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Role of viral infections in the development and exacerbation of asthma in children

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Activity Objectives:

1. To become familiar with current evidence pertaining to the role of viral respiratory tract infections in the development and exacerbation of asthma.
2. To provide an overview of interactions between aeroallergen sensitization and viral infection in the development of asthma.
3. To highlight the gaps in existing knowledge regarding the role of viral infection in asthmatic patients.

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Viral infections are closely linked to wheezing illnesses in children of all ages. Respiratory syncytial virus (RSV) is the main causative agent of bronchiolitis, whereas rhinovirus (RV) is most commonly detected in wheezing children thereafter. Severe respiratory illness induced by either of these viruses is associated with subsequent development of asthma, and the risk is greatest for young children who wheeze with RV infections. Whether viral illnesses actually cause asthma is the subject of intense debate. RSV-induced wheezing illnesses during infancy influence respiratory health for years. There is definitive evidence that RSV-induced bronchiolitis can damage the airways to promote airway obstruction and recurrent wheezing. RV likely causes less structural damage and yet is a significant contributor to wheezing illnesses in young children and in the context of asthma. For both viruses, interactions between viral virulence factors, personal risk factors (eg, genetics), and environmental exposures (eg, airway microbiome) promote more severe wheezing illnesses and the risk for progression to asthma. In addition, allergy and asthma are major risk factors for more frequent and severe RV-related illnesses. Treatments that inhibit inflammation have efficacy for RV-induced wheezing, whereas the anti-RSV mAb palivizumab decreases the risk of severe RSV-induced illness and subsequent recurrent wheeze. Developing a greater understanding of personal and environmental factors that promote more severe viral illnesses might lead to new strategies for the prevention of viral wheezing illnesses and perhaps reduce the subsequent risk for asthma. (J Allergy Clin Immunol 2017;140:895-906.)

Key words: *Asthma, bronchiolitis, child, exacerbation, respiratory syncytial virus, rhinovirus, virus, wheeze, wheezing*

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Abbreviations used
CDHR3: Cadherin-related family member 3
nBreg: Neonatal regulatory B
NGF: Nerve growth factor
OR: Odds ratio
RSV: Respiratory syncytial virus
RV: Rhinovirus
TLR: Toll-like receptor

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Bronchiolitis, acute wheezing illnesses, and asthma are a huge clinical burden. The prevalence of bronchiolitis is approximately 20% to 30% in the first year and 10% to 20% in the second year of life.[1,2] Up to 30% to 50% of children have acute wheezing at least once before school age.[1] Of these, 30% to 40% will have recurrent wheezing.[1] Eventually, the prevalence of asthma is approximately 5% to 10% in children.[3]

The diagnostics of viral respiratory tract infections has improved markedly during the last 2 decades because of the development of PCR techniques. Several new respiratory viruses and their subgroups have been discovered, and especially rhinovirus (RV) diagnostics have markedly improved.[4] We have learned that bronchiolitis and early wheezing episodes are almost always (90% to 100% of cases) associated with viral infections.[5,6] The overall virus detection rates slightly decrease by age, being 80% to 95% in older children.[7]

Prediction of childhood asthma has been limited for many years to assessment of traditional risk factors, such as atopic characteristics (aeroallergen sensitization, increased blood eosinophil count, or atopic eczema), parental asthma, or factors related to parental atopy. Acute wheezing illnesses with RV and respiratory syncytial virus (RSV) are early markers for recurrent wheezing.[6,8-14] In addition, RV-induced wheezing episodes in infancy are a major risk factor for later asthma, especially in children with atopic features. Once asthma is established, exposure to allergens and RV infections are important triggers of asthma exacerbations in children.[15]

This review will focus on the role of viral infections on the development and exacerbation of asthma in children. Understanding the mechanisms of these events could suggest novel insights into the pathogenesis of asthma and would help to identify novel strategies for the prevention and treatment of asthma.

CLINICAL DEFINITIONS

Bronchiolitis is a virus-induced infection with inflammation of the small bronchioles and their surrounding tissue. Clinically, it is characterized as the first expiratory breathing difficulty in children less than 2 years of age. Other lower respiratory tract symptoms include dry cough, tachypnea, hyperinflation, chest retraction, and widespread crackles or wheezing. In many studies wheezing is not a mandatory diagnostic criterion, and the upper age limit varies from 6 months to 2 years.[16]

Wheezing is defined as a whistling sound during expiration accompanied by dyspnea.[17] Wheezing can be diagnosed if there is a reversible expiratory airway obstruction and the illness does not fulfill the diagnosis of bronchiolitis or asthma. Moreover, wheezing is divided into different phenotypes based on natural history, such as "transient early," "persistent," and "late-onset" wheezing. Typically, the 2 latter phenotypes are more closely associated with sensitization and asthma.[1]

Asthma is a chronic disorder characterized by airway inflammation, increased mucus secretion, and bronchial hyperresponsiveness, all of which cause reversible airflow obstruction.[17] The chronic inflammation, disrupted epithelium, and airway remodeling increase the susceptibility to many environmental factors, such as viral infections and allergens.

