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The role of early life viral bronchiolitis in the inception of asthma

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Abstract

Propose of review—Cumulative evidence suggest that early life bronchiolitis is a major risk factor for subsequent wheezing episodes and asthma. The purpose of this review is to present the recent findings and current perspectives regarding the interplay between bronchiolitis and long-term respiratory outcomes.

Recent findings—Recent studies have supported the long-recognized link between early life severe Respiratory Syncytial Virus bronchiolitis and the physician diagnosis of asthma by school age, and this association appears to continue into early adulthood. Evidence is accumulating regarding the role of early life infection with human rhinovirus as an important antecedent for future asthma. Whether viral bronchiolitis is causal or an early manifestation of future asthma remains uncertain. Vitamin D status has emerged as a potential modifying factor for viral-induced wheeze and could potentially influence the development of asthma.

Summary—Viral bronchiolitis early in life is a major and potential long-term risk factor for subsequent wheezing and asthma. Whether the association between bronchiolitis and subsequent asthma is due to causality or a reflection of predisposition may be dependent on host factors and virus-specific effects.

Keywords

Viral bronchiolitis; asthma; wheeze; respiratory syncytial virus; rhinovirus

Introduction

Viral bronchiolitis in infancy has been known for decades to be an antecedent for subsequent wheezing and asthma during childhood. However, recent reports suggest that the risk for asthma following bronchiolitis may be higher than was previously estimated, and that this association may persist into early adulthood. Previously, most the research in this field focused on the role of Respiratory Syncytial Virus (RSV) in the inception of asthma. However, advancements in molecular viral diagnostic techniques have allowed for detection of previously undetectable or difficult to detect respiratory viruses, and have led to the increased recognition of the role of human rhinovirus (HRV) lower-respiratory-tract infection (LRTI) in asthma inception. This review discusses the recent evidence and concepts regarding the role of early life viral bronchiolitis and future asthma.

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The role of RSV bronchiolitis in the inception of asthma

The cohort established by Sigurs and colleagues[1] remains the longest prospective longitudinal cohort that has investigated the consequences of severe RSV bronchiolitis in infancy in terms of the development of subsequent recurrent wheeze (RW) and asthma. This Swedish cohort enrolled 47 infants with severe RSV bronchiolitis. For the purpose of this review, the term severe RSV bronchiolitis refers to an episode of bronchiolitis severe enough to require hospitalization. All infants enrolled were younger than one year of age at the time of the hospitalization, and more than 90% were younger than 6 months. Ninety-three age- and gender - matched children were recruited as controls. Children who experienced severe RSV bronchiolitis had a greater prevalence of asthma/recurrent wheezing (RW, 3 or more episodes) and allergic sensitization at the ages of 3, 7, and 13 years compared with the control cohort. The most recent report from this cohort[2] demonstrated that the association between severe RSV bronchiolitis and the outcomes of asthma and atopy persists into early adulthood. At the age of 18 years, significantly higher prevalences of the following outcomes were noted in the RSV bronchiolitis cohort compared with controls: asthma/RW (39% vs 9%), clinical allergic rhinoconjunctivitis (43% vs 17%), and sensitization to perennial allergens (41% vs 14%). Only severe RSV bronchiolitis in infancy and current allergic rhinoconjunctivitis were found to be significant predictors for current asthma/RW. In addition, at the age of 18 years, patients with history of RSV bronchiolitis had lower pulmonary function (FEV_1, FEV_1/FVC ratio), greater airway hyper-responsiveness, and greater bronchodilator response. These indicators of airway obstruction could already be detected at the age of 7 and 13 years. Although reduced spirometry indices among RSV patients were independent of current diagnosis of asthma/recurrent wheeze, small airway dysfunction measured by lung clearance index was lower among patients with a current diagnosis of asthma. Overall, these findings demonstrate that severe RSV bronchiolitis early in life is associated with an increased risk for asthma, airway hyper-responsiveness, and allergic sensitization, and suggest that this association might last into early adulthood.

