Viral infections and airway hyperresponsiveness (AHR) in atopic asthmatic individuals are independently associated with complex sequences of immunologic events. When they co-occur, viral infections and atopic asthma can dramatically influence the progression and severity of one another, often in unpredictable ways. Three overlapping classes of interaction are currently the focus of intensive research:

1. The effect of viral infections on AHR in asthmatic individuals
2. The potential for infection by certain viruses to protect against the development of asthma and allergies
3. The potential for other, mainly respiratory, viruses to trigger or even induce the development of asthma

In patients with existing asthma, respiratory infections often precipitate acute episodes of wheezing and airway obstruction.1,2 There have been investigations on the extent to which viruses are responsible for asthma exacerbations and the impact of asthma on the course of viral infections.

An intriguing hypothesis, supported by some epidemiologic studies (but not others), is that exposure to certain pathogens during early childhood may steer the development of the immune system away from a pattern of responses that mediate allergic reactions such as asthma.3 Recent evidence for and against this “hygiene hypothesis” is described.

Conversely, some viruses have been implicated as precipitating—not protecting against—the development of AHR. In most children, virus-induced wheezing is self-limiting and has long-term consequences, but in others, virus-induced wheezing is associated with asthma development and allergic sensitization.4 Respiratory syncytial virus (RSV) is a prime suspect in this regard. It remains controversial whether viral infection in infancy induces atopic asthma or merely triggers asthma development in children with a genetic predisposition to atopy.

Describing, interpreting, and managing the interactions between viruses and asthma or other allergic diseases require an understanding of underlying immunologic processes; this understanding remains only partially complete. The implications for treatment of current knowledge about these processes and interactions are discussed.

**ROLE OF VIRAL INFECTIONS IN ASTHMA EXACERBATIONS**

**INCIDENCE**

The capacity of viral infections to trigger exacerbations in patients with asthma is well established. Most lower respiratory tract illnesses accompanied by wheezing in the first years of life are caused by viruses,5 and viral infection coincides with 80 to 85% of exacerbations in asthmatic individuals 9 to 11 years of age.6 Predictably, respiratory viruses are the main culprits. In a study in which PCR was used to detect viruses in nasal aspirates from children 3 months to 14 years of age who were hospitalized for severe asthma attacks, rhinovirus was found in 46.9% and RSV in 21.2% of cases.7 Among adult asthmatic individuals, viral upper respiratory infections are associated with half of all asthma episodes.8

**ROLE OF INFLAMMATION**

Although patients with atopic asthma appear to be no more likely to contract colds than are healthy people, in response to rhinoviral infection they experience more frequent, more severe, and prolonged lower respiratory tract involvement.9 This relationship is somewhat surprising, given that rhinovirus has traditionally been considered a pathogen of the upper airways.10 In fact, in both asthmatic and healthy subjects, during active rhinoviral infection there is an increase in the numbers of lymphocytes and eosinophils in bronchial mucosa.11 This sets the stage in asthmatic subjects for inflammation to progress from the upper respiratory tract to the lower airways, leading to symptom exacerbation.

The greater impact of respiratory viral infections in atopic individuals appears to be due to dysregulation of the immune system.6 In response to infection, type 1 T-helper (Th1) cells predominantly produce cytokines associated with cell-mediated immunity, including interleukin-12 (IL-12) and interferon-γ (IFN-γ). On the other hand, type 2 T-helper (Th2) cells synthesize cytokines associated with humoral immunity, including IL-4, IL-5, IL-10, and IL-13, which are implicated in the promotion of allergic inflammation. Individuals with asthma and allergic diseases are disposed toward a Th2-type response. Individuals
who develop strong Th2 responses may not be able to clear viruses efficiently, leading to persistent infection and thus exacerbation of the inflammation associated with asthma. Among people with asthma or allergic rhinitis, those who produce higher levels of IFN-γ and lower levels of IL-5 tend to have fewer symptoms during the peak of a cold and a shorter duration of illness than individuals who show a more extreme Th2-type response. In addition, rhinoviral infection in subjects who have asthma or allergic rhinitis leads to neutrophilia in blood and nasal secretions and increased levels of granulocyte colony-stimulating factor and IL-8, suggesting that these proinflammatory cytokines also contribute to rhinovirus-induced inflammation in atopic individuals (Figure 41-1).