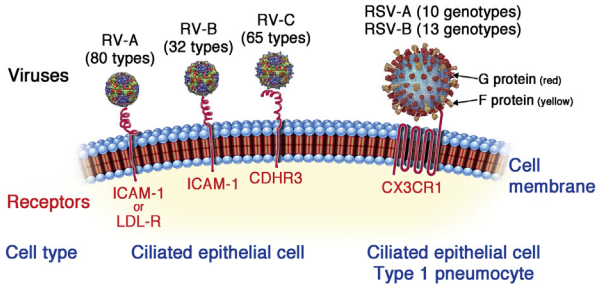

FIG 1. RV and RSV interactions with airway epithelial cells. *ICAM-1,* Intercellular adhesion molecule 1; *LDL-R,* low-density lipoprotein receptor.

VIRUS CHARACTERISTICS

RVs

RVs are nonenveloped positive-strand RNA viruses in the family Picornaviridae and genus *Enterovirus* and are classified into 3 species (RV-A, RV-B and RV-C; Fig 1).[18] There are more than 160 distinct RV genotypes, including 80 RV-A and 32 RV-B serotypes and 65 newly identified RV-C serotypes. RV structural and genetic variability has inhibited efforts to develop antivirals. For example, small molecules ("capsid binding agents") that inhibit RV-A and RV-B binding and replication are not effective against RV-C because of differences in capsid structure.[19] 3C protease inhibitors are effective *in vitro*, but results in clinical trials were disappointing.[20,21] The large number of antigenically distinct RV types has been a barrier to vaccine development, although new approaches have identified some degree of cross-reactivity among RV types,[22] and a highly multiplexed RV vaccine is immunogenic in animal models.[23]

Detection and epidemiology. RV-C does not grow in conventional cell cultures, which delayed its discovery until 2006,[24] approximately 50 years after the first discovery of RVs. PCR is the method of choice for identifying RVs from nasal mucus samples.[25] Up to 35% of asymptomatic subjects have positive results for RV,[26] but the virus does not cause chronic infection or "colonization" in healthy subjects.[27] Both symptomatic and asymptomatic infections can induce systemic immune responses in young wheezing children.[28]

RVs circulate year-round, with multiple coexisting genotypes,[29] and peak prevalence in temperate climates occurs in the early autumn and late spring. Most infections cause common cold symptoms.[30] The prevalence of RV-induced bronchiolitis/wheezing is age dependent. In children hospitalized for lower respiratory tract illness, RSV is detected most often until about 12 months of age, and RV is most common in older children.[7] RV predominates as an etiologic agent in 50% to

TABLE I. RV-induced wheezing illnesses during infancy and the risk of recurrent wheezing and asthma*

Study site	Inclusion criteria	First author, year	No.	Outcome, age (y)	Virus risk factors, OR (95% CI)†	Prevalence of recurrent wheezing/ asthma in virus groups	Other risk factors, OR (95% CI)†
Kuopio, Finland	Bronchiolitis, 1-23 mo, hospitalized	Kotaniemi-Syrjänen, 2003	82	Asthma, 7.2	RV: 4.1 (1.0-17), other viruses NS	RV: 52%	—
		Hyvärinen, 2007	81	Asthma, 12.3	NS	—	—
		Ruotsalainen, 2013	67 patients with bronchiolitis, 155 control subjects	Asthma, 16.5	RV: 7.3 (2.1-26), RSV: 5.7 (1.6-20)	RV: 28% RSV: 24%	B-eos: 21.3 (1.1-430), atopic dermatitis: 6.0 (1.3-27), as-IgE: 6.0 (1.1-33)
Madison, Wisconsin	Wheezing, <12 mo, outpatients, high atopy risk, birth cohort	Lemanske, 2005	275	Recurrent wheezing, 3-4	Wheezing <12 mo — RV: 10 (4.1-26), RSV: 3.5 (1.7-7.5), other: 4.6 (2.0-11)	Wheezing <12 mo — RV: 65%, RSV: 48%, other: 49%	Positive egg IgE level: 3.0 (1.1-7.8), older siblings: 2.6 (1.3-5.2)
		Jackson, 2008	259	Asthma, 6	Wheezing <12 mo — RV only: 2.9 (1.1-7.5), RSV only: 1.2 (0.4-3.2) Wheezing <24 mo — RV only: 5.6 (2.4-13), RSV only: 1.3 (0.4-3.8) Wheezing <36 mo — RV only: 43 (12-149), RSV only: 14 (3.4-54)	Wheezing <12 mo — RV only: 47%, RSV only: 27% Wheezing <24 mo — RV only: 61%, RSV only: 26% Wheezing <36 mo — RV only: 89% RSV only: 73%	Aeroallergen sensitization, first year: 4.3 (1.4-13)
		Rubner, 2017	217	Asthma, 13	Wheezing, <36 mo — RV: 3.3 (1.5-7.1), RSV: NS	Wheezing, <36 mo — RV: 40%	Aeroallergen sensitization, first year: 6.0 (2.5-14), aeroallergen sensitization, first 3 y of life: 21, with RV: 7.9
Turku, Finland	First wheezing, 3-23 mo, hospitalized	Lehtinen, 2007	118	Recurrent wheezing, 2.1	RV HR: 5.1 (1.0-25); non-RV/RSV HR: NS	RV: 50%	Atopy HR: 4.7 (1.9-11), eczema HR: 3.3 (1.3-8.4), age HR: 3.0 (1.4-6.6)
		Lukkarinen, 2017	127	Atopic and nonatopic asthma, 7.7	Atopic asthma — RV: 5.0 (1.1-22) Nonatopic asthma — non-RSV/RV: 8.0 (2.3-28)	RV without atopic characteristics: −, RV and sensitization: 50%, plus eczema: 71%, plus parental asthma: 100%	Atopic asthma — sensitization: 12 (3.0-44), eczema: 4.8 (1.4-17) Nonatopic asthma — age: 7.3 (1.7-31), parental smoking: 3.8 (1.2-13)

