

Viral infections, atopy, and asthma: Is there a causal relationship?

R. Stokes Peebles, Jr, MD, FAAAAI Nashville, Tenn

Respiratory syncytial virus (RSV) remains the chief cause of hospitalization for lower respiratory tract illnesses in both infants and young children, and can produce severe outcomes. In addition, several studies have suggested that infants in whom RSV bronchiolitis develops may have recurrent wheezing and asthma later in childhood. Further complicating the picture is the question of whether there is a link between RSV infection in infancy and the development of atopy later in childhood. This review will discuss existing data on RSV infection and respiratory complications later in life, as well as the link between RSV and allergic disease. (*J Allergy Clin Immunol* 2004;113:S15-8.)

Key words: Respiratory syncytial virus, asthma, atopy, allergy, bronchiolitis

Viral infections are a common source of disease throughout a person's entire life span; although most infections are self-limiting, others produce severe complications. There is tremendous ongoing research in the prevention and treatment of certain viral infections, and one virus that is ubiquitous worldwide is respiratory syncytial virus (RSV). The importance of understanding this particular viral infection in childhood is that it is proposed to have a causal link for the development of atopy and asthma later in life.

Atopy and asthma affect many members of our society with both short- and long-term complications. Understanding the causes and risk factors for these diseases may lead to future treatments and may prevent the complications that are so prevalent with these disorders. The following information is presented to review the link between severe RSV infection in early life and both atopy and allergy.

EPIDEMIOLOGY OF RSV

Respiratory syncytial virus (RSV) remains the most important infectious cause of lower respiratory tract illnesses in both infants and children.¹ Approximately 90,000 children are hospitalized for RSV each year in the United States.¹ Throughout the world, outbreaks of RSV are common during the late fall, winter, and early spring. In the United States, the season usually begins in Novem-

Abbreviations used

Ig: Immunoglobulin

RSV: Respiratory syncytial virus

ber and progresses through April.¹ RSV is very common; 50% of children are infected during the first year of life, and by 3 years of age, almost all children have been infected with RSV.¹

Most infections with RSV are symptomatic; however, the range of severity in infants and young children varies greatly. RSV infection primarily manifests as mild cold symptoms in young children, but, in infants, approximately 30% to 70% of those who are first exposed to the virus develop associated pneumonia or bronchiolitis.¹ In fact, RSV has been shown to cause anywhere from 50% to 90% of the cases of bronchiolitis in infants.¹ RSV infection is the leading cause of respiratory failure in infants and young children, and approximately 500 children die from RSV infection in the United States each year.² Children at greater risk for more severe pulmonary complications of RSV bronchiolitis include those with underlying cardiac or pulmonary disease.¹

Re-infection with RSV is common throughout life. Between 40% and 70% of preschool-age children are re-infected with RSV, and approximately 20% of school-age children, adolescents, and adults are re-infected.¹ Most cases of re-infection result in mild courses of upper respiratory tract infection. Immunocompromised adults, particularly those that have undergone lung or bone marrow transplant, have increased morbidity and mortality from RSV infection.¹

RSV INFECTION AS AN INDEPENDENT RISK FACTOR FOR ASTHMA AND ALLERGY

Several studies have suggested that infants in whom RSV bronchiolitis develops will have recurrent wheezing and asthma later in childhood.³⁻¹⁰ The reasons this occurs are still unknown; whether RSV is an actual causal factor for asthma or simply targets children who are predisposed to bronchial obstructive disease is still speculation. Further complicating the picture is the question of whether there is a link between RSV infection in infancy and the development of atopy later in childhood. Results from clinical studies have been contradictory, with some results supporting a link,^{6,8} and others disproving a link.³⁻⁵

The link between RSV infection and asthma

Several studies have shown a link between RSV infection and asthma. Because wheeze is a common symptom

From the Division of Allergy, Pulmonary, and Critical Care Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee.

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Reprint requests: R. Stokes Peebles, Jr, MD, Center for Lung Research, T-1217 MCN, Vanderbilt University Medical Center, Nashville, TN 37232-2650.

