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Rhinovirus and the Initiation of Asthma

James E. Gern, MD [Professor and Pediatrics of Medicine]
Division of Pediatric Allergy, Immunology, and Rheumatology, University of Wisconsin Medical School, 600 Highland Avenue K4/918, Madison, WI 53792-9988, Phone: +1 608-263-6201, Fax: +1 608-265-2207, E-mail: gern@medicine.wisc.edu

Abstract

Purpose of review—Virus-induced wheezing in infancy is a risk factor for asthma, and recent studies have highlighted the role of rhinoviruses in causing acute illnesses and as a possible contributing factor to chronic asthma.

Recent findings—Rhinoviruses (HRV) have long been known as the most common cause of the common cold in infants and children. Recent developments in molecular diagnostics have led to the discovery of new viruses, and have also provided data to implicate HRV as important causes of lower respiratory infections and acute virus-induced wheezing in preschool children. In addition, HRV-induced wheezing episodes appear to identify children who are at increased risk for the subsequent development of childhood asthma.

Summary—Collectively, these findings raise the possibility that LRI with pathogens such as HRV and RSV could participate in the causation of asthma, especially in children with suboptimal antiviral defenses. A variety of experimental models and clinical studies have been used to identify possible mechanisms related to the infection and the ensuing host response that could disturb normal lung and immunologic development to promote asthma. Defining these relationships could lead to new therapeutic and preventive approaches to common forms of childhood asthma.

Keywords

Rhinovirus; respiratory syncytial virus; children; asthma

Introduction

This question of whether respiratory infections with viruses can cause asthma is controversial, and has been argued for decades. Recently, the advent of molecular viral diagnostics has expanded our understanding of the epidemiology of respiratory illnesses in infancy by improved detection rates for known virus, and surprisingly, has led to an onslaught of discovery of previously unrecognized respiratory viruses [1*,2*,3*]. These new diagnostic techniques have been particularly helpful in understanding the role of human rhinoviruses (HRV), which are particularly difficult to grow in tissue culture, in acute illnesses, and in exacerbations of chronic disease such as asthma, chronic obstructive lung disease, and cystic fibrosis. In addition, recent clinical studies have highlighted the role of HRV as an important lower airway pathogen in infancy, and further suggest that children who wheeze with HRV may be at particularly high risk for the subsequent development of asthma. This review will focus on the role of HRV infections in early childhood respiratory illnesses, and discuss clinical evidence and mechanistic studies evaluating a potential role for HRV infections in the initiation of asthma.

Epidemiology of viral infections and wheezing in infancy

Viral respiratory infections are universal in the first few years of life, and cause wheezing illnesses in about 50% of affected infants. Bronchiolitis is the most common wheezing illness in infancy, and can be caused by a number of different viral infections (Table I). Interestingly, despite very different viral replication cycles, the clinical manifestations of infections with these diverse viruses are quite similar. RSV, HRV, and mixed viral infections are the most common causes of these illnesses: RSV infections are responsible for the majority of cases from December through April (offset by 6 months in the southern hemisphere), while HRV infections account for most cases during the rest of the year [4]. HRV, once considered to be limited to the upper airway, is now recognized as an important cause of lower respiratory infections [4,5**,6,7].

HRV are enterovirus species in the Picornaviradae family, and 100–101 prototypical strains have been divided into groups A and B based on patterns of inhibition with certain antiviral compounds, along with molecular analysis of partial genetic sequencing. HRV serotypes were originally identified by growth in tissue culture followed by inhibition with specific antisera; this work was largely completed in the 1980s, although nontypable HRV were occasionally reported. More recently, partial and complete genetic sequencing of viruses detected using molecular techniques have revealed that the number of HRV strains has been severely underestimated, and in fact evidence is growing for a third group of HRV ("HRV C"), that appears to be as different from HRV groups A and B as it is from other enteroviruses [6,8*, 9*,10*,11*]. These newly discovered viruses are quite common, and comprise up to 50% of HRV detected in some clinical studies [8*]. Clinical manifestations appear similar to other HRV, and they have been found to contribute to wheezing illnesses in infants, and in children with asthma. The frequency of detection appears to be consistently high in studies conducted in North America, Europe, Asia, and Australia [12].

