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Infections and Asthma: Impact on the Natural History of Asthma

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KEY POINTS

- Wheezing viral respiratory illnesses are the most common initial presentation of childhood asthma.
- Once asthma is established, viral infections, most notably rhinovirus (RV), are the most frequent trigger of severe asthma exacerbations. RV-C appears to be a particularly pathogenic virus in children with asthma.
- Evidence has recently emerged to suggest that bacterial pathogens in the lower airway may contribute to the expression of asthma. Ongoing studies are critical to our understanding of the role of the airway microbiome in asthma inception and exacerbation.
- Synergistic interactions between underlying allergy and virus infections play an important mechanistic role in asthma inception and exacerbation, and are an important therapeutic target.
- Novel therapies are needed to prevent and treat virus-induced wheezing and asthma exacerbations.

Introduction

Respiratory infections can cause wheezing illnesses in children of all ages and also influence the development and severity of asthma in several ways. First, viral wheezing episodes during infancy are a critical risk factor for asthma inception. Once asthma is established, viral upper respiratory tract infections (URTIs) are the most common trigger for acute exacerbations. Furthermore, a potential role for particular bacterial pathogens in the development of wheezing and asthma exacerbations has been identified. This chapter will review the relationships between infections and asthma inception and exacerbation. Additionally, we discuss mechanisms by which infections lead to lower respiratory inflammation and airway dysfunction. Finally, we discuss treatment strategies for virus-induced wheezing and exacerbations of asthma.

Relationships Between Early Life Infections and Childhood Asthma

VIRUSES

Viral respiratory illnesses leading to wheezing are one of the most common causes of hospitalization during infancy. Using multiple virus detection methods, including polymerase chain reaction (PCR), Jartti and colleagues[1] investigated the etiology of wheezing illness in 293 hospitalized children. Of the 76 infants with virus detected, 54% had respiratory syncytial virus (RSV), 42% had picornaviruses (human rhinovirus [RV] and enterovirus) and 1% had human metapneumovirus (hMPV). In older children, respiratory picornaviruses, most commonly RV, dominated (65% of children aged 1 to 2 years and 82% of children aged ≥3 years). Outpatient wheezing illnesses are also extremely common in young children, and viruses have been implicated in 67% to 90% of these episodes in different populations.[2,3]

Wheezing with viruses during infancy is often an early manifestation of asthma. Several large, long-term prospective studies of children have demonstrated that RSV bronchiolitis is a significant independent risk factor for recurrent wheezing and asthma, at least within the first decade of life.[4,5] A recent clinical trial comparing palivizumab (anti-RSV monoclonal antibody) to placebo in near preterm infants demonstrated reductions in recurrent wheezing during the first year of life in the children treated with palivizumab.[6] This is the strongest level of evidence to date in support of a causal role for RSV in recurrent wheezing. However, a longitudinal, population-based cohort study has demonstrated that the association between RSV lower respiratory infections during early life and both frequent (more than three episodes) and infrequent wheezing (less than three episodes) decreases with age and becomes nonsignificant by the age of 13 years.[4] These data suggest that although RSV infections contribute substantially to the risk of recurrent wheezing and asthma in early childhood, other co-factors (e.g. genetic, environmental, developmental) also contribute to the expression of asthma or modification of phenotypes over time. Interestingly, a 2013 study identified unique immune response profiles during and after RSV bronchiolitis in comparison with bronchiolitis caused by other viruses.[7]

With the development of molecular diagnostics, significant evidence has emerged to suggest that wheezing illnesses caused by RV identify children at highest risk for childhood asthma.[2,8] The Childhood Origins of ASThma (COAST) birth cohort study confirmed prior associations between RSV wheezing in the first 3 years of life and childhood asthma, but demonstrated that RV wheezing during this time is associated with a greater, 10-fold increased risk of childhood asthma.[2] Mechanisms by which recurrent RV infections may lead to wheezing and airway remodeling, particularly in susceptible hosts, have been described.[9] A new species of RV, RV-C, was recently discovered,[10,11] and has been shown to be an important cause of lower respiratory illnesses and wheezing in children.[12–14] A longitudinal analysis within the COAST study demonstrated that both RV-A and RV-C were more likely than RV-B to cause moderate-to-severe respiratory illnesses in infants.[15] Whether RV-C wheezing illnesses confer a greater risk of childhood asthma development is currently unknown.

Molecular diagnostics are not universally available to clinicians, so the question of whether season of wheezing is helpful

in delineating risk is an important one. Bronchiolitis during infancy is associated with an approximately 2-fold increased risk of early childhood asthma; however, this risk differs by season of bronchiolitis. Bronchiolitis occurring during RV-predominant months (spring and fall) was associated with an estimated 25% increased risk of early childhood asthma compared with RSV-predominant (winter) months. However, the proportion of associated asthma after winter season bronchiolitis is greater than RV-predominant months because of higher rates of bronchiolitis during the RSV season.[16] Season of birth also appears relevant: children born close to the onset of the winter virus season are most prone to the development of lower respiratory tract symptoms, and this is likely due to a developmental component in relationship to the timing of the winter virus peak.[17,18]

BACTERIA

It has been proposed that chronic bacterial infections or colonization with pathogenic bacteria could initiate chronic lower airway inflammation, impaired mucociliary clearance, increased mucus production and ultimately asthma.[19,20] Organisms primarily implicated in this process include *Chlamydophila pneumoniae*,[21–23] *Mycoplasma pneumoniae,*[24,25] *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis*.[20] Studies of chronic mycobacterial or *Chlamydophila* infection and asthma in children have yielded conflicting results, potentially in part due to the limitations of current diagnostics. Findings of diagnostic tests in the upper and lower airways are not always concurrent, and diagnosis of infection by serology leads to inaccuracies. The role of these bacteria in acute wheezing in young children is also unclear.