(Continued)

TABLE I. *(Continued)*

Study site	Inclusion criteria	First author, year	No.	Outcome, age (y)	Virus risk factors, OR (95% CI)†	Prevalence of recurrent wheezing/ asthma in virus groups	Other risk factors, OR (95% CI)†
Perth, Australia	Wheezing, <12 mo, outpatients, high atopy risk	Kusel, 2007	198	Recurrent wheezing, 5	RV: 2.5 (1.1-5.9) RSV: 2.5 (1.0-11.3)	—	Atopic by age 2 y and RSV: 4.1 (1.3-9.5), atopic by age 2 y and RV: 3.2 (1.1-9.5)
		Kusel, 2012	147	Asthma, 10	RV or RSV: NS	—	RV and atopic after 2 y: RR 3.4 (1.1-10)
Rome, Italy	First bronchiolitis, <12 mo, hospitalized	Midulla, 2012	262 patients with bronchiolitis, 39 control subjects	Recurrent wheezing, 14 mo	RV: 3.3 (1.0-11)	RV: 80%	Absence of lung consolidation: 2.6 (1.1-6.1), family history of asthma: 2.5 (1.2-4.9)
		Midulla, 2014	230	Recurrent wheezing, 3.2	RV: 3.2 (1.1-9.6)	RV: 64%	B-eos >400 cells/ μL: 8.4 (1.6-45)
Soma, Japan	Lower respiratory tract infection, ≤3 y, hospitalized	Takeyama, 2014	80 patients with wheezing and 136 patients without wheezing at admission	Recurrent wheezing, 4.2	Wheezing group: RV vs RSV, $P = .035$ Nonwheezing group: NS	Wheezing group — RV: 81%	—
Three centers, Finland	Bronchiolitis, <24 mo, hospitalized	Bergroth, 2016	365 total 177, <12 mo with first episode	Asthma, 1.7	All — RV: 9.1 (4.3-19) Non-RV/RSV: 2.7 (1.3-5.6) <12 mo with first episode — RV: 20.4 (4.9-86), non-RV/RSV: 3.8 (1.1-13)	All — RV: 61%, non-RV/RSV: 36% <12 mo with first episode, —	—

—, No data given; *as-IgE*, allergen-specific IgE; *B-eos*, blood eosinophil count; *HR*, hazard ratio; *NS*, nonsignificant; *RR*, risk ratio.
*Including prospective studies that have used both RV and RSV detection.
†Unless otherwise stated.

80% of wheezing episodes and asthma exacerbations in children.[6-8,31-33] In infants aged less than 12 months, RV causes approximately 20% to 40% of bronchiolitis or acute wheezing episodes in emergency department and hospital settings and is second only to RSV.[34,35] RV is also the leading cause of bronchiolitis, leading to hospitalization outside the winter RSV-induced bronchiolitis season.[36] RV-A and RV-C species cause more severe respiratory illness than RV-B species.[37]

School-age asthma after RV-induced bronchiolitis/ wheezing. RV-induced severe bronchiolitis/early wheezing is a more robust marker of asthma risk than wheezing episodes caused by RSV or other viruses (Table I).[6,8,13,14,38,39] High-risk birth cohorts, which have included wheezing children with at least 1 atopic parent, have shown a close association between early-life RV-induced wheezing and school-age asthma.[6,9] The Childhood Origins of Asthma (COAST) study demonstrated that the risk for asthma by age 6 years was increased if the children had wheezing with RV (odds ratio [OR], 9.8) versus RSV (OR, 2.6) during the first 3 years, and furthermore, 90% of the children with RV-induced wheezing in the third year of life had asthma by age 6 years (OR, 26).[6,40] Although RV-induced wheezing was an independent asthma risk factor, aeroallergen sensitization markedly increases the RV-associated risk of asthma.[6,9] An Australian birth cohort study showed that the risk for wheezing at age 5 years was increased if the wheezing at less than 1 year of age was associated with RV either alone (OR, 3.2) or with concomitant RSV (OR, 4.1) but only in children with sensitization at an age of less than 2 years.[9] Therefore data from these high-risk birth cohorts suggest that atopic airways have an increased susceptibility to long-term dysfunction after RV-induced wheezing illnesses.

In addition, the subsequent asthma risk has also been demonstrated in population-based long-term follow-up studies in children hospitalized for the wheezing episode.[8,12] In a Finnish study asthma at age 7 years was more common after RV-induced (52%; OR, 4.1) than after RSV-induced (15%) severe bronchiolitis.[8] In prospective studies viral wheezing episodes in infancy are associated with increased asthma risk for as long as 15 to 18 years.[11] One study focused on the first episode of severe wheezing and demonstrated an association between RV and

school-age atopic asthma (84%; OR, 5.5) in an 8-year follow-up.[13] When the upper age limit of bronchiolitis is set to 6 months, non–RSV-induced bronchiolitis (most of these cases are RV induced) has shown higher asthma risk (24%) at age 6.5 years than RSV-induced bronchiolitis (8%).[41] The association between RV-induced wheezing and the development of childhood asthma has been confirmed in a recent meta-analysis including 15 original articles.[42]