HRV, either alone or in combination with other viruses [13], are an important cause of wheezing illnesses, and yet are also the viruses most often detected in asymptomatic infants and children [4,14*,15]. The observed diversity in the severity of HRV clinical illness could be related to either host factors or the strain of infecting virus. An outstanding question is whether there are HRV strains that are inherently more virulent, and thus more likely to cause wheezing illnesses. This is certainly the case for other respiratory viruses (e.g. influenza): the large number of strains suggests that this is also true for HRV. Identifying more virulent strains, and the molecular mechanisms that determine this characteristic, will be important in developing new therapeutic strategies aimed at lessening the severity of HRV-related illness.

Rhinovirus and distribution in the lower airway

HRV replicate best at relatively cool temperatures (33–35°C), and so it was long assumed that infections were limited to the upper airway. Although lung parenchyma is at core temperature (37°C), airways are considerably cooler, and temperatures in large and medium sized airways are ideal for HRV replication [16*]. In fact, HRV has been demonstrated in lower airway fluids and cells and after experimental infection of the upper airway [17–19]. Furthermore, there is considerable clinical evidence linking HRV infections to lower respiratory infections in children, including those who are hospitalized for pneumonia [5–7,20]. A recent year-long population-based study of children < 5 year of age found that HRV was detected in 26% of children hospitalized for respiratory symptoms or fever [5]. HRV-related hospitalization rates were especially high for infants, and children with asthma (Table II). These findings suggest the possibility that infections with HRV, like RSV and other respiratory viruses, can directly injure airway tissues during the acute infection. One unique feature of HRV infections is the large number of serotypes and strains – well over 100. Thus, HRV infections occur frequently

in young children, and account for significant morbidity related to both upper and lower respiratory illnesses.

HRV infections in infancy and subsequent asthma

The coughing, wheezing, and tachypnea associated with viral respiratory illnesses closely resemble exacerbations of asthma in older children, and 30–50% of children with recurrent virus-induced wheezing in infancy go on to develop asthma. This progression suggests that viral respiratory infections might damage the airways and initiate asthma (Figure 1). It is also possible that the relationship is not causal, and that virus-induced wheezing episodes instead reveal a preexisting tendency for asthma secondary to impaired lung physiology or antiviral responses. A third possibility, which combines elements of the first two, is a “two hit hypothesis” in which viral infections promote asthma mainly in predisposed children [5,21]. Understanding the host-pathogen interactions that determine the severity of respiratory illnesses and long-term sequelae would be of great help in identifying at-risk individuals, and in designing new and more effective treatments and preventive strategies.

Risk factors for virus-induced wheezing

Risk factors for bronchiolitis and viral LRI include young age, especially the first 6 months of life, small lung size, and exposure to tobacco smoke [22**]. Lung-specific factors such as preexisting airway hyperresponsiveness [23] and/or limitation to airflow [22] also increase the risk of viral LRI. In addition, several genetic factors modify the risk of RSV-induced wheezing, including polymorphisms in genes encoding surfactant proteins, cytokines, and chemokines [24]. Although data are more limited for HRV infections, polymorphisms in IL-10 may influence the severity of illnesses with this virus [25].

Risk factors for asthma following viral infection

Long-term studies have demonstrated that infants hospitalized with RSV bronchiolitis have a 2–3-fold increase in the risk of developing asthma later in childhood. This risk is further increased by a strong family history of atopy, or the development of atopic features, particularly if this occurs during early childhood.

The type of virus-induced wheezing episode also appears to influence the risk of subsequent asthma. Wheezing illnesses caused by RSV, parainfluenza viruses, or influenza A appear to have similar long-term prognosis. In contrast, a case control study conducted in Finland demonstrated that infants hospitalized with HRV-induced wheezing were found to have a particularly high risk for subsequent asthma, and this relationship persisted at least through the late teen years [26,27**].