During virus-induced asthma exacerbations in children, nasal secretions show increased levels of the toxic eosinophil granule product major basic protein, as well as the chemokines regulated upon activation, normal T cell–expressed and secreted (RANTES), and macrophage inflammatory protein-1α. These and other eosinophil chemoattractants have been shown to promote AHR in mice. Activation of eosinophils by RSV has been seen in vitro, leading to elevated superoxide production and increased leukotriene C4 release.

The pathways by which respiratory viruses can lead to inappropriate immune responses in atopic individuals are becoming better understood. For example, rhinovirus infection of respiratory epithelial cells induces elevated expression of intercellular adhesion molecule-1 (ICAM-1), a cell surface glycoprotein that binds to ligands on eosinophils and CD4+ and CD8+ T cells and that may play a central role in the infiltration of these inflammatory cells into the lower airways of asthmatic individuals.

Wheezing in asthmatic individuals may also be exacerbated by direct binding of rhinovirus to the ICAM-1 receptor, which induces enhanced expression and activation of G protein in the airway smooth muscle. A recent study has demonstrated that even UV-irradiated rhinovirus, which is unable to replicate within cells, is still able to bind to ICAM-1 and thereby elicit airway smooth muscle hyperresponsiveness.

**OTHER MECHANISMS FOR VIRAL-INDUCED ASTHMA EXACERBATIONS**

Other noninflammatory mechanisms might also contribute to the wheezing associated with viral respiratory tract infection. In rodents, RSV infection of respiratory epithelium leads to decreased production of nitric oxide, a bronchodilator agonist of the nonadrenergic, noncholinergic inhibitory system, resulting in AHR. The generality of this result across respiratory viruses and its applicability to humans are complicated by the finding that exhaled nitric oxide levels in humans with asthma increase following rhinoviral infection, possibly limiting asthma exacerbations.

Enhanced stimulation of sensory C-fibers during infection may provoke release of substance P and neurokinin-A, which are both agonists of the nonadrenergic, noncholinergic activating system, inducing a brainstem reflex leading to bronchoconstriction. Neuropeptides released by sensory C-fibers can cause increased leukotriene synthesis, release of mast cell mediators, and increased mucous secretion. However, the role of sensory C-fibers in virus-associated asthma exacerbations in humans remains unclear.

Following viral infection, an inflammatory immune response and AHR linger in atopic individuals. In a guinea pig model of AHR, RSV infection causes hyperresponsiveness that lasts for at least 5 weeks, and viral antigen remains detectable during this period. In allergic human patients, nasal eosinophil influx following common cold infection is prolonged in comparison with nonallergic patients. Eosinophilia is also prolonged in asthmatic individuals in comparison with nonasthmatic individuals, as is enhancement of airway narrowing in response to methacholine, a bronchoconstrictor stimulus.

Viruses may persist in the airways of asthmatic individuals even after clinical resolution of symptoms. In a comparison of 50 asthmatic but currently asymptomatic children with 20 healthy control children, nasopharyngeal swabs revealed the presence of rhinovirus RNA and coronavirus RNA in 32.4% and 2.7% of asthmatic children, respectively, but in none of the control children. Adenovirus DNA was found in 78.4% of asthmatic children but in only 1 (5%) of the 20 control children.

Viral persistence in patients with asthma may have important consequences for the treatment of acute asthma episodes. In a study of 34 asthmatic children who responded poorly to standard corticosteroid and bronchodilator therapy, 31 (94%) tested positive for adenovirus. A possible mechanism underlying this observation is suggested by the finding that in the guinea pig, latent adenoviral infection causes the eosinophilic component of allergen-induced lung inflammation to become steroid resistant.

Taken together, these results highlight the value of protecting against respiratory viral infections in atopic individuals. For example, asthma management may benefit from wider application of influenza vaccination; a recent study showed that, after adjustment for asthma severity, the incidence of asthma exacerbations among patients 1 to 6 years of age was reduced by up to 41% following influenza vaccination in comparison with before vaccination. Furthermore, in a 1-year study of 57 asthmatic individuals, exacerbation of asthma symptoms by colds was positively correlated with levels of sulfur dioxide and nitrogen oxide, providing another reason to adhere to asthma guidelines that recommend reducing exposure to air pollutants.

