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Respiratory Viruses in Bronchiolitis and Their Link to Recurrent Wheezing and Asthma

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KEYWORDS

• Bronchiolitis • Asthma • Respiratory syncytial virus
• Rhinovirus • Wheezing • Vitamin D

One of the earliest and most common infectious respiratory conditions of childhood is bronchiolitis.[1,2] A child who has severe bronchiolitis (eg, an episode requiring hospitalization) is at increased risk for recurrent wheezing of childhood and eventual asthma.[3–5] Estimates vary but approximately 80% to 90% of asthma begins before age 6 years, with 70% of children who have asthma having asthmalike symptoms before age 3 years.[6,7] Although many environmental and genetic factors may play a role in the pathway from bronchiolitis to asthma,[3,8] this article focuses on the viruses that have been linked to bronchiolitis and how these viruses may predict or contribute to future wheezing and asthma. The article also discusses vitamin D as an emerging risk factor for respiratory infections and wheezing.

DEFINITIONS OF LOWER RESPIRATORY TRACT INFECTION

In the United States, lower respiratory tract infections (LRTI) represent almost 60% of infant infectious disease hospitalizations[9] and bronchiolitis is the most common LRTI.[10] Despite its high frequency, bronchiolitis remains a clinical diagnosis[11–13] without a common international definition.[10,14–18] In 2006, the American Academy of Pediatrics defined bronchiolitis as a child younger than 2 years of age who has

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"rhinitis, tachypnea, wheezing, cough, crackles, use of accessory muscles, and/or nasal flaring."[10] This definition is broad, and when children younger than 2 years of age present to care with symptoms suggestive of an LRTI, they receive various diagnostic labels, such as bronchiolitis, wheezing, cough, reactive airways disease, asthma, or pneumonia.[19]

As our understanding of LRTI evolves and we identify more clearly the risk factors for children developing recurrent wheezing in preschool years (and asthma as they grow older), we may need to adjust our LRTI definitions. Indeed, based on 259 wheezing hospitalized children aged 3 to 35 months participating in a systemic corticosteroid and wheezing study in Finland, Jartti and colleagues[18] recently suggested that the diagnosis of bronchiolitis should be restricted either to children younger than 24 months of age who have their first episode of wheezing or to children younger than 12 months of age.

BRONCHIOLITIS EPIDEMIOLOGY

With its broad definition, bronchiolitis is the leading cause of hospitalization for infants in the United States[20,21] and the associated hospitalization costs are more than $500 million per year.[22] In a nationally representative sample, bronchiolitis hospitalization rates increased 2.4-fold from 1980 to 1996[20] and in a Tennessee Medicaid database there was a 41% increase in bronchiolitis visits at all levels of care (ie, inpatient, emergency department [ED], and outpatient clinic) from 1996 to 2003.[2]

BRONCHIOLITIS PATHOGENS

Respiratory syncytial virus (RSV) is the most common pathogen associated with bronchiolitis.[1,23] Although most children are infected with RSV by age 2 years,[24,25] relatively few children (<40%) develop clinically recognized bronchiolitis.[24,26] Among those children who develop bronchiolitis, most have a mild course; approximately 2% to 3% will be hospitalized[20,27] and less than 1% will be admitted to an ICU, intubated, or die.[28–31]

Other viruses that have been linked to bronchiolitis include rhinovirus (RV),[32,33] human metapneumovirus (hMPV),[34] influenza A/B,[35,36] parainfluenza (PIV),[37] and adenovirus.[38,39] Coronaviruses also have been linked to lower respiratory tract disease in children,[40] including the strains NL-63[41] or New Haven[42] and HKU1.[43–45] More recently discovered viruses include human bocavirus[46–49] and the polyomaviruses WU[50] and KI.[51] The clinical relevance of these two polyomaviruses is uncertain.[52] Furthermore, there is conflicting literature about the relevance of bacterial coinfection in children who have viral bronchiolitis, especially those children requiring intensive care.[53–56]