This finding is corroborated by the results of two birth cohort studies. The Childhood Origins of Asthma (COAST) study is a high-risk birth cohort study in which families with at least one parent with allergies or asthma were enrolled prenatally, and both immune development and respiratory illnesses were prospectively evaluated [21]. Through the use of PCR technology, viral etiologies were identified in 90% of wheezing illnesses. Notably, moderate to severe HRV infections (with and without wheezing) during infancy were a significant risk factor (OR = 10) for persistent wheezing at age 3 years [4]. Moreover, RV wheezing illnesses in the first three years of life were significantly associated with the development of asthma at age 6 years [28**]. The combination of allergic sensitization and HRV-induced by age 3 was associated with the highest risk of developing asthma. Similarly, in high-risk infants who were followed prospectively in Australia, Kusel and colleagues prospectively evaluated 198 Australian children and compared respiratory illnesses in the first year of life to respiratory outcomes at age 5 years [29**]. Wheezing illnesses with either HRV or RSV were associated with asthma

at age 5 years. Interestingly, these associations were only significant in the children with early onset (by age 2 years) allergic sensitization. Both of these studies highlight the role of virus-induced wheezing in infancy, and HRV in particular, in determining the risk for subsequent asthma. Children who develop allergic sensitization at an early age and also wheeze with HRV are at high risk for developing asthma.

How do viral infections affect long-term airway physiology?

Infancy is a period of profound growth and development of the lungs, and these changes are occurring at the time of maximum susceptibility to viral LRI. This coincidence raises a number of questions related to long-term effects of viral infections on the structure and function of the developing lung.

Pre- and postnatal lung development

Lung development begins at about 4 weeks gestation, and continues even after birth.[30] The basic lung architecture, including differentiation of the respiratory airways and differentiation of future respiratory gas exchange (acinar) units, is largely completed by 40 weeks gestation. Postnatally, alveoli multiply (alveolarization), and this process continues for 2–3 years. Lung growth is maximal at this time, and involves continuous “remodeling” throughout childhood. Murine models of gene deletion and overexpression have identified key regulatory factors for lung growth and alveolarization, such as epidermal growth factor [EGF], vascular endothelial growth factor [VEGF], transforming growth factor-β (TGF-β), and platelet-derived growth factor [PDGF].

What happens to lung development when this carefully orchestrated process is disrupted by a viral respiratory infection? First, viral infections damage airway structures via replication, and also by inducing inflammatory immune responses. In vitro models demonstrate that HRV replication is enhanced in epithelium that is damaged, indicating that the barrier function of the epithelial layer is an important component of antiviral defenses [31,32]. Fibroblasts are also quite susceptible to HRV infection, and by extension, loss of the epithelial layer would provide viral particles with access to additional susceptible tissues. More severe infections that cause considerable damage to lung tissues, with directly or by inducing a harmful inflammatory response, could have adverse effects on lung development that lead to chronic lung disease.

Virus-induced antiviral and inflammatory responses

It is likely that the balance between an effective antiviral response and damaging inflammation influence both short and long-term effects on the developing lung. For viruses such as RV, which infect relatively few cells in the airway,[33,34] virus-induced inflammatory responses may be the driving force for airway symptoms and lower airway dysfunction. During the acute infection, epithelial edema and shedding together with mucus production promote airway obstruction and wheezing. Viral RNA activates innate immune responses by binding to molecules such as Toll-line receptor-3 (TLR-3), TLR-7, the dsRNA dependent protein kinase (PKR), RIG-I, and MDA-5.[35–37] These mechanisms activate a host of antiviral effector mechanisms, and also secretion of chemokines to recruit additional inflammatory cells into the airway [38]. Once replication is underway, mononuclear cells strengthen the antiviral response through the secretion of interferons, proinflammatory cytokines and chemokines.[39,40]