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**FIGURE 41-1** Immune response to viral infection in patients with allergic rhinitis or asthma. GM-CSF = granulocyte–macrophage colony-stimulating factor; IFN-γ = interferon-γ; IL = interleukin.
CAN VIRAL INFECTIONS PROTECT AGAINST THE DEVELOPMENT OF ASTHMA?

Hygiene Hypothesis
Early allergic sensitization is linked to delayed maturation of normal immune responses. Although, as seen above, certain viruses provoke asthma exacerbations, early exposure of the immune system to other viruses and bacteria has been suggested to prevent the development of atopy. However, Strachan's hygiene hypothesis, which originally proposed that early childhood infections might prevent allergic disease later in life, has received mixed support in the case of asthma.

Results Suggesting a Role for Viral Infection in Protecting Against the Development of Asthma
In a study of Italian air force cadets, subjects with no antibodies against the foodborne or orofecal pathogens Toxoplasma gondii, Helicobacter pylori, and hepatitis A virus were 2.7 times as likely to be highly atopic as were subjects with antibodies to two or three of these microbes. However, this study showed no relationship between risk of atopy and exposure to six other pathogens, including measles, that are transmitted by other routes. Indeed, a cross-sectional study in Finland that included more than half a million subjects showed a positive, not negative, correlation between natural measles infection and atopy; subjects who had previously had measles were 1.67 times as likely to have asthma as were those who had not.

The recently published results of a longitudinal birth cohort study of 1,314 German children suggest that repeated viral (but not bacterial, fungal, or gastrointestinal) infections in early childhood, other than lower respiratory tract infections (LRTIs), may reduce the risk of developing asthma by the age of 7 years. Recurrent runny nose in the first year of life and herpes-type viral infections were associated with half the risk of being diagnosed with asthma, current wheeze, or bronchial hyperresponsiveness at age 7 years. These results support the hypothesis that repeated viral infections other than LRTIs early in life may stimulate the immature immune system to adopt the Th1 phenotype.

These findings imply that vaccinating against common childhood diseases may have unintended negative consequences for asthma incidence. For example, in a survey of 1,265 children born in New Zealand in 1977, the 23 who received no immunizations against diphtheria, pertussis, tetanus, or polio had no recorded asthma or medical consultation for allergic illness by 10 years of age. In contrast, of the remaining immunized children, 23% experienced asthma attacks and 30% saw a doctor because of other allergic illnesses. Clearly, however, it would be premature to discontinue such immunization programs on the basis of the equivocal data gathered thus far.

Timing of Exposure May Be Crucial
It is noteworthy that the same pathogen might exert opposite effects on AHR, depending on the timing of exposure and atopic status of the exposed individual. An example is posed by endotoxin, a cell wall component of gram-negative bacteria. In children, endotoxin exposure is inversely related to the risk for atopic asthma, hay fever, allergic sensitization, and atopic wheeze. Production by leukocytes of the cytokines tumor necrosis factor-α (TNF-α), IFN-γ, IL-10, and IL-12 is inversely related to the endotoxin level in children's bedding, indicating that during childhood, immune responses to natural allergens are decreased by exposure to microbial products. However, in older patients with existing asthma, endotoxin promotes release of cytokines that lead to inflammation, including IL-1, TNF-α, and IL-8. In asthmatic individuals, therefore, airborne endotoxin increases AHR, increases susceptibility to rhinoviral infection, and can cause chronic bronchitis, emphysema, and irreversible airway obstruction.

CAN VIRAL INFECTIONS INDUCE ASTHMA?

Potential Causative Viruses
Far from exerting a protective effect against the development of AHR, certain viruses may be intimately involved in precipitating atopic asthma. Parainfluenza viruses, coronavirus, adenovirus, influenza virus, and enteroviruses have all been suggested not only to trigger exacerbations but also to contribute to the development of allergic asthma. A link may also exist for Epstein–Barr virus as antibody titers are higher in atopic individuals than in nonatopic controls.