Although myriad infectious causes are associated with bronchiolitis, it remains unclear if the viral cause of a child's bronchiolitis illness is clinically relevant for either the short- or long-term care of the individual child. For short-term care, knowing the infectious cause identifies children who have influenza who may benefit from oseltamivir; it also helps cohort hospitalized children. Otherwise the current consensus is that knowledge of the viral etiology—among those viruses with easily accessible point-of-care testing (eg, RSV and influenza)—does not affect treatment of the individual patient.[10] As rapid microarray testing becomes less costly and more widely used, however, we are likely to learn much more about the short- and long-term implications of the diverse viruses linked to bronchiolitis. Indeed, these new data could markedly change current understanding and consensus.

EPIDEMIOLOGY OF PATHOGENS AT DIFFERENT LEVELS OF CARE

Several studies have examined the epidemiology of different viruses associated with LRTI in hospitalized children,[33,37,57–61] but there are fewer studies investigating the epidemiology of viruses linked to bronchiolitis in children presenting to the ED or in outpatient clinics.[62–65] In this section, we present one representative study from the three levels of care (inpatient, ED, outpatient clinic) from different regions of the world.

An inpatient study by Wolf and colleagues[66] compared the clinical features of RSV, hMPV, influenza A, parainfluenza, and adenovirus in 516 Israeli children younger than 5 years of age who were hospitalized with LRTI over a 1-year period. The investigators detected a virus in 57% of the children tested in this single-center study. Children hospitalized with RSV were younger than those hospitalized with hMPV, but the severity of the respiratory illness caused by RSV and hMPV was similar and higher than that of influenza A.

In a multicenter ED-based study of 277 United States children who had physician-diagnosed bronchiolitis,[67] we examined the frequencies of RSV, RV, hMPV, and influenza A/B during one bronchiolitis winter season. We detected a virus in 84% of the samples; RSV was the most common (64%) and RV the second most common (16%).

In a community-based birth cohort sample of Australian children at high risk for atopy (ie, one parent with history of asthma, hay fever, or eczema), Kusel and colleagues[68] examined the frequency of nine different pathogens in these children during their first year. When the children had acute respiratory infections (either upper or lower) the children had nasopharyngeal samples taken. For upper and lower respiratory tract infections in the first year of life, RV was the most frequent cause (48%) and RSV the second most common (11%).

Most data indicate that RSV and RV are the two most common viruses associated with LRTI in early childhood. RSV is detected more frequently from children in the hospital or ED and RV is detected more frequently from children in the outpatient clinic setting.

COINFECTIONS

When considering the cohorting of inpatients, it is important to realize that the aforementioned infectious agents may cause bronchiolitis in isolation or in combination with other infectious agents. Although older studies report coinfections (eg, detection of two or more viruses from the same biologic sample) in 4.4% to 23.7% of children younger than 3 years of age who had respiratory illnesses,[69–74] recent studies have found 20% to 27% coinfections when testing hospitalized children who had LRTI.[59,61] There is a lack of clear data, however, about the clinical characteristics of children who have coinfections. Some studies have found no increase in the severity of disease from coinfections as measured by hospital length of stay,[75] clinical symptoms,[70,71] a severity score,[76] or duration of illness.[72] Other data, however, demonstrate that children infected with multiple pathogens have more severe bronchiolitis as measured by higher hospitalization rates[77] or degree of hypoxia and longer hospital length of stay.[61]