Interestingly, there are experimental and clinical data indicate that interferon responses in early life are inversely associated with the severity of viral respiratory illnesses. For example, airway epithelial cells cultured from subjects with asthma were reported to produce reduced amounts of IFN-β, IFN-γ and IFN-λ in response to HRV, and support enhanced viral replication [41*, 42**,43**]. Furthermore, there is clinical evidence that babies with low *ex vivo* interferon

responses in early life are more likely to have frequent viral respiratory illnesses, including those associated with wheezing [44**,45*,46*]. These experimental findings suggest that an impaired interferon response could increase the risk of more severe viral respiratory infections in infancy, and perhaps promote long-term damage to airway structures. Interestingly, reduced IFN-γ responses in infancy are also observed in children with atopic features, which could help to explain why atopy is a risk factor for virus-induced wheezing and the progression to asthma (Figure 2) [28**,29**].

The coordinate expression of adhesion molecules and secretion of chemokines by airway cells provides a potent stimulus for the recruitment of neutrophils, however, to date there is no convincing evidence that this is either beneficial or harmful to the host. Products of neutrophil activation can damage the airways, and the release of the potent secretagogue elastase can upregulate goblet cell secretion of mucus [47]. However, the rapid recruitment of these cells to the airways suggests that this response is important for host defense. The role of these responses in long-term outcomes has not been determined. HRV infections can also indirectly activate and cause degranulation of eosinophils through a lymphocyte-dependent mechanism [48]. This effect could contribute to the enhanced risk of virus-induced wheeze in children with allergic sensitization [49].

Effects of viral infections on growth factors

Acute infections with HRV and other viral infections can induce the synthesis of several factors that regulate airway remodeling and alveolar development, including VEGF [50,51*], NO [52], TGF-β [53,54], amphiregulin [51*], activin A [51*], and FGF [55]. Furthermore, viral infections can upregulate neurotropins that have the potential to cause remodeling of the airway neural network, and possibly promote nonspecific airway responsiveness [56]. How single or repeated bouts of virus-induced overexpression of these regulators of lung development and remodeling affects the ultimate lung structure and function is not known, but is of interest regarding the long-term effects on lung function and asthma. These questions may be best addressed in animal models, and recently two different models for HRV infections in the mouse have been published [57**,58*], as well as methods for serial passage of mouse epithelial cells for propagation of HRV [59].

Summary and conclusions

The pathologic features and physiologic abnormalities of asthma appear in the first few years of life, during a period of rapid growth and development. These observations raise the possibility that contracting recurrent viral LRI in infancy could be one of several pathways that lead to the development of asthma, especially in children with atopic features. Plausible mechanisms have been proposed, though not yet proven, to relate viral infections in early life to epithelial damage, airway remodeling, and intermittent airway obstruction leading to asthma. New experimental models are needed to answer questions about causality, and the relative importance of hereditary versus environmental or lifestyle-related factors in the progression from virus-induced wheezing to multifactorial childhood asthma.

Results of a recent nonrandomized clinical trial of palivizumab suggest that preventing or moderating the severity of RSV infections in infancy also reduces subsequent asthma [60*]. In addition, there is some evidence that treatment of infants with systemic corticosteroid during an acute HRV wheezing illness can reduce the subsequent risk of recurrent risk [61*]. These studies provide optimism that prevention or early treatment of viral LRI in early childhood could reduce long-term morbidity related to asthma. Further progress in this area would be advanced by the development of effective and practical antiviral strategies for HRV and other respiratory viruses.