This potential link is strongest, however, for RSV, which infects 70% of children during their first year and essentially 100% of children by 3 years of age (Figure 41-2). Of those infected, 20 to 30% will develop bronchiolitis, a disease of the lower respiratory tract. In tissue biopsy specimens from children with RSV bronchiolitis, mucous membranes are inflamed, and cellular debris and fibrin plug bronchioles, causing atelectasis and hyperinflation. Premature infants are more likely to be infected with RSV than infants born at term because they have incomplete passage of maternal IgG in utero. They also have more severe RSV infection because of their small airways, which are more readily obstructed by edema and necrotic debris.

Severe bronchiolitis is accompanied by wheezing and prolonged airway obstruction and is strongly correlated with the development of childhood asthma and AHR, which may persist for many years. Children hospitalized during infancy for RSV bronchiolitis are nearly 13 times as likely to have asthma at 7 years of age as are children who were not. The sequelae of RSV bronchiolitis over a 2- to 13-year follow-up period were investigated in a review of controlled studies between 1978 and 2000. In all nine qualifying studies, postbronchiolitis subjects had a significantly higher incidence of bronchial obstructive symptoms, diminished lung function, or increased bronchial reactivity to exercise or histamine challenge than did control subjects. The link is strongest for bronchiolitis cases severe enough to require hospitalization and remains after correction for family history of asthma and/or atopy.
MECHANISM OF ACTION: PREDISPOSITION AND/OR SKEWING TO A Th2 RESPONSE?

The inflammatory response in bronchiolitis includes high numbers of submucosal lymphocytes and epithelial eosinophils in the lower airways. Levels of soluble IL-2 receptor (sCD25) remain elevated for as long as 150 days after bronchiolitis, although they are not as high as during the acute stage. This indicates a persistent inflammatory process after bronchiolitis, contrasting with the rapid decline in sCD25 levels after acute measles or dengue fever. Patients who have suffered from RSV bronchiolitis during infancy show higher numbers of RSV-specific IL-4–producing cells 7.5 years later than do patients who experienced only mild RSV infection. This suggests either that RSV bronchiolitis causes proliferation of RSV-specific Th2 memory cells or that the symptoms of RSV infection are simply more severe in individuals predisposed to a Th2 response.

Strong evidence exists of a link between abnormal cellular immunity and wheezing following bronchiolitis. Five months after acute bronchiolitis, infants show high counts of CD4⁺, CD25⁺, and CD23⁺ cells, suggesting activation of cellular immunity. Among those infants who wheeze the most, production of IL-4 from peripheral blood lymphocytes in response to dust mite antigen is elevated 5 months later in comparison with those who wheeze less. There is also a positive correlation between the number of days of wheezing and blood eosinophil count (Figure 41-3). Predisposition toward a greater Th2 response in infants who suffer severe wheezing due to bronchiolitis is supported by the finding that during bronchiolitis their lymphocytes produce less INF-γ and more IL-4 upon stimulation with IL-2. Furthermore, there is a significant inverse correlation between IFN-γ production during bronchiolitis and pulmonary function at 4.9 months, as well as a significant positive correlation between pulmonary function at 4.9 months and a diagnosis of asthma 2 years later. Similarly, among infants with RSV bronchiolitis, those who have higher serum eosinophil cationic protein levels during the initial infection are at increased risk for developing persistent wheezing, detected at 5-year follow-up. Infants with serum eosinophil cationic protein levels of at least 8 μg/L are almost 10 times as likely to develop persistent wheezing as are infants with levels lower than 8 μg/L.

Although clinical studies have not yet shown whether lower IFN-γ production is present before bronchiolitis or is induced by bronchiolitis, epidemiologic studies suggest a genetic predisposition for asthma following viral infection. In the German birth cohort study discussed above, the number of LRTIs with wheezing in the first 3 years of life was positively associated with a diagnosis of asthma and current wheeze and bronchial hyperreactivity at age 7 years. The results of the same study, however, suggest that children predisposed to asthma might simply be more likely to develop symptoms of the lower respiratory tract. The
frequency of repeated LRTIs in this cohort was higher in children with a family history of atopy than in those with no atopic family member. Similar results were obtained by Angelakou and colleagues, who reported that a positive family history of atopy was associated with the development of severe wheezing.