It is likely that the clinical course of coinfections will differ; some combinations of viruses are more or less deleterious than others. One combination that is believed to increase the severity of illness is RSV and hMPV coinfection.[78] As part of a larger study examining severe bronchiolitis, RSV and hMPV were identified in the bronchoalveolar fluid of 70% of 30 intubated infants.[79] In a different study, 72% of 25 intubated children had RSV and hMPV coinfection compared with 10% of 171 children hospitalized on the general wards.[80] Interestingly, hMPV was also found in 5 of 9 patients

during the 2003 severe acute respiratory syndrome or SARS outbreak in Canada.[81] Recent studies investigating RSV and hMPV suggest that they may have distinctive pathogenesis,[66] elicit unique cytokine profiles,[82–85] and use different mechanisms to activate human dendritic cells, which play a key role in the adaptive immune response.[86] Moreover, a prospective study by Laham and colleagues[87] measured cytokine levels in Buenos Aires infants presenting with upper or lower respiratory tract illness and discovered that the 22 infants who had hMPV were poor inducers of inflammatory cytokines compared with the 46 infants who had RSV. The authors concluded that the viruses elicit disease by different mechanisms and therefore hMPV may augment RSV disease severity. To date, however, studies not only have not had the sample size to answer definitively if coinfection with hMPV and RSV increases bronchiolitis severity but also have been inadequate to determine the clinical implications of the many other pathogen combinations.

In a cooperative agreement with the National Institutes of Health, our research group, the Emergency Medicine Network (EMNet; www.emnet-usa.org), is currently conducting a prospective, multicenter study that will examine the clinical usefulness of testing for the causes of bronchiolitis in 2250 hospitalized children.[88] Based on the first year of our study, with a sample of 520 hospitalized children, we were able to detect a virus in 93% of the nasopharyngeal samples and found a 27% coinfection rate.[88] In the first year we have found that coinfection was significantly less likely for hospitalized children who had RSV (33%; 95% CI, 28%–38%) as compared with children who had RV (65%; 95%CI, 56%–73%).

WHEEZING AFTER SEVERE BRONCHIOLITIS

In 1959, Wittig and Glaser[89] noted a relationship between bronchiolitis and risk for asthma in 100 children in the United States. Over the past 50 years, several research groups have followed small cohorts of children hospitalized with bronchiolitis for the development of recurrent wheezing. For example, Carlsen and colleagues[90] found that 60% of 51 Norwegian infants hospitalized with bronchiolitis developed recurrent wheezing of childhood ($\geq$3 episodes of bronchial obstruction) by age 2 years compared with 4% of 24 control children. In a retrospective study from Qatar, 31 of 70 (44%) children younger than 12 months hospitalized with RSV bronchiolitis developed recurrent wheezing ($\geq$3 episodes of physician-diagnosed expiratory rhonchi) 2 years after admission, compared with 9 of the 70 controls (12%).[91] Sigurs and colleagues[92] followed a Swedish cohort of 47 infants hospitalized with RSV bronchiolitis and 93 controls up to age 13 years. At a mean age of 3 years, recurrent wheezing was diagnosed in 11 of 47 children (23%) in the RSV group versus 1 of 93 children (1%) in the control group.

Many of the children who have bronchiolitis who develop recurrent wheezing of childhood also develop childhood asthma. Unfortunately, the respiratory morbidity associated with childhood respiratory infections may be longstanding and influence the development and persistence of adult respiratory conditions.[93] In the Swedish cohort, the cumulative prevalence of asthma at age 7 years was 30% in the RSV group versus 3% in the control group[5] and at age 13 years the cumulative prevalence of asthma was 37% in the RSV group versus 5% among controls.[94] In the Tucson Children's Respiratory Study prospective birth cohort, having an RSV LRTI before age 3 years was an independent risk factor for wheezing up to age 11 years.[95] The association steadily subsides after age 3 years, however, and by age 13 years the association is no longer statistically significant.[95] Unlike the Swedish study, nearly all of the Tucson children who had RSV LRTI were not hospitalized and the respiratory

outcomes of these two populations (ie, inpatient and outpatient) may be quite different. Indeed, based on a Tennessee Medicaid database there is a dose–response relationship between bronchiolitis severity (as defined by inpatient, ED, and outpatient clinic) and the increased odds of early childhood asthma and asthma-specific morbidity.[96]