RSV

RSV is a pneumovirus in the Paramyxoviridae family and is a single-stranded enveloped RNA virus with 2 major antigenic groups, A and B (Fig 1). The genetic diversity of proteins among the A and B RSV groups forms several subgroups with 10 A genotypes and 13 B genotypes.[43] There is evidence that some strains are more likely to cause lower airway disease, and virulence factors have been identified.[44] Monoclonal antibodies to the RSV fusion (F) protein inhibit viral attachment and the severity of clinical illness. An RSV vaccine has been elusive, but several candidates are now in clinical development.[45,46]

Detection and epidemiology. Rapid RSV antigen detection and PCR appear to have equal sensitivity in detecting the virus[47]; however, the former is used more often in clinical decision making. RSV causes up to 80% of bronchiolitis cases, the peak incidence being in infants between 3 and 6 months of age. Epidemics occur typically at midwinter, and nearly all children have had RSV infection by age 2 years. During the first year of life, approximately 20% require outpatient medical care, whereas 2% to 3% with more severe illness need hospitalization caused by RSV-induced bronchiolitis/pneumonia.[2] Risk factors for severe RSV-induced bronchiolitis are age less than 3 months, prematurity with the presence of chronic lung disease, congenital heart disease, immunodeficiency, and neuromuscular disorders.[2,48-51]

Childhood asthma after RSV-induced bronchiolitis. Many prospective long-term follow-up studies have shown that RSV-induced bronchiolitis is associated with later development of asthma.[11,52,53] For example, the Tucson Respiratory Study linked RSV-induced bronchiolitis to asthma up to age 11 years, and a Finnish study linked RSV-induced bronchiolitis to self-reported asthma up to age 15 to 18 years.[11,52] A case-control study of Swedish children reported an association between RSV-induced bronchiolitis and subsequent allergic sensitization,[10,54-56] but this finding has not been reproduced in birth cohort studies.[53]

Whether this association is causal has been the subject of considerable debate. A retrospective cohort study including more than 95,000 infants showed that infants born 3 months before the RSV season had the greatest risk for hospitalization because of lower respiratory tract illness and the highest risk for having asthma between the ages of 4 and 5 years,[57] suggesting causality. A Danish study including more than 18,000 Danish twins reached a different conclusion: severe RSV-induced illnesses were associated with recurrent wheezing during early childhood,[58,59] but this was attributable to genetic predisposition for both more severe RSV-induced illness and asthma.[59] Two studies of RSV immunoprophylaxis with palivizumab in preterm or high-risk infants demonstrated that prevention of more severe RSV-induced illness decreased recurrent wheezing but not atopic asthma.[60,61]

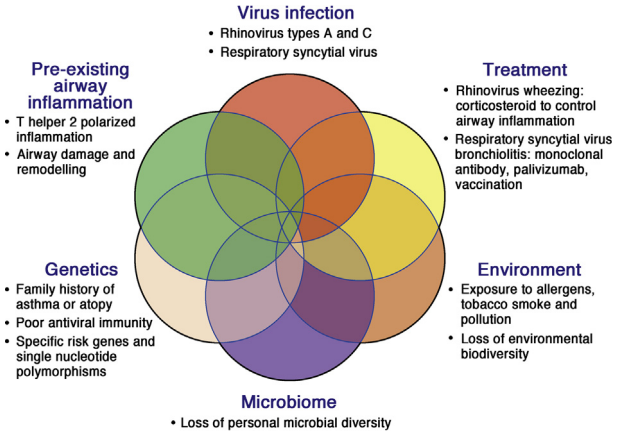

FIG 2. Interacting factors that contribute to the severity of virus-induced wheezing illnesses and the risk for subsequent development of childhood asthma.

SIMILARITIES AND DIFFERENCES BETWEEN RV AND RSV

Clinical characteristics

There are several differences between RV- and RSV-induced illnesses with respect to at-risk populations and clinical characteristics.[36,62] Children hospitalized for RV-induced wheezing tend to be older, are more likely to have wheezed previously, more often have allergic sensitization compared with those with RSV-induced wheezing,[5,7,33,63-66] and also show a favorable response to oral corticosteroid treatment whereas those with RSV-induced wheezing do not.[67,68] Although RSV can generally cause more severe infections in infants than RV, the inception of wheeze might be more rapid (and duration shorter) with RV compared with RSV infection.[69,70] These observations are further supported by cluster analysis, which included 2615 children with bronchiolitis and identified showed 4 different distinct clinical profiles.[70]

Pathophysiology

RV and RSV are both transmitted mainly through direct contacts and aerosol particles. Both viruses replicate in ciliated epithelial cells of the upper airways and in medium- to large-sized lower airways (Fig 1).[71] RSV infections can extend into the small airways and can also infect type I pneumocytes. These viruses attach to unique cellular receptors: intercellular adhesion molecule 1 used by RV-B and most RV-As, low-density lipoprotein receptor used by some RV-As, cadherin-related family member 3 (CDHR3) used by RV-C, and CX3CR1 used by RSV.[72,73] RSV induces epithelial cell apoptosis and necrosis and generally causes more damage to the airway epithelium compared with RV. Surfactant proteins have shown protective effects against RSV infection by regulating innate and adaptive immunity and participating in host defense pathways, such as regulation of proinflammatory cytokine production, chemotaxis, or tissue repair.