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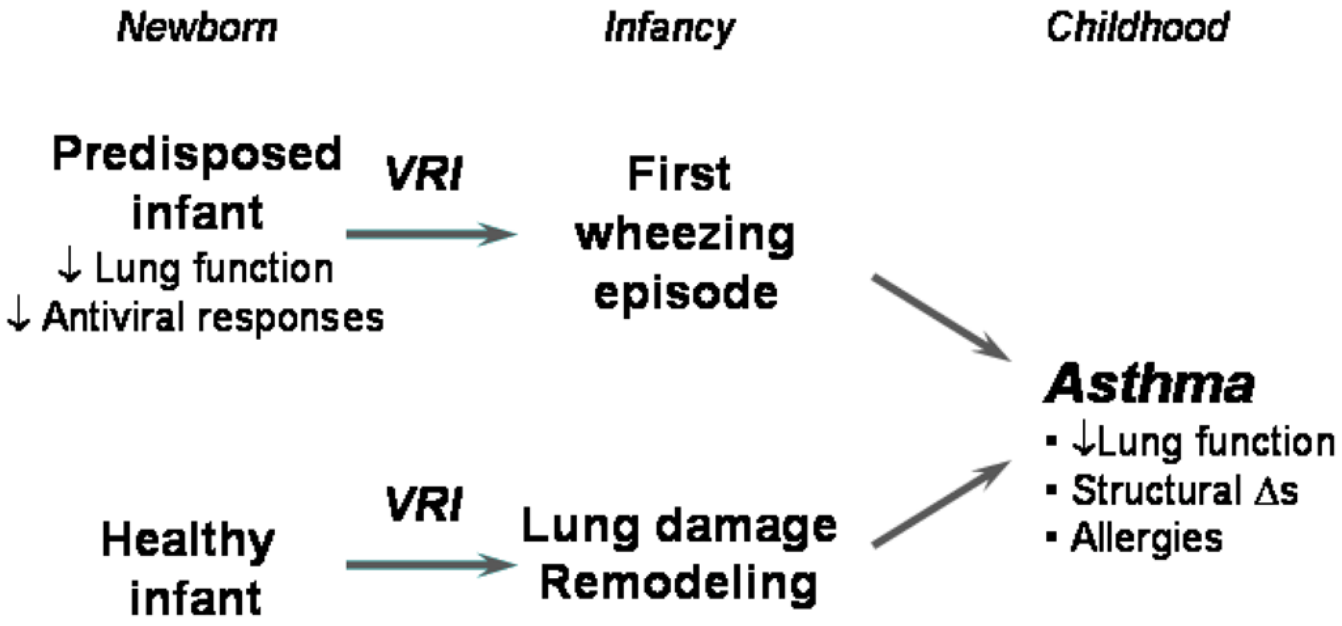

Figure 1.
Relationship of viral respiratory infections in early life to the development of asthma.