Recent publications have suggested that pathogenic bacteria may play a role in both acute wheezing episodes and asthma inception in preschool children. First, Bisgaard and colleagues found that neonates with *S. pneumoniae, H. influenzae* or *M. catarrhalis*, or with a combination of these organisms, in their hypopharynx are at increased risk for recurrent wheeze early in life and the diagnosis of asthma at the age of 5 years.[20] This original observation was made in infants of mothers with asthma, but the researchers were able to replicate some of these findings in an unselected cohort.[26] Further, these pathogens have been detected at higher rates in preschool children during acute wheezing episodes.[27] Interestingly, a similar predominance of Proteobacteria has been identified in the airways of older children and adults with established asthma.[28,29] Furthermore, in both human and animal studies, environmental exposure to 'protective' bacteria appears to have the capacity to prevent the development of wheezing and/or asthma in young children.[30–33] These studies of the role of microbial exposures and the microbiome in asthma inception are intriguing, and additional studies are a high priority to establish causality/protection and the specificity of these observations to asthma pathogenesis, and to define immunoinflammatory mechanisms contributing to these associations in both pediatric and adult patients.

Infections and Acute Exacerbations of Asthma

The relationship between viral infections and exacerbations of asthma has been clarified by the development of molecular diagnostic tests for viruses that are difficult to culture: RV, hMPV and bocaviruses. With the advent of these more sensitive diagnostic tools, information linking common cold infections with exacerbations of asthma has come from a number of sources. Prospective studies of children with asthma have demonstrated that up to 85% of exacerbations of wheezing or asthma in children are associated with viral infections.[34] Although many respiratory viruses can provoke acute asthma symptoms, RVs are most often detected, especially during the spring and fall RV seasons. In fact, the spring and fall peaks in hospitalizations because of asthma closely coincide with patterns of RV isolation within the community.[35] RV infections, most commonly RV-C, are frequently detected in children who present to emergency departments with acute wheezing and in children hospitalized for acute asthma.[12,14,36] Influenza and RSV are somewhat more likely to trigger acute asthma symptoms in the winter but appear to account for a smaller fraction of total asthma flares. Other viruses that are less frequently associated with wheezing and exacerbations of asthma include bocavirus,[37] metapneumovirus[38] and coronaviruses.[39] Together, these studies provide evidence of a strong relationship between viral infections, particularly those associated with RV, and acute exacerbations of asthma.

It is interesting that individuals with asthma do not necessarily have more colds, but have greater lower respiratory tract symptoms associated with colds. A prospective study of colds in couples consisting of one asthmatic and one healthy individual demonstrated that colds cause greater duration and severity of *lower* respiratory symptoms in patients with asthma.[40] These findings suggest that asthma is associated with fundamental differences in the lower airway manifestations of respiratory viral infections. In addition to provoking asthma, RV infections can increase lower airway obstruction in individuals with other chronic airway diseases such as chronic obstructive pulmonary disease[41] and cystic fibrosis.[42] Thus, common cold viruses that produce relatively mild illnesses in most people can cause severe pulmonary problems in susceptible individuals.

The role of respiratory viruses in exacerbations is particularly important in light of recent observations that severe asthma exacerbations may lead to progressive loss of lung function over time.[43,44] As seen in other chronic lung diseases, a paradigm by which recurrent severe exacerbations lead to progressive loss of lung function and enhanced disease severity over time appears to be emerging in asthma.

Sinus Infections and Asthma

The nature of the association between asthma and sinusitis in children (and adults) has been the subject of debate for many years. Much of the difficulty in defining this relationship results from the uncertainties in making the clinical diagnosis of sinusitis, because the signs and symptoms of sinusitis in children overlap with many common childhood respiratory disorders, including the common cold, allergic rhinitis and asthma. As reviewed in Chapter 26, untreated sinus disease may contribute to unstable asthma control in some patients. Because bacterial infections are clearly involved in acute and chronic sinus disease, the mechanisms by which these microbes may promote hyperreactivity in the lower airway have been of great interest. These relationships are covered in depth elsewhere in this text and therefore are not further reviewed in this chapter.

Mechanisms of Infection-Induced Wheezing Illnesses

Clinical studies and in vitro studies have provided a number of insights into the pathogenesis of virus-induced wheezing illnesses and exacerbations of asthma (Box 31-1).

SPREAD OF INFECTION FROM THE UPPER TO THE LOWER AIRWAYS

Respiratory viruses such as RSV and influenza are well known to infect the lower airway, and both can cause bronchitis, bronchiolitis and pneumonia. RV has traditionally been considered to be an upper airway pathogen because of its association with common cold symptoms and the observation that it replicates best at 33–35°C, which approximates to temperatures in the upper airway. In fact, lower airway temperatures are conducive to RV replication down to fourth-generation bronchi and exceed 35°C only in the periphery of the lung.[45] Moreover, some RV types, including RV-C isolates, replicate equally well at 33 and 37°C.[46,47] RV appears to replicate equally well in cultured epithelial cells derived from either upper or lower airway epithelium.[48] Finally, RV has been detected in lower airway cells and secretions by several techniques after experimental inoculation.[49–51] Titers of infectious virus in lower sputum reach or exceed those found in nasal secretions in some individuals.[50] In addition to evidence from experimental infection models, RV is frequently detected in infants and children with lower respiratory signs and symptoms, including children hospitalized for pneumonia.[52,53] Collectively, these findings suggest that respiratory viruses, including RV, can cause wheezing illnesses and exacerbations of asthma mainly by infecting lower airways and causing or amplifying lower airway inflammation.

VIRUS-INDUCED CYTOPATHIC EFFECTS

First, viral infections damage airway epithelial cells and can cause airway edema and leakage of serum proteins into the airway. These effects, together with shedding of infected cells into the airway, can lead to obstruction and wheezing. In addition, viral infections stimulate mucus secretion and can also promote the formation of additional goblet cells (mucoid metaplasia) that can enhance mucus secretion that can persist even after the acute infection has resolved. Virus-induced injury to the epithelium can disrupt airway physiology through a number of different pathways (Box 31-2). For example, viral infections can increase the permeability of the epithelium,[54] which may facilitate contact of irritants and allergens with immune cells, leave neural elements exposed and promote secondary infection with bacterial pathogens. In addition, the combination of epithelial edema and sloughing together with mucus production can lead to airway obstruction and wheezing.