After RV attachment, infected cells recognize RV pathogen-associated molecular patterns through interaction with 2 different families of pattern recognition receptors: Toll-like receptor (TLR) 2, TLR3, TLR7, and TLR8 and retinoic acid–inducible gene I–like receptors.[74,75] TLR4 is a key regulator

of both innate and adaptive immune responses in RSV infection.[43] These receptors activate transcription factors (eg, interferon regulatory transcription factor 7 and nuclear factor κB) that promote the expression of type 1 and type III interferons and several inflammatory cytokine genes.[76] Early innate immune responses, such as type 1 interferons, occur very rapidly after either RV or RSV infection of the epithelium.[36] Both viruses induce cytokines (IL-1, TNF, IL-6, IL-12, IL-18, and IFN-γ), chemokines (CCL3, CCL5, CXCL8, and CXCL10), and growth factors that activate and attract granulocytes, dendritic cells, and monocytes at the site of infection. Transcriptional profiling of PBMCs during RSV infections demonstrates stimulation of innate immune and cell-cycle pathways and downregulation of B and T cell–related genes. The latter finding was more pronounced in infants infected with RSV compared with RV, which is consistent with other studies that have demonstrated virus-specific patterns of gene expression.[77,78] Interestingly, RSV can infect B cells,[79] whereas some RVs can bind to B cells and induce proliferation.[80] The combined effects of the virus and the inflammatory response lead to epithelial damage and sloughing, mucus production, and ultimately airway obstruction leading to wheezing.[36,51,81,82]

Recent findings from cross-sectional and birth cohort studies indicate that environmental exposures modify the host response to respiratory viruses in early childhood. For example, children on European dairy farms are less likely to have transient wheezing illnesses, which are mostly of viral cause.[83] Similarly, children from Wisconsin dairy farm families have fewer medically attended respiratory illnesses compared with those from nonfarm families.[84] *Lactobacillus johnsonii*, an environmental microbe associated with pet ownership, can protect against RSV-induced pathology in a mouse model.[85] In urban areas early-life exposure to high levels of indoor allergens (cockroach, mouse, and cat) and diverse microbes in household dust are related to reduced risk of recurrent wheeze.[86]

Finally, there is evidence that viruses and bacteria interact in patients with respiratory illnesses. Viral infections and illnesses are associated with transient detection of common bacterial pathogens (*Moraxella catarrhalis*, *Streptococcus pneumoniae*, and *Haemophlius influenzae*).[87,88] Furthermore, airway microbiome communities dominated by these organisms were associated with increased risk of wheezing illnesses.[87] Finally, hospitalization for RSV-induced bronchiolitis is associated with airway microbiomes dominated by *H influenzae* or *Streptococcus* species, which were in turn associated with enhanced innate immune activation.[89]

WHY IS VIRUS-INDUCED WHEEZING DURING INFANCY ASSOCIATED WITH CHILDHOOD ASTHMA?

There are several interacting factors that contribute to the strong linkage between virus-induced wheezing illnesses and the risk of childhood asthma (Fig 2). First, some host factors can predispose children to more severe RV or RSV infections and later to asthma. Second, viral wheezing illnesses might damage the airways to promote variable airway obstruction. Third, there might be interactions between risk factors and environmental exposures that promote asthma. Finally, antibiotic use, urbanization, and increased hygiene cause loss of microbial biodiversity (measures of richness and species distribution) and eventually dysbiosis (imbalance in a microbial ecosystem) to promote allergic diseases.[90-92] In contrast, diverse microbial communities might help maintain normal airway physiology during viral infection and thereby moderate or prevent respiratory symptoms.[93]

TABLE II. Genes linked to both RSV-induced bronchiolitis and asthma

Cytokines	Receptors	Other
CCL5	*CCR5*	*ADAM33*
CXCL8	*CX3CR1*	*MS4A2*
IFNG	*IL4RA*	*NOS2A*
IL4	*TLR4*	*TNX*
IL6	*TLR10*	*SPA1*
IL10	*VDR*	*SPA2*
IL13		*SFTPD*
IL17		
IL18		
TGFB1		

Mechanisms linking RV-induced wheezing to asthma development

The susceptibility to RV-induced bronchiolitis/early wheezing seems to be linked to predisposition because the prevalence of RV-induced bronchiolitis has been as high as 50% to 80% during the first year of life in infants with recurrent moderate-to-severe respiratory illnesses from atopic families.[29] Genetic variation at the 17q21 locus increases the risk for RV-induced wheezing in early childhood.[94] Although the mechanism for this effect is still unknown, it is notable that farm exposure also interacts with 17q21 polymorphisms to influence the risk for allergy and asthma.[95]

In addition, low interferon responses secondary to young age, allergic sensitization, or both could increase susceptibility to viral infections and illnesses.[96,97] Many studies have linked RV-induced wheezing in early life to other atopic biomarkers, allergen-specific sensitization, increased eosinophil counts in nasal mucus or blood, or the presence of atopic eczema, which have additive effects on asthma risk.[5,7,9,96,98,99] Allergen exposure and high-affinity IgE receptor cross-linking have been shown to impair virus-induced type I and III interferon production in peripheral blood cells.[100] Also, type 2 inflammatory cytokines can inhibit antiviral responses in airway epithelial cells.[101] The interaction between RV-induced wheezing and atopy is likely to become stronger by increasing age in children because the prevalence and intensity of respiratory allergy increases with age.[7,39]