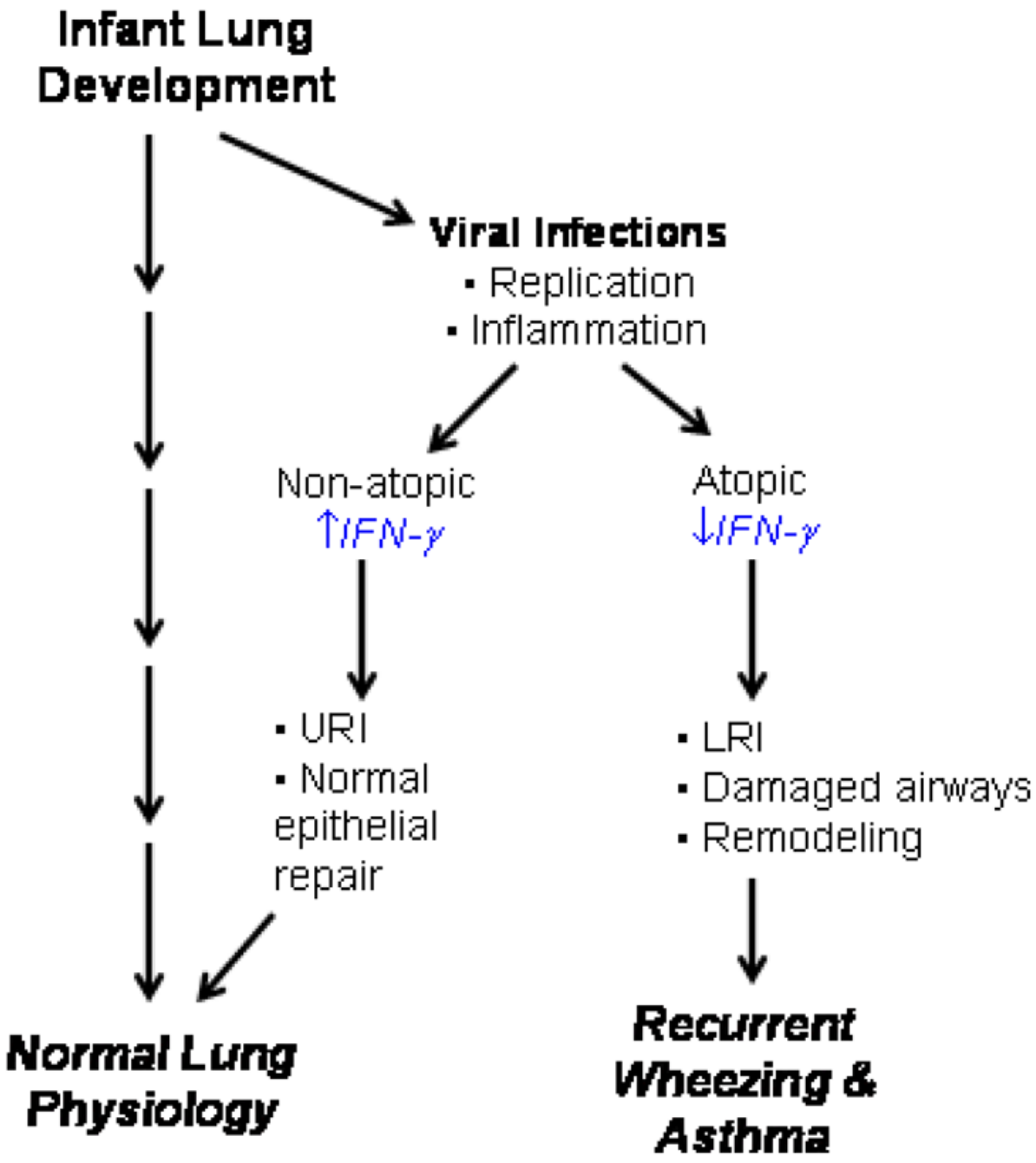

Figure 2.
Atopy, wheezing, and asthma. Viral respiratory infections are common during the first 3 years of life, a period of rapid lung development. Children with atopic features tend to have reduced IFN–γ responses, which is also associated with increased susceptibility to viral LRI. Viral replication and the induction of inflammation in the lower airway during this period of rapid development could lead to long term changes in airway structure (fibrosis), abnormal physiology (airway hyperresponsiveness), and clinical asthma.

Table I

Viruses* associated with bronchiolitis in infancy

Viruses	Family	Genome†
RSV	Paramyxovirus	ssRNA (−)
PIV	Paramyxovirus	ssRNA (−)
Influenza	Orthomyxovirus	ssRNA (−)
MPV	Pneumovirus	ssRNA (−)
HRV A, HRV B, **HRV C**	Picornavirus	ssRNA (+)
Enteroviruses	Picornavirus	ssRNA (+)
OC43, **NL63, HKU1, SARS**	Coronavirus	ssRNA (+)
Bocavirus	Parvovirus	ssDNA (−)
WU, KIP	Polyomavirus	dsDNA
Adenoviruses	Arenovirus	dsDNA

*Bold print indicates viruses that were recently discovered using molecular diagnostics.

†Abbreviations: ss, single stranded; ds, double stranded; (+) and (−) refer to the polarity of the genome.

Table II

Age-specific rates for HRV-related hospitalization in children*

Age (months)	Hospitalization rates†
0–5	17.6 (14.9 – 20.6
6–23	6.0 (5.0 – 7.0)
24–59	2.0 (1.6 – 2.4)
Asthma	
Yes	25.3 (21.6 – 29.5)
No	3.1 (2.7 – 3.5)

*From reference [5]

†Rates per 1000 children (95% confidence interval)