As reviewed under 'Viruses', there is clinical evidence that the RV-B species may be less virulent than other RVs. Moreover, there is corresponding evidence from in vitro studies that RV-B viruses replicate more slowly, produce less cytopathic effect and induce lower interferon and inflammatory responses compared to other RVs.[55] Overall, these viruses appear to be attenuated.

ROLE OF ANTIVIRAL IMMUNE RESPONSES

Virus-induced immune responses are necessary to clear the viral infection but they can also contribute to airway dysfunction and symptoms by causing an influx of inflammatory cells that adversely affect lower airway physiology. Antiviral immune responses are initiated within the epithelial cell and amplified by resident and recruited leukocytes in the airway. For viruses such as RV that infect relatively few cells in the airway, virus-induced inflammation may be the primary mechanism for the pathogenesis of respiratory symptoms and lower airway dysfunction.[56] Viral respiratory infections can also induce the synthesis of many of the factors that regulate airway and alveolar development and remodeling, including vascular endothelial growth factor (VEGF), nitric oxide (NO), metalloproteinases and fibroblast growth factor (FGF).[57–60] How single or repeated bouts of virus-induced overexpression of these regulators of lung development and remodeling affect the ultimate lung structure and function is not known, but they could exert long-term effects on lung function and asthma following viral infection in infancy.

Epithelial Cells

The processes associated with viral replication trigger innate immune responses within the epithelial cell. Virus attachment to cell surface receptors can initiate some immune responses. For example, RSV infection activates signaling pathways in airway epithelial cells through the innate immune system through Toll-like receptor (TLR)-4.[61] Furthermore, the development of oxidative stress during viral infections can activate epithelial cell responses. Inside the cell, viral RNA is detected by innate immune sensors on endosomal surfaces (TLR-3, TLR-7, TLR-8) and intracellular proteins, such as the dsRNA-dependent

BOX 31-1 KEY CONCEPTS

Proposed Mechanisms of Virus-Induced Wheezing

- Viral infection spreads from the upper to the lower airway
- Virus-induced damage to airway epithelium
- Airway edema and transudation of serum proteins
- Mucus hypersecretion
- Cellular inflammation: mononuclear cells and neutrophils
- Neuroinflammation
- Enhanced airway responsiveness
- Interactions between respiratory viral infections and preexisting airway inflammation
- Secondary bacterial infection

BOX 31-2 KEY CONCEPTS

Role of the Epithelium in Virus-Related Inflammation and Injury Pathogenesis

- Airway epithelial cells serve as hosts for viral replication
- Viral replication initiates the immune response to virus
- Interferon secretion to inhibit inflammation and injury of neighboring cells
- Chemokine secretion to recruit leukocytes into the airway
- Virus-induced epithelial cell damage can disrupt barrier function
- Viral infection induces mucus secretion and mucous metaplasia

protein kinase (PKR) and retinoic acid-inducible gene I (RIG-I), to activate the innate antiviral immune response.[62] Through these pathways, viral replication stimulates antiviral effector molecules such as RNase L, and inhibition of protein synthesis within infected cells. In addition, innate antiviral responses induce chemokines (e.g. CXCL10) that recruit inflammatory cells into the airway and type I (IFN-α and IFN-β) and type III (IFN-λ1 and IFN-λ2) interferons that have autocrine and paracrine antiviral effects.

Leukocytes

Respiratory viruses activate monocytes, macrophages and dendritic cells to secrete an array of proinflammatory cytokines such as IL-1, IL-8, IL-10, tumor necrosis factor (TNF)-α and IFN-γ. In animal models, respiratory viral infections lead to a prominent expansion of mature dendritic cells in the lung.[63] Significantly, pulmonary dendritic cells express high levels of Toll-like receptors, and secrete large amounts of interferons in response to viral infection. Dendritic cell interferon responses are impaired in early life, which likely contributes to increased susceptibility to viral infections in infancy.[64]

Acute respiratory viral infections are often accompanied by pronounced neutrophilia of upper and lower respiratory secretions, and products of neutrophil activation contribute to airway obstruction and lower airway symptoms. For example, neutrophil elastase can up-regulate goblet cell secretion of mucus.[65] P2X7 is a cation channel expressed by leukocytes and airway epithelial cells that is important to pathogen control and neutrophilic inflammation. Attenuated P2X7 function, which is common in mild to moderate asthma, is associated with reduced recruitment of neutrophils to the airway during RV colds, and an increased risk of acute asthma symptoms.[66]

Lymphocytes are recruited into the upper and lower airways during the early stages of a viral respiratory infection, and it is presumed that these cells help to limit the extent of infection and to clear virus-infected epithelial cells. This is consistent with reports of severe viral lower respiratory infections in immunocompromised patients.[67] B cell responses to respiratory viruses also serve to limit duration and severity of illness, as indicated by the finding of frequent and prolonged viral illnesses in patients with X-linked agammaglobulinemia.[68]

Neuroinflammatory Mechanisms

Viral respiratory infections can induce inflammation through mechanisms involving neural mechanisms. These responses are difficult to study in humans, but studies in animal models have provided insights. For example, RSV infection in rodents leads to overproduction of nerve growth factor,[69] which promotes airway inflammation. This observation has also been confirmed in studies of babies with RSV bronchiolitis.[70] In a guinea pig model, virus infection causes dysfunction of M2 muscarinic receptors on parasympathetic nerves, leading to overproduction of acetylcholine and airway hyperresponsiveness. These responses appear to be driven by virus-induced acute phase cytokines such as IL-1β and TNF-α.[71]

