

Why does respiratory syncytial virus appear to cause asthma?

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Multiple studies have demonstrated that being admitted to the hospital during infancy for respiratory syncytial virus (RSV)–induced bronchiolitis predicts an increased risk of asthma-like disease in later life.^{1–3} Although RSV is the most common virus in hospitalized children with bronchiolitis, rhinoviruses are by far the most frequently detected type of virus in patients with asthma exacerbations.⁴ The question remains of whether these are previously healthy infants in whom RSV causes the development of later asthma or whether these are simply infants with a predisposition to later asthma who are responding to an RSV infection with their first virus-induced asthma attack.

Bacharier et al⁵ report 7-year follow-up data from one of the largest prospective cohorts of infants admitted to the hospital for RSV-induced bronchiolitis. Past criticism of such cohorts has been the age of hospitalization, with older children appearing to be more representative of an asthma-like exacerbation. This cohort was focused correctly on the younger age of less than 12 months. There was a great deal of quality data to consider in this study, which is a credit to the authors.

Although the conclusions appear to be valid, there remain important parts of this study to discuss. As the authors note, there was a significant retention bias of children with mothers who have asthma. This is a frequent problem in such studies because parents with the disease are more motivated to see the study through. Familial history of asthma provides a personal incentive for remaining in the study and a greater awareness of the symptoms, potentially leading to increased diagnoses of asthma. That being said, the authors note that the rate of maternal asthma among those who remained in the study through age 6 years (34%) was substantially lower than the rate of physician-diagnosed asthma (49%). They also included maternal history of asthma as a covariate in the multivariate analyses, and although it remained an independent predictor of physician-diagnosed asthma and active asthma at baseline, maternal asthma was no longer a significant predictor of these outcomes at 3 years of age. The authors suggest that maternal history did not remain a significant risk factor for asthma outcomes at age 6 years or became nonsignificant, whereas other risk factors emerged as significant.

Overall, it would be hard to design a study to avoid this problem. One could blindly pair infants with a positive family history with those who do not have such a history and then remove both infants if a partner infant withdraws. However, this would require a great number of children at enrollment.

Increased CCL5 (RANTES) expression in nasal epithelial cells during RSV infection carried an odds ratio of 3.8 for the subsequent development of physician-diagnosed asthma. Rhinovirus also increases CCL5 release from human subjects both *in vivo*⁶ and *in vitro*.^{7,8} Ninety percent of children have an RSV infection by age 2 years, with up to 40% having lower respiratory tract involvement.^{9,10} With such a high rate of infection and so many affected by lower airways disease, if RSV were truly a causal agent in asthma pathogenesis, it seems unclear why the association occurs only with hospitalized cases. Unfortunately, this study design did not allow the measurement of RANTES expression before RSV infection. Such a prospective design could have discerned whether there was evidence of allergic immune responses at play before RSV infection. Thus the question remains of whether the expression of RANTES is related to the severity of RSV infection or is related to an underlying predisposition to asthma-like inflammatory responses.

The authors report that having a dog in the home at the time of RSV infection could increase the risk of later asthma. This is in line with data in animal models that the combination of a virus with an allergen can increase the chance of an allergic airway response.^{11,12} Prospective studies of RSV prevention with palivizumab also suggest more than 1 mechanism is at work in the later development of asthma after RSV-induced bronchiolitis. It appears that palivizumab cannot prevent later asthma in infants with a strong predisposition to asthma.¹³ In contrast, for those without this predisposition, RSV prevention seems to have a strong preventative effect for later asthma. Overall, although the mechanism of possible synergistic interaction between RSV and the host remains incompletely understood, it is important to remember that RSV-induced bronchiolitis occurs during a window of opportunity when an infant's immunity to the environment is still being developed. As such, this idea of synergy could still be an important mechanism to keep in mind for future research.

The study could be criticized for its definition of asthma. The authors relied on a physician's diagnosis of asthma and parent-reported wheeze. Previous studies have demonstrated discordant views on the importance of clinical factors in the diagnosis of asthma.^{14,15} Not all wheeze is caused by asthma, and there is frequent parental confusion between wheeze and other noisy breath sounds. Although the questionnaire was standardized for this study (ie, the same questions were asked to all families), it appears to rely on the parents' understanding of wheeze. This lack of a clear definition of asthma has been an issue raised in other studies^{1,2} and is a shortcoming of most preschool studies of wheeze. In addition, the

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lung function data did not appear to help clarify the diagnosis because even the nonasthmatic group had airway hyperresponsiveness and no significant difference in FEV₁ at age 7 years.

Finally, it is important to comment that most of the children presenting to the hospital with RSV-related disease (83% of 1026 children) could not be enrolled in this study. This was because of age (>12 months) but also because of a history of previous airway difficulties (ie, prior wheezing, excessive gastroesophageal reflux/pulmonary aspiration, and congenital airway anomalies). Again, considering the lung function data, most children had airway hyperresponsiveness irrespective of whether the diagnosis of asthma was made. The authors acknowledge there might be previously undiagnosed conditions in the included group and agree this could account for the severity of the disease leading to hospitalization. In our experience many pediatricians caring for infants with bronchiolitis in the hospital expect that once the infant is safe to go home, no further workup should be considered. To the contrary, these data suggest that another “real-world take-home message” is that that RSV in the hospital setting is also a marker of underlying chronic airway difficulties before infection. Some of this could be asthma, but many other diagnoses need to be considered. Viral illnesses are a leading cause of asthma exacerbations⁴ but also exacerbations of other chronic airway disorders.^{16,17} Thus it could be suggested that hospitalization for RSV should warrant an overall reconsideration of the previous health status of a child and that underlying predisposition to chronic airway diseases in general should be sought even beyond asthma. This could lead to better prevention of chronic airways disease.

In summary, the evidence currently supports the notion that severe RSV-induced bronchiolitis in infancy is a risk factor for subsequent wheezing episodes and the diagnosis of asthma. It is still unclear whether RSV acts as a causal agent in the pathogenesis or whether severe RSV-induced bronchiolitis represents a first exacerbation of asthma in susceptible subjects.

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