**Viral Infections and Allergic Sensitization**

In a birth cohort stratified by the type of virus detected during respiratory tract infections before 3 years of age, children with RSV infection had an increased risk for wheezing at 6 years, but the risk diminished with age and was not significant by 13 years. The prevalence of allergic sensitization at any age did not differ between children with or without respiratory tract infections, suggesting that RSV infection did not lead to allergic sensitization but rather that RSV infection and atopy were independent risk factors for asthma development.

In the absence of large, prospective, controlled trials in which infants are experimentally infected with RSV to identify a causal connection with atopy, whether or not RSV infection induces allergic sensitization in humans remains unclear. Of seven epidemiologic studies of RSV bronchiolitis serious enough to require hospitalization, three showed an increased risk of sensitization, whereas four did not. The balance of evidence suggests that mild RSV infection either does not increase the risk of sensitization or does so only within the first year of life.

**RODENT MODELS OF VIRAL INFECTION AND AHR**

**ROLE FOR A COMBINATION OF VIRAL INFECTION AND ALLERGIC SENSITIZATION**

Because of the ethical difficulties inherent in manipulating the sequence of viral infection and allergic sensitization in human infants, much of our current understanding derives from animal models, in which infection, allergic sensitization, and components of the immune response can be perturbed. Recently, a mouse model for the exploration of the role of viral infection (particularly by RSV) in respiratory illness has been developed, in which the respiratory function of infected BALB/c mice is measured in a plethysmograph. These mice show heightened airway responsiveness to methacholine challenge. RSV or influenza A virus infection alone is insufficient to cause chronic AHR in mice. Sensitization to ovalbumin (OVA) without RSV infection leads to AHR that resolves shortly after discontinuation of OVA aerosol administration, but RSV infection during OVA aerosol treatment leads to AHR that lasts for more than 2 weeks following the infection. The combination of influenza A infection and OVA sensitization also increases AHR in mice.

In mice, inhalation of nebulized OVA 4 to 10 days after infection with either RSV or influenza A virus induced specific serum antibodies, and intradermal skin challenge with OVA on day 18 caused acute systemic illness and collapse. By contrast, in uninfected mice, inhalation of OVA did not induce production of specific serum antibodies, and skin challenge on day 18 elicited no response. This suggests that infection with respiratory viruses affects lung permeability and enhances allergy development.

The outcome of the interaction between viral exposure and allergic sensitization depends upon the timing of these events. In a mouse model of asthma, intranasal administration of OVA led to CD4+ T-cell tolerance to OVA. However, infection with influenza A virus 3 days before OVA administration disrupted the normal development of immunologic tolerance to the allergen, leading to the development of AHR and the production of IgE, IL-4, IL-5, IL-13, and IFN-γ upon subsequent OVA challenge. On the other hand, when OVA was administered 15 or 30 days after influenza A virus infection, subsequent OVA challenge caused a predominantly IFN-γ response, protecting against the development of AHR.

**ROLES OF CELLS AND CYTOKINES**

The mouse RSV model has clarified the relative roles of various immunologic components in the development of AHR following allergic sensitization and infection. For example, discrimination of the roles of different T cells in RSV-induced lung eosinophilia and AHR was facilitated by transplanting CD4 or CD8 T cells from mice that had been infected with RSV into naive mice that were subsequently sensitized to OVA. When the mice were challenged with methacholine, AHR developed in the naive mice that had received CD8 but not CD4 T-cell transplants.