This finding of a persistently elevated risk for asthma in adulthood after severe RSV bronchiolitis[1] differs from the effects reported by Stein and colleagues[3], who found that RSV bronchiolitis in the Tucson Children's Respiratory Study (TCRS) was an independent risk factor for the subsequent development of wheezing up to age 11 years, but this risk became non-significant by the age of 13 years. However, the children in the TCRS cohort had less severe RSV bronchiolitis, as they experienced predominantly outpatient episodes. These differences in long-term outcome may be a reflection of a differential relationship of bronchiolitis severity on subsequent respiratory disease, as demonstrated by a recent study by Carroll and colleagues[4],. They noted a gradient of increasing risk of asthma following bronchiolitis based upon the level of heath care utilization (i.e., ambulatory clinic visit vs. emergency department visit vs. hospitalization) during bronchiolitis, with the greatest risk of asthma following bronchiolitis hospitalization[4].

The RSV Bronchiolitis in Early Life (RBEL) study, a prospective cohort of infants hospitalized for RSV bronchiolitis focused on the identification of determinants of post-RSV asthma, recently reported asthma-related outcomes in the 6 years following the initial infection[5]. Among the 206 children enrolled with severe RSV bronchiolitis during the first year of life, 48% had received a physician diagnosis of asthma by the seventh birthday. Risk factors for an asthma diagnosis were identifiable during the first year of life, with maternal asthma and high levels of dog allergen exposure being associated with an increased risk of asthma, while Caucasian ethnicity and daycare attendance were associated with decreased risk of asthma. Allergic sensitization at age 3 years was also associated with an increased risk of physician diagnosis of asthma. The authors identified a biological predictor of post-

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RSV asthma - greater levels of nasal epithelial expression of the chemokine CCL5 during acute bronchiolitis were strongly predictive of physician-diagnosed asthma by the seventh birthday. These findings support severe RSV bronchiolitis as a substantial risk factor for asthma by school age and identify a novel biological predictor for asthma risk, namely nasal CCL5 expression.

The role of non-RSV bronchiolitis in the inception of asthma

Recent advances in virologic detection methodologies have led to the identification of additional non-RSV viral induced LRTIs in early childhood, particularly HRV, as important risk factors for future asthma.

Valuable insight on the association between early life HRV LRTI and the risk of future asthma was reported from the Childhood Origin of Asthma (COAST) project. COAST is a birth cohort study of infants at high risk for allergic diseases and/or asthma based on parental history of respiratory allergies and/or a history of physician-diagnosed asthma[6]. 238 children have been followed up to the age of 8 years[6]. The investigators collected data on the causative virus for each LRTI in this cohort, and previously reported that HRV LRTIs during the first year of life, even though most were outpatient LRTIs, were a significant predictor of asthma at age six years[7]. A recent report from this group suggested that the occurrence of a HRV associated wheezing illness in the first 3 years of life was associated with an obstructive lung function pattern at age 5–8 years[8], while small airway dysfunction at school age was not associated early life wheezing episodes triggered by RSV or other respiratory viruses[8]. It should be noted that COAST is a cohort of children at increased risk to develop asthma; therefore, these findings may not necessarily be applicable to the general population. Nevertheless, these findings provide additional support of the association between early life HRV associated wheezing and future asthma.