Despite the generally strong associations, no one has been able to identify reliably the subset of children hospitalized with bronchiolitis at increased risk for developing recurrent wheezing or if most of this large group of children will ultimately develop asthma.[97] Hampering this pursuit has been the terminology used to describe wheezing in preschool children[4] and the recent appreciation that asthma is a heterogeneous disease with multiple complex causes.[8,98,99]

RHINOVIRUS BRONCHIOLITIS

Although RSV is the most common pathogen associated with severe bronchiolitis[1,23] and has been effectively used to define cohorts of children who have bronchiolitis,[28,91,92] other pathogens may have a stronger association with recurrent wheezing.[100–103] The most intriguing virus in studying recurrent wheezing and asthma is RV. Several recent single-center studies have linked RV infection to asthma exacerbations in children and adults,[104,105] infant wheezing,[68,106] and infants who have recurrent respiratory symptoms and abnormal lung function.[107] Recent evidence also links LRTIs with RV-related wheezing in infancy to later development of recurrent wheezing of childhood[63] and asthma at age 6 years.[108–110] For example, in the Childhood Origins of ASThma (COAST) birth cohort study, which involves 289 children at high risk for developing asthma, the most significant independent predictor of recurrent wheezing at age 3 years was a moderate to severe RV illness with wheezing during infancy.[63] Furthermore, a Tennessee study showed that bronchiolitis during RV-predominant months was associated with a 25% increased risk for childhood asthma over bronchiolitis during RSV-predominant months.[111] Our prospective multicenter data of children younger than 2 years of age presenting to the ED with bronchiolitis found that children who have RV bronchiolitis have similar demographics, medical histories, and ED treatments as older children who have an asthma exacerbation.[67]

Of particular interest, and with potentially large clinical implications, are the results from one small trial of prednisolone for 3 days versus placebo for children hospitalized with their first or second episode of wheezing due to RV. In this trial, Jartti, Lehtinen, and colleagues[112] found that children who had RV who received prednisolone had reduced relapses during a 2-month period after the hospitalization and reduced recurrent wheezing at 1 year.[113] Indeed, children who develop wheezing due to RV seem to have a high likelihood of recurrent wheezing of childhood and eventually later developing asthma.[110] Further investigation is warranted to clarify the potential value of targeting children who have RV bronchiolitis for the primary prevention of asthma.

Although this review focuses on viruses, we want to remind readers that the specific bacteria colonizing an infant's hypopharynx also may play an important role in the risk for recurrent wheezing and childhood asthma.[114] In other words, a child's long-term outcome probably represents an interaction between the infecting virus, bacterial milieu (colonization or super-infection), and undoubtedly other factors (see **Fig. 1**).

VITAMIN D AND WHEEZING

Although there are many risk factors for the development of severe bronchiolitis[2,115] and the development of recurrent wheezing/asthma,[58,96,116–119] an emerging risk

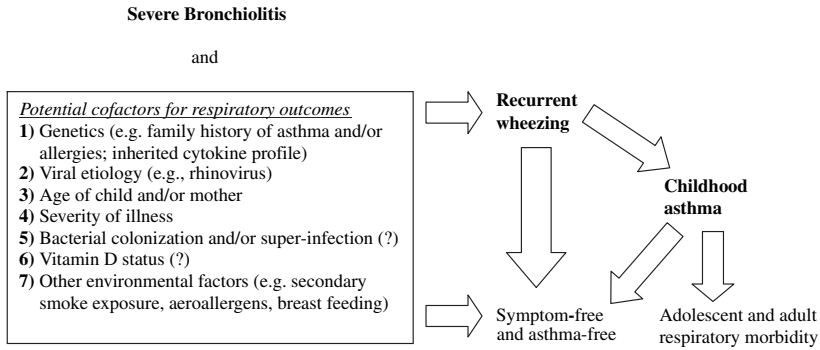

Fig. 1. Respiratory outcomes after severe bronchiolitis. After a child develops severe bronchiolitis (eg, an episode requiring hospitalization), several factors may influence the respiratory outcome. The actual percentages of children who develop each outcome remain unclear.