Mediators

Mediators that are produced in excess during respiratory illnesses include NO, leukotrienes, prostaglandins, kinins and oxidative metabolites,[72–74] and inhibition of specific mediators can ameliorate some cold symptoms.[75] Histamine does not appear to play a role in common cold pathogenesis.[76]

RELATIONSHIP OF CELLULAR ANTIVIRAL RESPONSES TO OUTCOME OF VIRAL INFECTIONS

Several studies have tested the hypothesis that individual variations in cellular immune responses and patterns of cytokine production are related to the outcome of respiratory infections. In clinical studies, reduced IFN-γ responses of blood mononuclear cells ex vivo are associated with a significant increase in viral respiratory illnesses during infancy.[77–79] In addition, several studies have found that asthma is associated with impaired virus-induced secretion of interferons by airway and peripheral blood cells.[80–83] Together, these experimental findings suggest that individual variability in the cellular immune response to respiratory viruses, and interferon responses in particular, can influence the clinical and virologic outcomes of infection.

INTERACTIONS WITH BACTERIA

It is well established that viral illnesses of the middle ear, sinuses and lungs can promote secondary infections with bacterial pathogens such as *S. pneumoniae*, *M. catarrhalis*, and *H. influenzae*. As reviewed under 'Bacteria', colonization with these bacteria in early childhood is also a risk factor for acute wheezing episodes and asthma.[20] In school-aged children, these pathogens are more likely to be detected in association with a viral infection or just after a viral infection.[84] Furthermore, the risk of illness vs asymptomatic infection was greater in children who had both viruses and bacteria detected. Similarly, for children with asthma, moderate exacerbations were most likely to occur in viral infections in which *S. pneumoniae* or *M. catarrhalis* were also detected.[84] These findings suggest that viruses and bacteria may work together to promote airway pathology and respiratory symptoms.

ENVIRONMENTAL FACTORS AND VIRAL ILLNESSES

Environmental factors strongly influence the probability of exacerbations and appear to act together with viral infections in an additive fashion. As discussed in the next section, allergy is a strong risk factor for the development of asthma after virus-induced wheezing episodes in infancy and is also closely associated with virus-induced exacerbations of asthma in older children and adults with asthma. Accordingly, the combination of allergy and exposure to a relevant allergen contributes to virus-induced exacerbations of asthma.[85] Similarly, exposure to greater levels of air pollutants such as NO_2 and SO_2 also enhances the risk of virus-induced exacerbation.[86,87]

Interactions Between Allergy and Infections

Allergic sensitization has been defined as a clear risk factor for the development of asthma.[88] Children with 'multiple early sensitization' to aeroallergens have been identified as a phenotype at particularly high risk for asthma inception and severe exacerbations leading to hospitalization.[89] A sequential relationship whereby allergic sensitization precedes viral wheezing, most notably with RV, has been described.[90] Furthermore, children

who develop both risk factors in early life are at highest risk for subsequent asthma.[2,91]

There is convincing evidence to implicate respiratory allergy as a risk factor for wheezing with common cold infections later on in childhood. In studies conducted in an emergency department, risk factors for developing acute wheezing episodes were determined.[85,92,93] Individual risk factors for developing wheezing included detection of a respiratory virus, most commonly RV, positive allergen-specific IgE and presence of eosinophilic inflammation. Notably, viral infections and allergic inflammation synergistically enhanced the risk of wheezing, and higher levels of allergen-specific IgE conferred the greatest risk. This synergism may be particularly notable for RV-C.[14]

There are multiple mechanisms by which viral infections are thought to interact with allergic inflammation in order to lead to airway dysfunction, wheezing and asthma exacerbations.[94] First, viral infections can damage the barrier function of the airway epithelium, leading to enhanced absorption of aeroallergens across the airway wall and enhanced inflammation, while allergic inflammation may also lead to enhanced viral replication.[95,96] Next, allergic inflammation enhances airway responsiveness to RV.[97] There is also significant evidence that allergic asthmatic individuals have impaired antiviral responses as noted above. Furthermore, allergen exposure and high-affinity IgE receptor cross-linking has been shown to impair virus-induced type I and III interferon production in peripheral blood cells.[98,99] This may lead to both enhanced viral replication and also type 2 inflammation.[100,101]

Treatment of Infection-Induced Wheezing and Asthma

VIRUS-INDUCED WHEEZING IN INFANCY

Acute lower respiratory tract illnesses during the first one to two years of life are usually termed 'bronchiolitis' and are most likely due to infection with viral respiratory pathogens. The efficacy of various interventions for the treatment of the acute lower airway symptoms of wheezing, tachypnea, retractions and hypoxemia that occur as a result of these infections has been controversial due to variations in study design, the inability to rapidly and conveniently measure pulmonary physiologic variables, the confounding of results by the inclusion of children with a history of multiple wheezing episodes (i.e. asthmatic phenotypes) and the choice of outcome measures that have been evaluated.[102] In a recent series of meta-analyses evaluating various therapies, the routine use of bronchodilators,[103] steam or nebulized normal saline,[104,105] anticholinergics[106] and steroids[107] has not been shown to be of consistent benefit.

A more recent study suggests that the timing of the administration of epinephrine may influence the observed benefit. In an eight-center randomized, double-blind trial with a two-by-two factorial design, investigators compared inhaled racemic epinephrine with inhaled saline and on-demand inhalation with fixed-schedule inhalation (up to every 2 hours) in infants (>12 months of age) with moderate-to-severe acute bronchiolitis.[108] Length of stay, use of oxygen supplementation, nasogastric tube feeding, ventilatory support and relative improvement in the clinical score from baseline (preinhalation) were similar in the infants treated with inhaled racemic epinephrine and those treated with inhaled saline. However, the strategy of inhalation on demand was superior to that of inhalation on a fixed schedule for many of the outcome measures evaluated.