Until recently, most of the evidence regarding the association between early life human HRV LRTI and future asthma was based largely on outpatient cohorts[9–11], with limited data available on the association between non-outpatient HRV LRTI and future wheezing and asthma[12]. Three recent publications from Europe[13–15] present new information regarding the association between non-RSV severe bronchiolitis and future wheezing episodes and/or asthma. Midulla and colleagues[15] investigated risk factors for 2 or more episodes of wheezing during the year following hospitalization for viral bronchiolitis. Within 3 days of hospitalization, nasal washes were assayed for nucleic acid from 14 respiratory viruses. The study population included 313 infants, all younger than one year, who were hospitalized with a first episode of viral LRTI. All children were recruited between the months of October to May over 5 consecutive years. An additional 39 infants without acute respiratory disease were recruited as controls. The rate of recurrent wheezing was highest after HRV bronchiolitis compared to other respiratory viruses: 80% for HRV, 67% for human Bocavirus (hBoV), 50% for other viruses, 46% for RSV plus hBoV, and 44% for RSV. Independent risk factors for recurrent wheezing were HRV infection (although marginally significant), and a positive family history for asthma. Koponen and colleagues[13] followed 166 children hospitalized for viral bronchiolitis before the age of 6 months for 6 years. The overall asthma prevalence was 13% in this cohort, but it was significantly higher in non-RSV patients (24%) than in RSV patients (8%). 14% of former RV patients were diagnosed with asthma. Atopic dermatitis, non-RSV bronchiolitis, and maternal asthma were independent significant early-life predictors for asthma in this cohort. Mikalsen and colleagues[14] followed children for 11 years after hospitalization for viral bronchiolitis in the first year of life. This study identified RSV as the causative virus in 74% of the children, but did not examine for evidence of other viruses. Compared to a group of unselected age-matched controls, hospitalized children had a higher prevalence of asthma, an obstructive

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lung function pattern, and greater bronchial hyper-responsiveness. However, asthma prevalence was significantly higher only after RSV-negative bronchiolitis, and the obstructive lung function pattern was most prominent after RSV-negative bronchiolitis[14].

Taken together, these 3 recent studies[13–15] highlight the emerging importance of severe non-RSV bronchiolitis early in life as a major risk factor for future wheezing and/or asthma. In addition, the rates of asthma following severe non-RSV bronchiolitis in infancy among these European cohorts are generally lower than was recently reported in a US cohort following severe RSV bronchiolitis[5]. Potential explanations for these differences include study population characteristics such as social/environmental factors including maternal stress[16–18] and exposure to pollution[19] that might have modifying roles on the interaction between early life bronchiolitis and asthma.

Viral bronchiolitis in early infancy and future asthma: “the chicken and the egg” dilemma

As described above, abundant evidence supports an association between early life viral bronchiolitis and future asthma. However, it remains uncertain whether severe bronchiolitis early in life is the cause of future asthma or serves as a marker for susceptibility to bronchiolitis that identifies children with asthma predisposition.

Evidence from murine models of viral bronchiolitis suggests that the viral infection can induce allergic predisposition. It was shown that murine parainfluenza LRTI causes an up-regulation of the high-affinity IgE receptor on lung antigen presenting cells, production of Th2 inflammatory cell and inflammatory mediators, and eventually results with an increased immune response to inhalant allergens[20–24]. The importance of the viral infection as the initial event (“the first hit”) to create airway allergic inflammation was further demonstrated in additional models involving innate immunity and invariant natural killer T cells[25, 26]. All together, these findings obtained in animal models of bronchiolitis highlight the importance of an interaction between viral infection and inhalant allergen exposure: the viral infection is able to set the appropriate pro-allergic milieu, and if within the appropriate time-frame the animal is exposed to inhalant allergens, then allergen-specific airway inflammation may developed.

Previous epidemiological data also support a direct causal role of RSV infection in the pathogenesis of asthma[27], with a recent report showing that provision of RSV prophylaxis with palivizumab to premature infants without a family history of asthma and/or atopy reduced the risk of recurrent wheezing between the ages of 2 to 5 years by 80%[28]. Interestingly, such a protective effect was not found among pre-term infants with atopic backgrounds, suggesting that different mechanisms may be at play in the inception of asthma based on the atopic background of the child[28].