factor of particular interest to our research group is vitamin D status.[120] Vitamin D3 (cholecalciferol) comes from two sources: exposure to sunlight and dietary intake. The major source of vitamin D for most humans is from exposure of skin to the B fraction of ultraviolet light (UVB). In northern latitudes between November and March there are insufficient UVB rays to produce vitamin D, however.[121] Sunscreen use is recommended to protect against future skin cancer,[122–124] and this further decreases vitamin D skin production.[125] Unfortunately, lifestyle changes over the past few decades have made vitamin D deficiency increasingly common.[121,126,127]

The evidence for the possible link between vitamin D and respiratory disease comes from multiple studies. Two family-based studies demonstrated that gene polymorphisms on the vitamin D receptor were associated with childhood and adult asthma[128,129] and vitamin D deficiency is correlated with lower pulmonary function in adolescents[130] and adults.[131] Of greater relevance, Camargo and colleagues[132] discovered in a prospective birth cohort in Massachusetts that lower maternal intake of vitamin D during pregnancy is associated with increased risk for recurrent wheezing in the mothers' young children. These findings were replicated in 5-year-old Scottish children.[133] Camargo and colleagues[134] recently confirmed these novel findings in a separate birth cohort of 922 children from New Zealand (41°–43° S) where low 25-hydroxyvitamin D (25[OH]D) levels in cord blood were associated with increased risk for respiratory infections and childhood wheezing. Moreover, Litonjua and colleagues[135] recently examined the association between serum 25(OH)D levels and risk for an asthma-related ED visit or hospitalization. Among 1022 children who had asthma in the Childhood Asthma Management Program (CAMP),[136] those who had low baseline 25(OH)D levels (<75 nmol/L) were more likely to have a severe asthma exacerbation over a 4-month period (OR 1.50; 95%CI, 1.13–1.98). Finally, Brehm and colleagues[137] recently reported that among 616 children in Costa Rica who had asthma, higher 25(OH)D levels were significantly associated with reduced odds of any hospitalization and reduced use of anti-inflammatory medications.

The pathophysiology of these associations may relate to vitamin D's role in the activity of the innate immune system.[138–140] The innate immune system, specifically the activity of cathelicidin, helps prevent infections with bacteria and viruses.[141–145] In 2006, Liu and colleagues[146] reported in *Science* a link between Toll-like receptors (TLR), low vitamin D, and the reduced ability to support cathelicidin messenger RNA

induction. Wang and colleagues[138] also have demonstrated that vitamin D is a direct inducer of the cathelicidin gene. Most recently, Janssen and colleagues determined that single nucleotide polymorphisms in four of the innate immunity genes, including the vitamin D receptor, helped predict susceptibility to RSV bronchiolitis.[147,148] Taken together, the clinical and mechanistic data support a role for vitamin D as an important factor in the relation between respiratory viruses in bronchiolitis and their link to recurrent wheezing.

SUMMARY

Bronchiolitis is the leading cause of hospitalization for children younger than 1 year of age and these hospitalized children have an increased risk for developing childhood asthma. It remains unclear, however, which children who have severe bronchiolitis (eg, an episode requiring hospitalization) will develop recurrent wheezing or asthma. Two intriguing factors are bronchiolitis due to RV and low levels of vitamin D. Developing a clearer understanding of the complex pathway from bronchiolitis to asthma would help identify the subset of children who have severe bronchiolitis who are at high risk for developing asthma. This understanding would not only help clinicians target follow-up care but also advance bronchiolitis and asthma prevention research by better routing high-risk children into future randomized trials.

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