The atopic background of the patient (eczema or asthma in a first-degree relative) may influence the response to oral corticosteroid administration. Infants aged ≤18 months presenting to a care facility for treatment of moderate-to-severe bronchiolitis and who had a positive history of eczema or were known to have a parent or a full sibling with a prior physician diagnosis of asthma were treated with oral dexamethasone, 1 mg/kg, then 0.6 mg/kg for 4 more days, or matching placebo. All patients received albuterol nebulization delivered through a tight-fitting face mask with pressurized oxygen. Dexamethasone plus albuterol treatment shortened time to readiness for discharge from the unit. However, there was no difference between the treatment groups in terms of infirmary and clinic visits during the week following discharge.[109]

VIRUS-INDUCED WHEEZING IN PRESCHOOL CHILDREN

Therapeutic approaches for virus-induced wheezing in preschool children (ages 2–5 years) are challenging due to the fact that many children only wheeze with the 'common cold' and are totally asymptomatic in between these episodes, while others may have symptoms more or less on a daily basis as well. In addition, these episodes may range in severity from mild wheezing and coughing to severe respiratory distress that requires prompt medical intervention. Standard therapy for virus-induced wheezing in young children generally includes a stepwise addition of medications, typically commencing with a bronchodilator. If lower respiratory tract symptoms become increasingly severe or respiratory distress develops, oral corticosteroids are often added. Recent clinical trials in the management of these wheezing episodes also have included the use of high-dose inhaled corticosteroids (both prophylactically and/or as an acute intervention) and leukotriene receptor antagonists.

THE ROLE OF ORAL CORTICOSTEROIDS IN ACUTE EXACERBATIONS OF ASTHMA IN YOUNG CHILDREN

Numerous studies have been undertaken to assess the role of corticosteroid therapy in acute episodes of asthma in children and adults.[110] Meta-analyses of these studies support the early use of systemic corticosteroids in acute exacerbations based upon a reduction in the admission rate for asthma and prevention of relapse in the outpatient treatment of exacerbations.[111,112] As a reflection of such information, the most recent National Heart, Lung, and Blood Institute (NHLBI) Guidelines for the Diagnosis and Management of Asthma recommend the addition of corticosteroids for asthma exacerbations unresponsive to bronchodilators; in contrast to previous versions of these guidelines, doubling the dose of inhaled corticosteroids to prevent further progression of the airway obstruction is not recommended.[113]

Unfortunately, the applicability of these recommendations to young children and infants whose acute wheezing episode is primarily related to viral respiratory tract infections has not been as thoroughly examined. Moreover, in studies that have been conducted in this age group, the results are conflicting.[114–118] Limitations of these studies include inclusion of multiple

wheezing phenotypes,[116,118] relatively small sample sizes, poor adherence to study medication and protocol in the outpatient studies,[115,118] and episodes of relatively mild severity in both outpatient and inpatient studies.[115,118] A recent randomized, double-blind, placebo-controlled trial compared a 5-day course of oral prednisolone (10 mg once a day for children 10–24 months of age and 20 mg once a day for older children for a total of 5 days) with placebo in over 650 children between the ages of 10 months and 60 months. The primary outcome, the duration of hospitalization, was no different between the treatment groups.[116] An accompanying editorial for this published study challenged the clinical research community to conduct additional prospective trials to clearly establish the efficacy of oral corticosteroid treatment of these 'asthma-like' episodes in preschool children.[119]

To address these concerns further, the Childhood Asthma Research and Education (CARE) network investigated whether oral corticosteroids reduced symptom scores during acute lower respiratory tract illnesses (LRTIs) in preschool children with recurrent wheeze. The investigators performed post hoc and replication analyses in two outpatient cohorts of children[120,121] aged 1 to 5 years with episodic wheezing that had participated in previous CARE-conducted studies.[122] Comparisons were made of symptom scores during LRTIs that were or were not treated with oral corticosteroids, adjusting for differences in disease and episode severity. The primary outcome was the area under the curve of total symptom scores among the more severe episodes. In both of the two cohorts studied independently, oral corticosteroid treatment did not reduce symptom severity during acute LRTIs. Moreover, subgroups of children who might have been more likely to experience benefit, such as those with asthma risk factors (positive modified asthma predictive index,[123] personal eczema and/or family history of asthma), did not appear to have a greater benefit than those without such characteristics. The investigators emphasized, however, that these results were hypothesis generating and needed to be confirmed in randomized prospective studies.[124] Taken together, however, these studies indicate that acute asthma-like episodes of airway obstruction in preschool children appear to respond less well to oral corticosteroid administration than do similar episodes in older children and adults.

THE ROLE OF INHALED CORTICOSTEROIDS IN THE PREVENTION AND TREATMENT OF ACUTE WHEEZING EXACERBATIONS

The CARE network conducted a 3-year prospective trial in preschool children, all of whom had a modified positive asthma predictive index.[125] The overall goal of the study was to determine if early recognition and treatment of children who were at increased risk of developing childhood asthma could prevent the disease process from expressing itself and, further, if it could reduce losses of lung function that have been described during the first six years of life in children who develop persistent wheezing by age 3 years.[126] Children, 2 to 4 years of age, were randomized to receive either fluticasone propionate 88 μg twice daily or matching placebo using a valved spacer with mask. Treatment was for 2 years followed by a 1-year observation period off all study medication. The primary outcome measure was episode-free days. During the active treatment phase, children receiving inhaled corticosteroid (ICS) had a significantly increased number of episode-free days. In addition, they had significant reductions in oral corticosteroid-requiring exacerbations (37% reduction) and less use of a prespecified step-up plan. Pulmonary function was also significantly better at the end of the treatment period in those children who had received ICS for the previous two years. Unfortunately, about three months into the observation period, there was no longer any significant difference in any of these outcome measures and at the end of the observation period (1 year later), pulmonary function was also no different between the two groups.[127] These data indicate that continuous therapy with ICS in preschool children at high risk of developing asthma reduces lower respiratory tract exacerbations that are most frequently caused by respiratory pathogens in this age group.

