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.

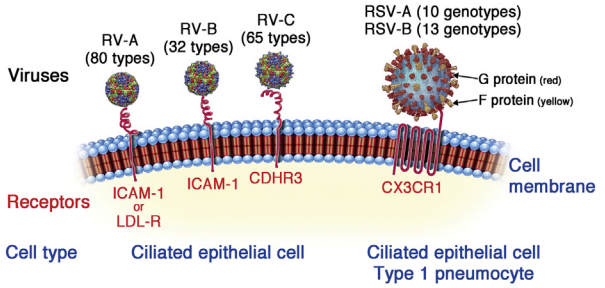

FIG 1. RV and RSV interactions with airway epithelial cells. *ICAM-1,* Intercellular adhesion molecule 1; *LDL-R,* low-density lipoprotein receptor.

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