The mouse model has been particularly useful for dissecting the effects of various cytokines and chemokines. In IL-10-deficient mice, AHR does not develop in response to inhaled methacholine following OVA sensitization and challenge, as it would in IL-10–competent mice. AHR does develop in IL-10–deficient mice, however, if they are infected with RSV following OVA sensitization but before OVA challenge. Epithelial cells produce more IL-11 following infection by RSV, parainfluenza virus, and rhinovirus.
Although the role of IL-11 in viral infection is not yet clear, administration of IL-11 in the lungs of mice leads to increased airway responsiveness to methacholine challenge.\(^4\)

In mice that show only mild disease in response to RSV infection, IL-12 titer quadruples.\(^50\) Treatment of RSV-infected mice with anti–IL-12 leads to increased AHR, mucus production, and eosinophilia. When mice with a deficiency in the Stat-4 intracellular signal transducer are infected with RSV, they show similarly severe disease. As IL-12 activation is Stat-4 dependent, these results indicate that IL-12 plays an important role in clearing RSV infection and protecting against inappropriate inflammatory responses.\(^50\)

Conversely, in this model there is an increase in IL-13 level as the AHR progresses, and treatment of mice with anti–IL-13 during RSV infection decreases allergen-induced AHR.\(^51,52\) Neutralization of IL-13 is followed by an increase in IL-12 production in the lungs. Stat-6–deficient mice show a decreased response, similar to that seen with anti–IL-13 treatment. In mice sensitized to cockroach allergen, production of IL-13 during a previous RSV infection exacerbates asthma-like symptoms produced by later exposure to cockroach allergen. These results imply that increased production of IL-13 could interfere with an effective antiviral response and lead to chronic RSV-induced AHR.\(^51\)

Experiments in rodents have highlighted the dominating influence of IL-5 on the eosinophilic component of inflammation following RSV infection and the subsequent development of AHR to methacholine challenge.\(^4\) RSV infection leads to airway eosinophilia and AHR in response to methacholine challenge in IL-4–deficient and IFN-γ-deficient mice but not in IL-5–deficient mice, indicating that IL-5, but not IFN-γ or IL-4, is necessary for infiltration of eosinophils into the lung and the development of AHR.\(^53\) The timing of these events, however, is critical; mice treated with anti–IL-5 during acute RSV infection but not during later sensitization to OVA show reduced AHR and lung eosinophilia in response to methacholine challenge.\(^54\) Administration of IL-5 to both IL-5–deficient and IL-4–deficient mice during RSV infection is sufficient to restore strong responses to allergen. IL-5 administration only during sensitization restores responses in IL-4–deficient mice but not in IL-5–deficient mice.\(^54\)

In the guinea pig, virus-induced AHR also depends on IL-5, but eosinophil influx does not.\(^3\) Cationic proteins released by eosinophils bind to presynaptic M2 muscarinic receptors on postganglionic parasympathetic airway nerves, blocking an inhibitory feedback mechanism and resulting in increased acetylcholine release and airway muscle tone and reactivity. This mechanism occurs in allergic sensitization and following acute viral infection. Parainfluenza virus neuraminidase can bind directly to M2 muscarinic receptors and may trigger the mechanism just described, even in the absence of eosinophils.\(^4\) Viral neuraminidase may deglycosylate the M2 receptor, decreasing its affinity for acetylcholine, whereas viruses and IFN-γ decrease M2 receptor gene expression.\(^55\)

In humans with asthma, eosinophil numbers in airway mucosa are often elevated even during asymptomatic periods. Experiments in mice show that although IL-5 and the chemokine eotaxin promote airway eosinophilia, they do not themselves cause eosinophil degranulation and AHR.\(^56\) Allergen challenge in the presence of eosinophilia results in degranulation and AHR. The mouse data suggest a pathway in asthmatic individuals whereby eosinophils that have infiltrated into airways in response to IL-5 and eotaxin can become activated by allergen provocation, leading to AHR.\(^56\)

**IMPLICATIONS FOR ASTHMA TREATMENT**

**Prevention**

The results summarized here demonstrate the importance of considering viral infection and its sequelae for the effective management of asthma and other allergic diseases. These results also suggest possible preventive and treatment strategies for AHR with viral involvement. The strategies fall into two categories: prevention of viral infections or use of antiviral agents to treat infections in their early stages and inhibiting proinflammatory immune responses to viral infection.