Many preschool children wheeze only with respiratory tract pathogens and are asymptomatic between these episodes. Therefore, a 1-year randomized, double-blind comparison among intermittent treatment with high-dose ICS, a leukotriene receptor antagonist (montelukast) and scheduled albuterol (so-called 'standard of care') was conducted in preschool children with histories consistent with this type of respiratory pattern.[120] Therapy was initiated by the family, based on the participant achieving a symptom profile threshold that the child had exhibited in the past that would usually foreshadow the development of more significant lower airway involvement. After 1 year of treatment, the three groups did not differ in proportions of episode-free days (primary outcome), oral corticosteroid use, healthcare utilization, quality of life or linear growth. However, during respiratory tract illnesses, both ICS and montelukast therapy led to modest reductions in trouble breathing and interference with activity scores compared to those children only treated with albuterol. These differences were significant only in those children with a positive asthma predictive index prior to enrollment. In a post hoc analysis, similar findings were obtained when the cohort was stratified by oral corticosteroid use (0 vs ≥1 course) during the year preceding participation in the trial.

The observations that both the continuous[127] and intermittent[120] use of ICS had an effect on both the frequency and severity of exacerbations that were most likely related to a concomitant viral or bacterial respiratory tract illness provided the impetus for a third CARE network-initiated trial.[121] This trial studied 278 children between the ages of 12 and 53 months who all had positive modified asthma predictive indices, recurrent wheezing episodes with a low grade of interval impairment, and at least one exacerbation in the previous year. Children were randomly assigned to receive nebulized budesonide suspensions for 1 year as either an intermittent high-dose regimen (1.0 mg twice daily for 7 days starting at the onset of predefined respiratory tract illness symptoms) or a daily low-dose regimen (0.5 mg nightly) with corresponding placebos in both treatment arms. The two regimens were similar with respect to exacerbation frequency (primary outcome) and other measures of asthma severity including the time to first exacerbation. The mean exposure to budesonide was 104 mg less with the intermittent regimen.

Although the results of this trial indicate that, in preschool children with this type of pre-asthma phenotype, intermittent therapy versus continuous therapy would be a therapeutic consideration, the lack of a placebo group in this study does not permit more exact interpretations of these findings. Inclusion of a placebo group was not permitted by the various human subjects committees of the clinical centers participating in this

trial. This was due to the intensity of the symptom severity pattern present in the children prior to enrollment in the trial.

ROLE OF LEUKOTRIENES MODIFIERS IN VIRAL-INDUCED WHEEZING

The cysteinyl leukotrienes have been identified as important mediators in the complex pathophysiology of asthma.[128] Leukotrienes are detectable in the blood, urine, nasal secretions, sputum and bronchoalveolar lavage fluid of patients with chronic asthma. In addition, leukotrienes are released during acute asthma episodes. As a result of the potential for these mediators to influence airway tone, inflammatory cascades and mucus secretion, antagonists for their receptors have been developed and extensively studied. The cysteinyl leukotriene receptor antagonist, montelukast, has been the most frequently studied in both preschool and school-aged children.[120,129–136]

In one of the initial clinical trials designed to primarily evaluate safety, patients aged 2 to 5 years were treated for over 12 weeks with montelukast administered as a 4-mg chewable tablet.[129] Efficacy outcomes were also evaluated secondarily. Compared with placebo, montelukast produced significant improvements in multiple parameters of asthma control including: daytime asthma symptoms (cough, wheeze, trouble breathing and activity limitation); overnight asthma symptoms (cough); the percentage of days with asthma symptoms; the percentage of days without asthma; the need for beta-agonist or oral corticosteroids; physician global evaluations; and peripheral blood eosinophils. The clinical benefit of montelukast was evident within 1 day of starting therapy. Improvements in asthma control were consistent across age, sex, race and study center, and whether or not patients had a positive in vitro allergen-specific IgE test.

Robertson et al evaluated the intermittent use of montelukast in 2- to 14-year-old children with histories of intermittent asthma.[136] The family was instructed to begin a 7-day treatment with montelukast (age-appropriate dose) at the onset of asthma symptoms or the first sign of an upper respiratory tract illness that had previously been associated with the subsequent development of lower airway asthma symptoms. Compared to placebo, montelukast treatment resulted in a modest reduction in acute healthcare resource utilization, symptoms, time off from school and parental time off work in children with intermittent asthma.

Bisgaard et al evaluated the efficacy of 1-year daily treatment with montelukast in children with intermittent asthma in reducing exacerbations.[134] The primary efficacy endpoint was the number of asthma exacerbation episodes defined as any three consecutive days with daytime symptoms (average score of four daily daytime symptom questions of at least 1.0 on each day) and at least two treatments of beta-agonist per day, or rescue use of oral/inhaled corticosteroids during 1 or more days, or a hospitalization because of asthma. Over 12 months of therapy, montelukast significantly reduced the rate of asthma exacerbations by 31.9% compared with placebo. The average rate of exacerbation episodes per patient was 1.60 episodes per year on montelukast compared with 2.34 episodes on placebo. Montelukast also delayed the median time to first exacerbation by approximately 2 months and the rate of inhaled corticosteroid courses compared with placebo. Unfortunately, treatment did not reduce the necessity for oral corticosteroid administration. One of the remarkable aspects of this trial was the marked seasonal variation in exacerbation rates, with the summer months having less frequent exacerbations and no observed treatment effects. These data are an excellent documentation of the 'honeymoon' period from asthma symptoms that many clinicians observe in their patients during the summer months, most likely related to reduced numbers of respiratory tract illnesses.