In contrast to the evidence supporting a direct causal role of viral bronchiolitis in the pathogenesis of asthma, two previous epidemiologic studies conducted among monozygotic twin pairs, discordant for severe RSV bronchiolitis in infancy, did not support the theory that RSV bronchiolitis causes asthma[29, 30]. Poorisrisak and colleagues did not detect a difference in pulmonary function, exhaled nitric oxide levels, asthma prevalence, asthma medication use, or sensitization between monozygotic twins discordant for RSV bronchiolitis hospitalization in infancy who were studied at a mean age of 7.6 years[30]. Thomsen and colleagues used genetic variance components models and direction of causation models in 8,280 pairs of twins and concluded that severe RSV bronchiolitis most likely represents a genetic predisposition to asthma[29]. In addition, 2 recent studies support the position that viral LRTI is a marker for atopic predisposition and not the cause of future

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wheezing and asthma. A report[31] from the COAST project aimed to determine the developmental sequence of allergic sensitization and viral wheeze. By using a longitudinal evaluation of this cohort, allergic sensitization to aeroallergens, beginning at the first year of life, was identified as a significant risk factor for viral induced wheeze, and this was significant for HRV but not for RSV. However, having viral wheeze did not increase the risk of developing allergic sensitization[31]. Another report[32] from the Copenhagen Prospective Study of Asthma in Childhood birth cohort, a high risk cohort of infants born to mothers with asthma, also suggested that severe bronchiolitis is a result of pre-existing susceptibility of the airway to react to viral infections. These investigators measured infant lung function and bronchial responsiveness to methacholine at the age of one month and before the infants had any respiratory symptoms. Children who later had acute severe bronchiolitis had a 2.5-fold increased responsiveness to methacholine at the age of one month.[32]. Taken together, these 2 studies suggest that allergic sensitization and /or airway dysfunction may serve as predisposing factors that increase host susceptibility to viral bronchiolitis, with allergic sensitization increasing HRV bronchiolitis risk. Therefore, in these cohorts, the occurrence of viral bronchiolitis appears to be a reflection of predisposition to wheeze with viral infections rather than the viral infection serving as a causative factor for subsequent asthma. However, it should be noted that the high-risk nature of these 2 birth cohorts decreases the generalizability of these findings to non-high risk populations, and it remains possible that viral bronchiolitis precedes the development of airway dysfunction among children without atopic predispositions.

It is probable that these 2 scenarios, either bronchiolitis as a cause or a marker for asthma theories, are not mutually exclusive. Children who wheeze in early life due to HRV differ from those who wheeze in early life due to RSV: they are older and more likely to have personal and family history of asthma[33, 34]. These differences in underlying atopic backgrounds influencing the likelihood of wheezing in the context of different viral infections suggest that 2 different pathways may exist: HRV-induced wheeze (most likely to occur in the outpatient setting) might be more of a marker for asthma tendency, while RSV (especially more severe disease warranting hospitalization) might have a more causative role in the pathogenesis of disease. This postulate could be supported by the successful wheezing prevention conferred by RSV prophylaxis with palivizumab only among non-atopic children, suggesting a different consequence of the viral infection depending on atopic predisposition[28]. Additional evidence that these 2 respiratory viruses might have a different roles in the pathogenesis of asthma was recently provided by the Tennessee Children's Respiratory Initiative[35]. In this study, the investigators aimed to determine whether maternal asthma was associated with a higher risk of infant respiratory tract infection with HRV versus RSV, and whether maternal asthma was associated with increased infection severity. They reported that having a mother with atopic asthma significantly increased the risk of the infant experiencing HRV infection compared to RSV infection, and maternal asthma increased the severity of infant HRV infection but not the severity of RSV infection. These findings support the hypothesis that, compared to infants with RSV infection, infants with HRV infections are more likely to have an atopic predisposition reflected by positive family history; and it might be that this atopic predisposition modulates the increased risk for asthma among children who wheeze with HRV[35].

