Clin Immunol*. 2003;112:64-71.
43. Ehlenfield DR, Cameron K, Welliver RC. Eosinophilia at the time of respiratory syncytial virus bronchiolitis predicts childhood reactive airway disease. *Pediatrics*. 2000;105:79-83.
44. Welliver RC, Wong DT, Sun M, Middleton E Jr, Vaughan RS, Ogra PL. The development of respiratory syncytial virus-specific IgE and the release of histamine in nasopharyngeal secretions after infection. *N Engl J Med*. 1981;305:841-846.
45. Welliver RC, Sun M, Rinaldo D, Ogra PL. Predictive value of respiratory syncytial virus-specific IgE responses for recurrent wheezing following bronchiolitis. *J Pediatr*. 1986;109:776-780.
46. Dakhama A, Park JW, Taube C, et al. The role of virus-specific immunoglobulin E in airway hyperresponsiveness. *Am J Respir Crit Care Med*. 2004;170:952-959.
47. Welliver RC, Wong DT, Middleton E Jr, Sun M, McCarthy N, Ogra PL. Role of parainfluenza virus-specific IgE in pathogenesis of croup and wheezing subsequent to infection. *J Pediatr*. 1982;101:889-896.
48. Henry RL, Hodges IG, Milner AD, Stokes GM. Respiratory problems 2 years after acute bronchiolitis in infancy. *Arch Dis Child*. 1983;58:713-716.
49. Webb MS, Henry RL, Milner AD, Stokes GM, Swarbrick AS. Continuing respiratory problems three and a half years after acute viral bronchiolitis. *Arch Dis Child*. 1985;60:1064-1067.

50. Hall CB, Hall WJ, Gala CL, MaGill FB, Leddy JP. Long-term prospective study in children after respiratory syncytial virus infection. *J Pediatr*. 1984;105:358-364.
51. Sigurs N, Gustafsson PM, Bjarnason R, et al. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *Am J Respir Crit Care Med*. 2005;171:137-141.
52. Stein RT, Sherrill D, Morgan WJ, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet*. 1999;354:541-545.
53. Korppi M, Piippo-Savolainen E, Korhonen K, Remes S. Respiratory morbidity 20 years after RSV infection in infancy. *Pediatr Pulmonol*. 2004;38:155-160.
54. Kneyber MCJ, Steyerberg EW, de Groot R, Moll HA. Long-term effects of respiratory syncytial virus (RSV) bronchiolitis in infants and young children: a quantitative review. *Acta Paediatr*. 2000;89:654-660.
55. Noble V, Murray M, Webb MSC, Alexander J, Swarbrick AS, Milner AD. Respiratory status and allergy nine to 10 years after acute bronchiolitis. *Arch Dis Child*. 1997;76:315-319.
56. Tepper RS, Rosenberg D, Eigen H. Airway responsiveness in infants following bronchiolitis. *Pediatr Pulmonol*. 1992;13:6-10.
57. Proud D, Chow CW. Role of viral infections in asthma and chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol*. 2006;35:513-518.
58. Williams JV, Harris PA, Tollefson SJ, et al. Human metapneumovirus and lower respiratory tract disease in otherwise healthy infants and children. *N Engl J Med*. 2004;350:443-450.
59. Lugo RA, Nahata MC. Pathogenesis and treatment of bronchiolitis. *Clin Pharm*. 1993;12:95-116.
60. Randolph AG, Wang EE. Ribavirin for respiratory syncytial virus infection of the lower respiratory tract. *Cochrane Database Syst Rev*. 2000:CD000181.
61. Snell NJ. Economic and long-term benefits of ribavirin therapy on respiratory syncytial virus infection. *Lung*. 1990;168(suppl):422-429.
62. Simoes EAF. Treatment and prevention of respiratory syncytial virus lower respiratory tract infection. Long-term effects on respiratory outcomes. *Am J Respir Crit Care Med*. 2001;163:S14-S17.
63. Domachowske JB, Rosenberg HF. Advances in the treatment and prevention of severe viral bronchiolitis. *Pediatr Ann*. 2005;34:35-41.
64. Kneyber MC, Kimpen JL. Advances in respiratory syncytial virus vaccine development. *Curr Opin Investig Drugs*. 2004;5:163-170.
65. Polack FP, Karron RA. The future of respiratory syncytial virus vaccine development. *Pediatr Infect Dis J*. 2004;23(1 suppl):S65-S73.
66. The PREVENT Study Group. Reduction of respiratory syncytial virus hospitalization among premature infants and infants with bronchopulmonary dysplasia using respiratory syncytial virus immune globulin prophylaxis. *Pediatrics*. 1997;99:93-99.
67. 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;102:531-537.
68. Wenzel SE, Gibbs RL, Lehr MV, Simoes EAF. Respiratory outcomes in high-risk children 7 to 10 years after prophylaxis with respiratory syncytial virus immune globulin. *Am J Med*. 2002;112:627-633.
69. Simoes EAF, Carbonell-Estrany X, Kimpen J, et al. Palivizumab use decreases risk of recurrent wheezing in preterm children [abstract]. *Eur Respir J*. 2004;24:212S.
70. Mejias A, Chavez-Bueno S, Rios AM, et al. Comparative effects of two neutralizing anti-respiratory syncytial virus (RSV) monoclonal antibodies in the RSV murine model: time versus potency. *Antimicrob Agents Chemother*. 2005;49:4700-4707.
71. Venkatesh MP, Weisman LE. Prevention and treatment of respiratory syncytial virus infection in infants: an update. *Expert Rev Vaccines*. 2006;5:261-268.
72. Hayden FG. Respiratory viral threats. *Curr Opin Infect Dis*. 2006;19:169-178.