Because infections with RSV in early life have been associated with an increased risk of developing recurrent wheezing and later asthma, two studies have evaluated the effects of montelukast treatment on the development of subsequent reactive airway disease symptoms. In the first 'pilot study',[133] children without a diagnosis of asthma (3–36 months old), hospitalized with acute RSV bronchiolitis, were randomized into a double-blind, parallel comparison of 5 mg montelukast or placebo given for 28 days starting within 7 days of the onset of symptoms. Infants on montelukast were free of any symptoms on 22% of the days and nights compared with 4% of the days and nights in infants on placebo. Daytime cough was significantly reduced, as were exacerbations in those children on active treatment. In contrast, in a follow-up study in children 3 to 24 months of age conducted over a period of 24 weeks, montelukast treatment did not alleviate post RSV-induced respiratory tract symptoms.[135]

In school-aged children, montelukast has been shown to be less effective compared to inhaled corticosteroid treatment in reducing the need for oral corticosteroid use and time to treatment failure over a 1-year time period.[131] Both of these outcomes could be considered surrogates for respiratory pathogen-induced asthma exacerbations or worsening of overall asthma control.

ANTI-INFECTION THERAPY

Therapy for infection-induced asthma could potentially include one or more of the following approaches: avoidance, non-medicinal interventions, vaccination, antimicrobial drug therapy and/or immunotherapy (monoclonal antibodies directed against the relevant pathogens). The ubiquitous nature of respiratory pathogens in the environment and the social nature of interactions in childhood (daycare, school, older siblings, etc.) make avoidance strategies unfeasible. Indeed, on average, children experience 2 to 8 or more 'colds' per year during their preschool years.

The cure for the common cold remains elusive; as such, a number of non-medicinal interventions have been tried. Vitamin C has long been touted for common cold treatment; however, a meta-analysis of common cold treatment studies found no significant effects on either prevention or treatment.[137] A Cochrane review of clinical studies found evidence that zinc lozenges reduce common cold duration but have significant side-effects including bad taste and nausea.[138] Large-scale trials of Echinacea have provided no evidence of efficacy.[139,140] There is evidence that warm drinks, as recommended for generations, can provide symptomatic relief from malaise and nasal symptoms without troublesome side-effects.[141] These approaches obviously are aimed at symptom reduction of the common cold but their effects on asthma control or exacerbations have not been directly evaluated.

Given the close relationship between viral infections and wheezing illnesses in children, it would be attractive to apply antiviral strategies to the prevention and treatment of asthma,

and both RV and RSV are obvious targets. Attempts at developing an RSV vaccine have so far been unsuccessful; however, recent data have provided renewed encouragement.[142,143] Unfortunately, vaccination to prevent RV infection is even more challenging due to the large number of serotypes. As an alternative, several types of antiviral agents are in development, and several compounds with activity against RV have been tested in clinical trials.

Improved knowledge of RV molecular virology has led to several attempts to develop antiviral agents. Interferon-α has antiviral effects in vitro and shortens the duration and severity of colds, but topical application led to nasal irritation and bleeding.[144–146] Anti-ICAM-1 and soluble ICAM-1 were developed to prevent binding of major group viruses to their receptor.[147–149] Capsid binding agents that bind to the VP1 pocket and inhibit viral binding and/or uncoating[150–152] have shown modest antiviral effects and efficacy in clinical trials.[153,154] An inhibitor to the 3C protease (rupintrivir) also showed broad anti-HRV activity in vitro and efficacy in clinical trials.[155] Unfortunately, these antiviral approaches have not so far led to development of a clinically useful medication. The molecules tested to date have been limited by combinations of modest efficacy, side-effects and/or drug interactions.[156]

Another new approach has been to boost antiviral defenses in the lung with inhaled IFN-β. In a randomized study, subjects with persistent asthma and a history of exacerbations with colds were treated with either nebulized IFN-β or placebo within 24 hours of the onset of cold symptoms.[157] In the intent-to-treat population, there were no significant effects on the asthma symptoms scores (which was the primary outcome) but IFN-β treatment improved recovery of peak expiratory flow. Notably, IFN-β was well tolerated and also induced expression of innate antiviral effectors in the blood and sputum. In a subgroup analysis of study subjects with more severe asthma (British Thoracic Society Step 4 and 5), colds were associated with increased symptoms in the placebo group but not in IFN-β-treated subjects. These exciting new findings, if confirmed, suggest that inhaled IFN-β used at the first sign of a cold could be a useful adjunct to standard therapy in patients with more severe asthma.

Two recent trials evaluating the efficacy of monoclonal antibody therapy directed specifically against RSV and the allergic antibody, IgE, have yielded interesting results. The first trial studied the anti-RSV monoclonal antibody, palivizumab, in a double-blind, placebo-controlled trial: 429 otherwise healthy preterm (33–35 weeks' gestational age) infants were randomly assigned to receive either monthly palivizumab injections or placebo during the RSV season. The prespecified primary outcome was the total number of parent-reported wheezing days in the first year of life. Nasopharyngeal swabs were taken during respiratory episodes for viral analysis. Palivizumab treatment resulted in a relative reduction of 61% in the total number of wheezing days during the first year of life (1.8% vs 4.5% in the placebo group). During this time, the proportion of infants with recurrent wheeze was 10 percentage points lower in patients treated with palivizumab (11% vs 21%). As discussed above, the data generated thus far cannot ascertain what effect such treatment may have on the subsequent development of asthma in later childhood.

The second trial evaluated the anti-IgE monoclonal antibody, omalizumab, which specifically targets the Fc portion of IgE to prevent binding to the surface of cells and is therefore a narrowly focussed intervention for type I hypersensitivity. In a placebo-controlled trial of guidelines-based asthma treatment compared to omalizumab added to standard therapy, omalizumab prevented the seasonal increases in exacerbations during the fall and spring, which are peak times for viral exacerbations (Figure 31-1).[158] Analysis of viruses in nasal secretions during a subset of exacerbations confirmed that the treatment group had fewer viral and nonviral exacerbations. This study provides direct evidence that IgE-mediated inflammation contributes to the risk of virus-induced exacerbations of asthma. These observations indicate that interactions between allergic sensitization (antigen-specific IgE antibody formation) and viral respiratory illnesses play an important role in asthma control. Finally, it will be of interest to determine whether other drugs targeting specific type-2 cytokines (e.g. mepolizumab and IL-5)[159] can also reduce the risk of virus-induced exacerbations.