Vitamin D status as a potential modifying factor of the relationship between viral infections and asthma inception

While severe bronchiolitis in infancy is a major risk factor for the development of recurrent wheezing and asthma, it is clear that not all infants who have severe viral bronchiolitis will develop subsequent recurrent wheezing and/or asthma. Therefore, additional host factors such as atopic predisposition, allergic sensitization, immune response factors, and illness

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severity, along with environmental exposures might serve as modifying factors for the risk of developing asthma[20, 33]. Vitamin D has emerged as a potential factor which may modulate asthma severity and activity. Recent reports showed that low serum vitamin D levels are associated with increased asthma severity and poor asthma control among school age children and adolescents[36–42]. Among younger children, vitamin D may be a modifying factor for the progression from viral bronchiolitis to asthma through multiple mechanisms: in-utero effects on lung growth and maturation, enhancement of viral immunity and as a result prevention and/or attenuation severity of viral bronchiolitis, and attenuation of allergic sensitization[43]. Three recent studies revealed that maternal vitamin D levels during pregnancy[44], or in cord blood[45, 46] are inversely associated with the risk of viral respiratory tract illness (RTI) during the first year of life. The most relevant evidence was provided by Belderbos and colleagues[45] who reported a six-fold increased risk of RSV LRTI during the first year of life among infants with cord blood vitamin D levels below 50 nmol/L (20 ng/ml) compared to infants with adequate (>75 nmol/L (30 ng/ml)) cord blood vitamin D levels. However, although these studies provide evidence for the potentially protective effects of higher vitamin D levels for the prevention of RTI, there were conflicting results regarding the effect of maternal serum vitamin D levels on the risk of future wheezing episodes during early childhood. While one study[46] showed that lower cord blood vitamin D levels were associated with higher risk of wheezing episodes (but not with the diagnosis of asthma), another study failed to confirm this association[44]. However, the timing of maternal vitamin D measures differed between the studies - in the study that reported a protective effect of vitamin D[46], levels were measured in cord blood while in the negative study[44], levels were measured during pregnancy, which might result in a less accurate estimation of vitamin D status in the newborn. In addition, 2 studies[47, 48] did not find an association between child's serum vitamin D levels and the risk of hospitalization for viral LRTI; however, one of these studies[47] suggested that vitamin D might modify the severity of the acute LRTI, since mean vitamin D level among LRTI patients admitted to the intensive care unit was significantly lower than that observed in patients admitted to the general pediatrics ward. Taken together, these studies suggest that adequate vitamin D levels at birth might prevent early life viral infection; however, the consequence of vitamin D status on subsequent wheezing episodes remains unclear, although ongoing trials of maternal vitamin D supplementation will hopefully clarify this situation. No data are currently available to determine if adequate serum vitamin D levels in early infancy can prevent severe bronchiolitis requiring hospitalization or the respiratory outcomes that follow this event.

Conclusions

Recent evidence supports the importance of early life viral bronchiolitis in the developmental pathway of asthma. Multiple specific viral respiratory infections appear to serve as antecedents to childhood asthma, and future research is certain to identify additional viral pathogens which precede or signal the development of asthma. The dilemma of whether bronchiolitis early in life is the cause of future asthma or a marker for susceptibility for asthma is not yet resolved; most likely both of these pathways are relevant, and there may be differential effects based on the child's atopic predisposition and the specific virus. Finally, host and environmental factors likely modify the risk of asthma following early life bronchiolitis, and further research is needed to explore the potential roles of modifiable factors, such as vitamin D status, on these processes and outcomes.

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Abbreviations

COAST project	Childhood Origin of Asthma project
HRV	human rhinovirus
LRTI	Lower Respiratory Tract Infection
RBEL	RSV Bronchiolitis in Early Life
RSV	Respiratory Syncytial Virus
RTI	Respiratory Tract Infection
TCRS	Tucson Children's Respiratory Study

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Key Points

- The risk for asthma following severe Respiratory Syncytial Virus (RSV) bronchiolitis may be higher than was previously estimated, and this association might last into early adulthood.
- Emerging data suggest that non-RSV bronchiolitis, and mainly human rhinovirus (HRV) bronchiolitis, is a major risk factor for future asthma
- Whether bronchiolitis is related to future asthma causality or serves as a marker of asthma predisposition remains uncertain.