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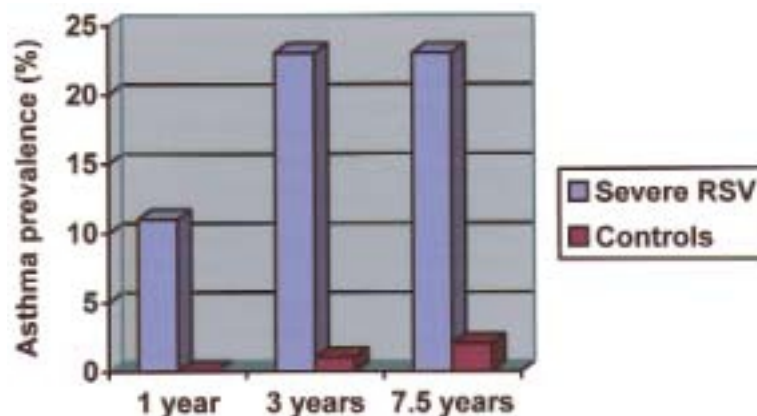


FIGURE. Prevalence of asthma was significantly increased in 47 children who had severe RSV bronchiolitis and subsequent hospitalization compared with matched controls. (Adapted from Sigurs N. *Ped Resp Rev* 2002;3:177-83.)

of asthma and may even signal a predisposition towards later development of asthma, it is often used as a marker in clinical studies. Sims et al demonstrated that severe RSV bronchiolitis in infancy increased recurrent wheezing in early childhood, but not at age 8 years.¹¹ Pullan and Hey found that RSV bronchiolitis in infancy resulted in increased episodes of wheezing in later childhood,³ as did Schauer et al.¹² In a report by Sly and Hippert, 44 of 48 children with RSV bronchiolitis in infancy were later diagnosed with asthma.¹³

A study by Korppi et al prospectively examined the effects of RSV and asthma in children 8 to 10 years of age.¹⁴ The study group consisted of 62 children with early childhood bronchiolitis, 29 children with early childhood pneumonia without wheezing, and 52 control children.¹⁴ The investigators found that the children with bronchiolitis had an increased risk of developing bronchial asthma.¹⁴ They also concluded that there was increased risk of bronchial hyperreactivity in children with bronchiolitis and pneumonia.¹⁴

To investigate the link between RSV and asthma, Sigurs et al followed a cohort of children from birth until age 7.5 years.^{9,10} Forty-seven infants infected with RSV bronchiolitis and subsequently hospitalized were compared with a matched control group of 93 children.^{9,10} The children were followed up at mean ages of 1, 3, and 7.5 years of age to determine frequency of asthma and recurrent wheezing.^{9,10} There was a statistically significant increase in asthma frequency among the RSV group compared with the control group at all follow-up points (Fig 1).^{9,10} The authors also found that the cumulative prevalence of asthma in the RSV group was 30% compared with 3% in the control group ($P < .001$); cumulative prevalence of "any wheezing" was 68% in the RSV group and 34% in the control group ($P < .001$).⁹

Link between RSV infection and atopy

The link between RSV infection and atopy is less clear. Although evidence exists showing that the devel-

opment of atopy is more common in children who have had RSV infection in early childhood, it is unknown whether the RSV infection leads to the development of atopy or if these children are "preprogrammed" to develop more severe manifestations of atopy in response to a viral respiratory infection. As part of their cohort study, Sigurs examined the frequency with which children with severe RSV developed allergic disease compared with the control group.¹⁰ At both 3 and 7 years of age, allergic sensitization as defined by either a positive skin test or specific immunoglobulin (Ig)E in vitro blood test was significantly increased in children with a history of RSV hospitalization.^{9,10}

Another cohort study by Schauer et al followed 42 infants who had been hospitalized with severe RSV bronchiolitis. At one year of age, 33% (14/42) of infants who had been infected with RSV tested positive for serum IgE antibodies compared with only 2.3% (2/84) of a matched control group.¹²