Interactions between allergic sensitization and RV-induced wheezing have been described. For example, both RV infections and allergens can enhance the airway epithelial cell production of IL-25 and IL-33, which promotes type 2 airway inflammation and remodeling.[102,103] The IL-33 polymorphism is linked to intermediate and late-onset wheezing and allergic sensitization.[104] The first line of defense against RV infection is the airway epithelium, which is relatively resistant to infection when undamaged. Disrupted airway epithelium can favor RV replication by opening the way to deeper cell layers in which RV replicates most actively and by increasing the number of intercellular adhesion molecule 1 receptors as shown in

recent *in vitro* studies.[105] Damaged barrier function of the airway epithelium can also lead to enhanced absorption of aeroallergens or invasion of bacterial pathogens through the airway wall.[106] Finally, RVs can contribute to airway remodeling by inducing vascular endothelial growth factor, TGF-β, and chemoattractants for airway smooth muscle cells.[107,108] These effects might be more pronounced for RV infections in early life.[109] Thus repeated RV infections that extend to the lower airways could damage the airways and lead to remodeling of airway structures.

RSV-induced wheezing and asthma

RSV-induced bronchiolitis is linked to an increased risk for asthma. The severity of the acute illness is related to the subsequent risk for asthma.[110] Polymorphisms in a number of genes, mostly related to immune regulation, are associated with increased risk for both RSV-induced bronchiolitis and asthma (Table II).[43,111] Other risk factors include young age and low lung function, but unlike RV-induced wheezing illnesses, atopic children are probably not at increased risk for RSV-induced bronchiolitis.[63]

The risk of more severe RSV infections has been linked to the balance between type 1 and 2 immune responses. Infants with more severe versus mild RSV have shown reduced IFN-γ expression in PBMCs and airway cells, and IFN-γ expression has been correlated with subsequent asthma.[112-114] TLR4 polymorphisms and LPS have been linked to induction of type 2 immune responses, and these factors also influence the severity of RSV-induced illness in children.[114] Recently, it was shown in mice that aeroallergen-induced IL-33 predisposes to pneumovirus-induced asthma by dampening impaired IFN-α and IFN-λ production.[115] Also, IFN-β has immune-modulating properties and can inhibit eosinophilic asthma–like pathophysiology in pneumovirus-infected mice.[116]

Overall, RSV-induced bronchiolitis typically affects neonates at the critical time window of lung development and therefore might have long-term influences. Murine models have shown that RSV infection causes more lung damage during the proliferative stage of lung growth compared with the equilibrated stage.[43] Neonatal regulatory B (nBreg) cells are highly permissive to RSV infection, and the frequency of nBreg cells has predicted the severity of acute bronchiolitis disease.[79] Thus nBreg cell activity might have an important role in modulating an early-life host response to RSV. RSV infection increases the expression of nerve growth factor (NGF) and its receptors in the developing lungs.[117] NGF controls the structural development of nervous system and its ability to respond to environmental changes. Neurotrophin levels have correlated with the intensity of allergic conditions, including asthma, and overexpression of NGF could lead to airway hyperreactivity during and after RSV infection.

Other viruses. Nearly all acute wheezing episodes are associated with viral infection.[5] Although RV and RSV most commonly cause wheezing illnesses, other contributing viruses include enterovirus,[7,118] bocavirus,[119] parainfluenzavirus,[6,8] coronaviruses,[9,29,88] metapneumovirus,[32] influenza virus,[9,120] and adenoviruses.[32] Polyomaviruses have also been detected in the lower airways but almost always with other viral pathogens, and it is uncertain whether they contribute to wheezing illnesses.[121] It should be noted that only RSV- or RV-induced wheezing illnesses are associated with increased risk for recurrent wheeze and asthma; infections of lesser severity with these viruses are ubiquitous. It remains to be determined whether less severe infections with these viruses, other viruses, or even certain bacteriophages could protect against the acquisition of asthma.

Prevention of asthma related to viral wheeze

Antiviral and anti-inflammatory treatments have been tested for long-term efficacy in prevention recurrent wheezing and asthma. Palivizumab, an mAb that reduces the rate of severe RSV infection, decreased recurrent wheezing in up to a 6-year follow-up in preterm infants but did not affect rates of atopic asthma.[61,122] For infants with an initial RV-induced wheezing episode, a 3-day course of oral prednisolone decreased the time to initiation of asthma control therapy in the subgroup of children with high RV genome load.[67,68] Interestingly, all children with high RV genome load who were treated with placebo required asthma control medication within just 14 months. These studies indicate that preventive strategies targeting either the virus or the inflammatory response could help prevent recurrent wheezing and perhaps some asthma phenotypes.

ASTHMA EXACERBATION

Several factors can contribute to asthma exacerbation, including infections, underuse of asthma control medications, or exposure to allergens or pollutants.[123] In most cases there is more than 1 contributing factor, and this is especially true for severe exacerbations. Viral infections are of special importance because they contribute to up to 90% of exacerbations, especially during the fall and spring in temperate climates, when viral respiratory tract infections are most common. Furthermore, viral infections play a major role in seasonal peaks of exacerbations that coincide with the return of children to schools after summer and spring breaks.[124]

Among the plethora of respiratory viruses that can cause wheezing illnesses, RVs are most closely associated with exacerbations of childhood asthma.[125,126] RVs can cause a spectrum of illnesses ranging from asymptomatic infections to severe lower respiratory tract illnesses. This is also true for children with asthma, and in fact, most RV infections in children with asthma do not cause exacerbations.[127-129] There are a number of cofactors that are associated with a greater likelihood of more severe RV-induced illnesses, and the list of contributing factors is quite similar for infants (Fig 2) and children with asthma. It is the more severe RV-induced illnesses, accompanied by an increased inflammatory response, that promote asthma exacerbations.[130]