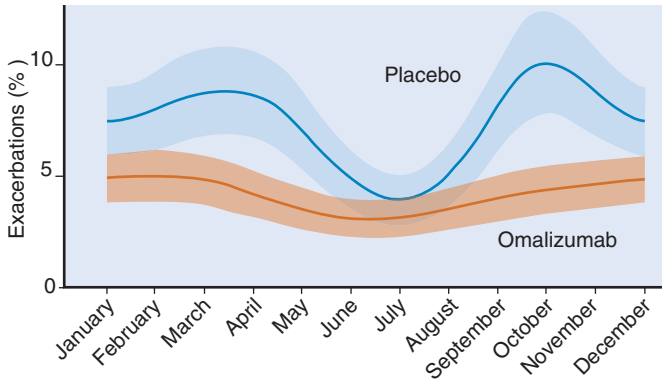

Figure 31-1 The figure shows the seasonality of asthma exacerbations in children and demonstrates that blocking IgE responses with omalizumab blunts the seasonal rise in virus-induced exacerbations. *(With permission from Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. N Engl J Med 2011;364(11):1005–15.)*

Use of Antibiotics in Asthma

Asthma guidelines both in the USA (http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/full-report.htm) and internationally (http://www.ginasthma.org) have not recommended the use of antibiotics to treat asthma exacerbations because the majority of the exacerbations have been considered to be triggered by viral respiratory tract infections. Nonetheless, oral antibiotics are frequently prescribed for wheezing illnesses in preschool children (650 antibiotic prescriptions/1,000 wheezing children).[160] Furthermore, recent data indicate that 28% of preschool children who make a physician visit for wheezing receive a prescription for an antibiotic within 2 days of the visit, and 77% receive a prescription for an antibiotic within 7 days. These prescriptions are dominated by azithromycin, the use of which increased 15-fold between 1995 and 2001.[160]

As noted previously, bacteria (either alone or in combination with viral pathogens) have now been demonstrated to potentially play a role in acute wheezing episodes and increases in asthma symptoms in children.[27,84] These observations might be an explanation as to why antibiotic administration has been observed to provide some clinical benefit by practitioners. Recent findings indicate that certain antimicrobials may have

not only antibacterial properties but antiviral and/or antiinflammatory properties as well.

As a class, macrolides have been demonstrated to provide clinical benefit in airway diseases such as cystic fibrosis[161] and diffuse panbronchiolitis,[162] possibly through mechanisms unrelated to antimicrobial activity. Viral infections, particularly those caused by RV, are associated with neutrophilic inflammation and increased IL-8 expression.[163] Neutrophils are the predominant inflammatory cell at the onset of most infections,[164] including those with RV,[163,165] and although many chemoattractants participate in summoning neutrophils to the site of infection, IL-8 seems to play a central role.[166] Neutrophils are relatively insensitive to the therapeutic effects of corticosteroids[167] but, interestingly, azithromycin has been demonstrated to attenuate immunoinflammatory responses and may reduce the ensuing destructive neutrophilic inflammation. In addition, recent data demonstrated that azithromycin reduces RV replication and increases interferon gene expression in human bronchial epithelial cells.[168] These effects may have substantial clinical relevance, as recent studies have demonstrated that primary bronchial epithelial cells from asthmatics have deficient ex vivo induction of IFN-β and IFN-λ after infection with RV,[81] and the levels of IFN-λ were inversely related to severity of RV-induced asthma exacerbations in terms of decline in FEV_1 and viral load. These findings are especially important because, in children, viral infections have been shown by many investigators to be a major etiologic agent in episodes of clinically significant lower respiratory tract symptoms.[3,92,169]

In contrast to in vitro observations indicating a potential useful role of these agents in treating infection-induced loss of asthma control or exacerbations, their efficacy in humans has not been consistently shown. Black et al were one of the first groups to demonstrate a potential beneficial effect. They studied the effect of roxithromycin in subjects with asthma and immunoglobulin G (IgG) or IgA antibodies to *Chlamydophila pneumoniae*. Subjects were randomized to 6 weeks of treatment with roxithromycin or placebo. This intervention led to improvements in asthma control but the benefit was not sustained.[170] Kraft and colleagues performed an additional study using a different antimicrobial. They found that treatment with clarithromycin for 8 weeks was beneficial in improving lung function, but only in those patients with positive PCR findings for *Mycoplasma pneumoniae* or *C. pneumoniae*.[171] These initial intriguing results were later expanded upon by the Asthma Clinical Research Network who treated asthma patients that were not adequately controlled on inhaled corticosteroid monotherapy with clarithromycin or placebo for 16 weeks. They found that this treatment intervention did not further improve asthma control. Although there was an improvement in airway hyperresponsiveness with clarithromycin, this benefit was not accompanied by improvements in other secondary outcomes.[172] One additional study suggested that some benefit might be possible following intervention with this antimicrobial class. Johnston et al administered the ketolide telithromycin (a semisynthetic derivative of erythromycin) for 10 days to adults with asthma seen within the first 24 hours of acute asthma episodes. This intervention resulted in significant improvements in symptom scores and lung function over the next 7 days relative to placebo.[173] However, there was no relationship between bacteriologic status and the response to telithromycin treatment, suggesting a mechanism of action unrelated to the antimicrobial properties of telithromycin.

Conclusions

Infections play a critical role in the inception and exacerbation of asthma. Viral infections are the most common cause of wheezing in infants and children. Interactions between underlying allergy and virus infections lead to the greatest risk of asthma inception and exacerbation. New data indicate that the airway microbiome may play a critical role in modulating the response to respiratory viral infections, and virus-induced alterations in airway microbial populations likely also contribute to illness severity. Treatment of virus-induced wheezing and asthma exacerbations remains challenging and novel therapies and approaches to the prevention of asthma and asthma exacerbations are needed.

The complete reference list can be found on the companion Expert Consult website at http://www.expertconsult.inkling.com.

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