An interesting theory recently proposed is the possible genetic link between atopy and the severity of RSV infection and wheezing later in life.¹⁵ In a study involving Korean children hospitalized for RSV, Choi et al found an overrepresentation of an interleukin-4 gene haplotype in patients who had severe RSV.¹⁵ The importance of this finding is that this particular haplotype is associated with an increase in interleukin-4 transcriptional activity and a predisposition for the development of asthma.¹⁵ Animal studies have yielded contradictory results regarding whether RSV infection predisposes a person to atopy. Schwarze et al have reported that in mice, RSV infection enhances subsequent allergic inflammation.¹⁶ In contrast, one group has found that previous infection with RSV decreases inflammation resulting from allergic sensitization as well as airway hyperresponsiveness.¹⁷ However, RSV infection during the development of active allergic inflammation does result in airway hyperresponsiveness without increases in IgE levels.¹⁷

TABLE. Adjusted odds ratios for frequent wheeze after exposure to lower respiratory tract illness¹⁹

	RSV	Para-influenza	Other agents	Negative tests	None
Wheeze after 3 years of age					
6 y	4.3	2.4	2.9	1.9	1.0
8 y	1.9	0.4	1.3	2.3	1.0
11 y	2.4	2.3	1.0	2.0	1.0
13 y	1.4	1.3	3.1	2.1	1.0

TUCSON CHILDREN'S RESPIRATORY STUDY

In 1980, one of the longest running respiratory cohort studies was formed to investigate the link between early life lower respiratory tract infection and the development of obstructive lung disease.¹⁸ The Tucson Children's Respiratory Study followed more than 1200 children born between 1980 and 1984. Today, more than 970 subjects are still being tracked.¹⁸

These investigators analyzed recurrent wheezing, atopic status, and pulmonary function in children with documented viral lower respiratory disease in the first 3 years of life. RSV infection was confirmed by viral culture and immunofluorescopy. Lower respiratory tract RSV infection before 3 years of age was associated with an increased risk of wheezing by 6 years of age and up to 11 years of age (Table).¹⁹ The risk of wheezing was inversely related to the children's age; RSV infection was no longer a risk factor for wheezing when a child reached 13 years of age. These investigators also found no association between lower respiratory tract RSV infection and allergic sensitization as defined by positive immediate hypersensitivity skin tests to aeroallergens.¹⁹

EFFECT OF RSV IMMUNE GLOBULIN IN PREVENTING ATOPY AND ASTHMA

Because serious lower respiratory infections with RSV may later predispose a child for developing asthma, it has been theorized that treating RSV infection with RSV immune globulin will lessen the risk of later complications. Wenzel et al evaluated this hypothesis by studying the general health status of 13 children who had been treated prophylactically 7 to 10 years earlier with RSV immune globulin.²⁰ They were compared with 26 matched controls who had not received prophylactic treatment. At the time of follow-up, children treated with immune globulin had improved forced expiratory volume at one second/forced vital capacity ratios, less atopy, and decreased frequency of ever having had an asthma exacerbation.²⁰

The results of this study are provocative and seem to suggest that severe RSV bronchiolitis might lead to an increased incidence of allergy and asthma. However, several factors, including small sample size, the non-randomized design, and retrospective nature, suggest that a larger, prospective, randomized study is necessary to obtain a better understanding of whether preventing severe RSV infection has an impact on the development of allergy.

CONCLUSIONS

Numerous studies have suggested that there may be a link associating severe RSV infections early in life and the development of atopic disease. A better understanding of the origins of these diseases, as well as their risk factors carries quality of life, financial, and social implications. Examination of the studies presented here provides the foundation for the research that is sure to come on this fascinating, yet complex connection. Directions for future research include addressing atopy that persists beyond childhood and into adulthood and the link between RSV, atopy, and genetics. Once an understanding of this process is achieved, clinicians can work towards developing treatment strategies aimed at prevention.

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