Viral factors. Just as RV-A and RV-C are associated with wheezing illnesses in early childhood, these viruses are also more often associated with exacerbations of asthma compared with RV-B. RV-C might be more strongly associated with more severe exacerbations, including those requiring hospitalization.[131-134] This could be due to faster replication rate and induction of more robust cellular responses, as demonstrated in cultures of differentiated airway epithelial cells.[135] In cohort studies RV-B

infections do not increase the risk for exacerbations,[129] but they might slightly increase the risk of exacerbation in children whose asthma is of greater severity.[127]

Host factors. In children with established asthma, allergy and genetic factors can increase the risk of virus-induced wheezing illnesses and asthma exacerbations. Allergy is an important factor, and in fact, allergy and viral respiratory tract infections synergistically increase the risk for acute asthma exacerbations.[33] The effects of allergy are dose related. For example, in a cohort of Costa Rican children, the quantity of dust mite IgE was positively associated with the risk for RV-induced asthma exacerbations.[136] In addition, in a Boston cohort of children with acute exacerbations of asthma, the severity of acute RV-induced exacerbation was positively related to IgE specific for either dust mite or mouse proteins.[137] Furthermore, in a study of children with asthma who were monitored for viral infections during the peak months (April and September) for RV infections, allergic sensitization was associated with a greater severity of RV-induced respiratory illnesses and RV-induced symptoms of asthma.[128]

Recent studies with omalizumab, which prevents IgE binding to its receptor, have established that neutralizing allergic inflammation can enhance interferon responses and reduce RV-induced illnesses and asthma exacerbations. For example, urban children with moderate-to-severe asthma were randomized to treatment with either standard asthma controller therapy or standard therapy plus omalizumab. In 2 separate studies both year-round and preseasonal treatment with omalizumab eliminated the seasonal peaks in exacerbations, most of which are associated with viral infection.[138,139] Analysis of weekly samples of nasal secretions confirmed that omalizumab reduced virus-induced exacerbations, and this effect was most pronounced in children with more severe asthma.[138] Furthermore, omalizumab increased IFN-α responses of blood cells stimulated with RV *ex vivo*. This finding suggested that omalizumab, by neutralizing IgE, indirectly improved antiviral responses. This theory is further supported by the findings that omalizumab reduced the frequency, quantity, and duration of RV detection in nasal secretions sampled weekly and also reduced the frequency of RV-induced colds by about one third.[127] In a study of children with acute asthma exacerbations, RV-induced exacerbations were less severe in those children who had been treated with omalizumab compared with other controllers.[140]

Collectively, these findings suggest that allergic inflammation impairs antiviral responses, and in fact, there is considerable evidence that childhood asthma is associated with reduced interferon responses of blood cells and the airway epithelium (see review in this issue by Edwards et al[141]). In adults with allergic asthma, inhaled IFN-β was administered during colds in an attempt to prevent viral exacerbations. Although the primary end point was not achieved, IFN-β improved lung function in the study population and also improved asthma control in a subset of adults with more severe asthma.[142]

Several genetic factors have been linked to the risk of asthma exacerbations.[143] Of these factors, a polymorphism (rs6967330) in CDHR3 is associated with acute severe exacerbations in young children, including asthma-related hospitalizations.[144] This polymorphism is in the coding region (C529Y) and leads to increased CDHR3 expression on the cell surface.[144] Interestingly, CDHR3 is the cell-surface receptor for RV-C, and the rs6967330 polymorphism leads to increased RV-C cell binding and replication.[73] These findings suggest that the linkage between rs6967330 and exacerbations of asthma is due to greater severity of RV-C infections.

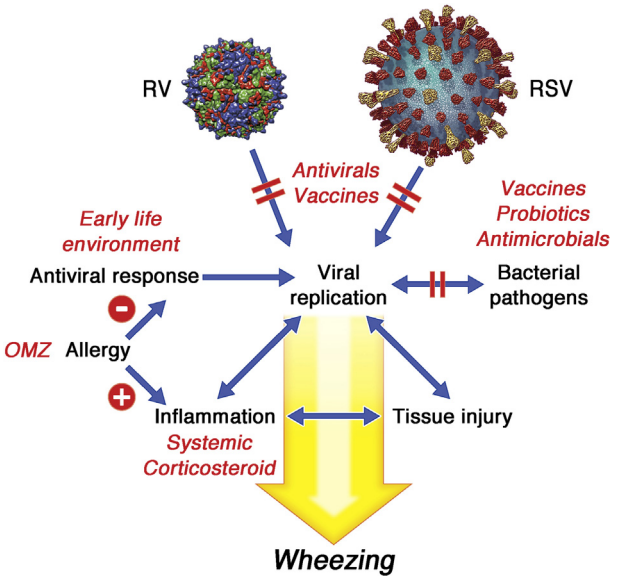

FIG 3. Opportunities for treatment or prevention of virus-induced wheezing illnesses. Potential interventions are shown in red. *OMZ,* Omalizumab.

Environmental factors

Several environmental factors can influence the severity of illness during RV infections and increase the probability of RV-induced exacerbation in children with asthma. Observational studies demonstrated that exposure to pollutants, such as NO_2, can increase the severity of virus-induced lower respiratory tract symptoms and reductions in lung function in children with asthma.[145] In addition, high exposure to allergens in children with allergic asthma increases the risk for virus-induced exacerbations.[146] Maternal stress and depression have been associated with acute wheezing illnesses (which are predominantly viral) in young children; the mechanism of this association is unknown but was not due to enhanced T_H2 responses or impaired antiviral responses as measured in PBMCs.[147] Vitamin D levels were inversely related to measures of asthma severity, including hospitalization for severe exacerbations.[148] However, in a randomized clinical trial vitamin D supplementation of adults with low vitamin D levels did not reduce rates of clinical colds or exacerbation rates.[149,150]

Viral infections are generally recognized as important contributors to acute asthma exacerbations. However, prospective monitoring of nasal secretions during the peak season for RV infections and asthma exacerbations provides evidence of a close relationship between viral, bacterial, and respiratory symptoms. RV infections increase the frequency and quantity of *S pneumoniae*, *M catarrhalis*,

and *H influenzae* detected in airway secretions.[129] In addition, viral infections associated with detection of these common bacterial pathogens are more likely to be symptomatic, and in children with asthma, they are more likely to be associated with asthma exacerbations.[129]

Additional studies were conducted to identify differences in the microbiome composition of asymptomatic viral infections compared with those associated with asthma exacerbations.[151] Compared with baseline samples before RV infection, samples during acute RV-induced exacerbations had increased detection of *Moraxella* species. In contrast, asymptomatic infections were associated with increases in *Corynebacterium* species compared with the baseline samples. These findings suggest that RV infections modify the upper airway microbiome and that quantitative and qualitative changes in the airway microbiome modify the probability that RV infection will lead to an exacerbation of asthma.

CONCLUSIONS AND THERAPEUTIC OPPORTUNITIES

Respiratory viruses interact with host and environmental factors to increase the risk of wheezing illnesses in infants and to increase the risk of exacerbations in asthmatic children. These findings suggest that there are a number of therapeutic opportunities to reduce the frequency and severity of viral respiratory illnesses and hopefully secondary effects on the incidence and exacerbation of asthma (Fig 3). The search goes on for effective antivirals and vaccines for RV and RSV, and several candidates are currently in clinical trials (reviewed by Edwards et al[152]). Antiviral approaches also include strategies to enhance resistance to multiple respiratory viruses through administration of interferons or other immunostimulatory molecules. Furthermore, the search is on to identify biologic exposures (eg, microbes and proteins) that might help to promote the development of healthy mucosal immune responses that resist viral infection. Research into the airway microbiome has identified a number of intriguing associations with bacteria that might either protect against viral illnesses or add to the problem. These findings suggest possibilities for 2 new therapeutic approaches: (1) identify a new class of probiotics selected to promote resistance to viral illnesses and (2) develop strategies to inhibit pathogenic bacteria that synergize with viruses and add to illness severity. The latter approach could involve antibacterial vaccines or probiotics. Targeted antimicrobial therapy could also be considered, although potential benefits must be weighed against further selection of antimicrobial-resistant organisms and possible short- and long-term detrimental effects on commensal or beneficial airway or gut bacteria. Finally, treatments that can either prevent allergy or moderate its severity could secondarily boost antiviral responses and also reduce inflammatory responses that lead to airway obstruction and remodeling.

Collectively, these new approaches provide hope that new insights into personal risk factors (genetics, allergy, and antiviral immunity), environmental exposures (farm, urban, and microbes), and viral virulence can be harnessed to reduce the morbidity of viral respiratory illnesses and childhood asthma.

What do we know?

- **Risk factors for RV-induced wheezing in early childhood include low lung function, genetic predisposition, and atopic characteristics, and the combination of RV-induced wheezing and atopy predicts a high likelihood of subsequent childhood asthma.**
- **Risk factors for RSV-induced bronchiolitis include genetics, low lung function, and young age but not atopy. RSV-induced bronchiolitis also predicts recurrent wheezing and childhood asthma.**
- **The airway inflammation that predisposes to early RV-induced wheezing appears to be responsive for corticosteroid medication.**
- **Prevention of RSV-induced bronchiolitis with the anti-RSV mAb palivizumab decreases risk of severe RSV-induced illness, recurrent wheezing, and perhaps nonatopic asthma.**
- **In children with asthma, infections with respiratory viruses, most commonly RV, contribute to most acute exacerbations.**
- **Virus-induced exacerbations are usually multifactorial, and other contributing factors include allergy, airway bacteria, genetics, medication adherence, and exposure to allergens and pollutants.**

What is still unknown?

- **Do RV infections cause asthma, unmask asthma, or both?**
- **Will prevention of bronchiolitis (either RV or RSV induced) and other viral wheezing illnesses in early life lead to preservation of lung function and reduced rates of persistent childhood asthma?**
- **Biomarkers are needed to serve as early clinical markers for susceptibility to viral illnesses and the progression to asthma; these biomarkers could be used to identify patients for secondary prevention trials of asthma.**
- **Which lifestyle factors and environmental exposures (microbial and others) lead to the development of robust antiviral immune and lung development to reduce the risk for virus-induced wheezing illnesses?**
- **During viral infections, what are the microbial mechanisms that modify airway inflammation and influence airway physiology?**
- **What is the role of the host antiviral immune response in causing airway obstruction and respiratory symptoms?**

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