Because certain viruses are known to provoke AHR and may even induce or at least trigger the development of atopic asthma, avoiding infection by these pathogens holds out the promise of significantly reducing the medical burden of asthma. Both RSV and parainfluenza virus are spread by direct contact with infected secretions or contaminated objects, highlighting the importance of hand washing to decrease transmission.\(^34,57\) Adoption in hospitals of stringent hygiene protocols, including cohorting of patients, staff, or medical equipment by patient RSV status, has been shown to significantly reduce nosocomial RSV infection rates.\(^34\)

Unfortunately, there are few effective vaccines for the viruses chiefly implicated in asthma development and exacerbations. A notable exception is influenza; as noted above, asthmatic individuals immunized against influenza A virus experience significantly fewer exacerbations.\(^25\) Furthermore, a prospective, randomized, double-blind study involving over 2,000 patients revealed that influenza vaccination itself does not exacerbate asthma symptoms and is safe in both children and adults with asthma.\(^38\)

The apparently key role of RSV infection in the development of AHR argues strongly for effective vaccination against RSV. An intramuscular formalin-inactivated RSV vaccine was developed in the 1960s, but this did not protect against subsequent RSV infection. On the contrary, vaccinated infants had more severe disease in the next season,\(^34\) with even more lower respiratory tract involvement than in natural RSV bronchiolitis and evidence of pneumonia.\(^33\) Mice immunized with formalin-inactivated RSV vaccine showed increased Th2 cytokine production and AHR.\(^59\) Although it does not offer full protection against re-infection either, live RSV vaccine administered parenterally does not lead to enhanced illness in subsequent RSV infection.\(^33\) Mice immunized with live RSV, then sensitized with OVA, and later infected with RSV, showed no increase in airway response to methacholine challenge in comparison with control mice.\(^59\)
Prophylaxis of RSV with intravenous RSV immunoglobulin (RSV-IVIG) is an alternative strategy that may reduce the risk for developing reactive airway disease in childhood. In a small study of children with chronic lung disease who had received RSV-IVIG 5 to 9 years earlier, pulmonary function was significantly better than in matched controls, and there was less atopy and a lower frequency of asthma attacks in the treated group. This supports the hypothesis that RSV prophylaxis may have long-term benefit in reducing the risk of AHR.

Palivizumab, a neutralizing monoclonal antibody to RSV fusion protein, may be a better choice than RSV-IVIG. Palivizumab prophylaxis opposes the penetration of infectious particles into the lower respiratory tract epithelium, inhibiting up-regulation of the neurokinin-1 receptor gene and its associated inflammatory effects. In the rat, palivizumab is twice as effective as RSV-IVIG at preventing the proinflammatory effects of substance P released from sensory nerves. Prophylaxis with palivizumab prevents acute neurogenic inflammatory changes in the rat lower respiratory tract infected with RSV and protects against the development of long-term susceptibility to neurogenic-mediated inflammation after the infection. Although it may be too expensive for widespread use, palivizumab for the prevention of severe infections is potentially cost-effective in infants with chronic lung disease.

Therapy
A fundamental problem with using antiviral agents is that once infections are recognized, it is usually at a late stage in the illness, and many of these agents, such as neuraminidase, are only effective if used early in the course of illness. As prophylactic use of neuraminidase can prevent about 80% of influenza cases, it may be effective to extend this approach to high-risk individuals for protection against rhinoviruses, which present too many serotypes for vaccination to be practical. Antirhinoviral agents include soluble ICAM-1 and capsid-binding agents, and new compounds, such as inhibitors of rhinovirus 3C protease, are potential treatments.

An alternative strategy to reduce AHR due to viral infection is to target, during infection, specific signaling pathways, proinflammatory cytokines, and other mediators of inflammation. In mice treated with type 4 phosphodiesterase inhibitors during RSV infection, for example, AHR and eosinophil infiltration into the lung in response to methacholine challenge were reduced in comparison with RSV-infected control mice. Anti–TNF-α treatment might also reduce the severity of RSV bronchiolitis associated with either an eosinophilic response or with activated CD8+ T cells.

Antinflammatory therapy, already in widespread use, may be an effective treatment approach. Systemic glucocorticoids administered at the first sign of cold have been shown to reduce airway obstruction and risk of hospitalization for acute asthma exacerbations. In a study in which budesonide was administered to asthmatic subjects 2 weeks prior to experimental rhinovirus 16 infection, AHR was improved and eosinophil levels were lowered prior to infection in comparison with controls who did not receive budesonide. The improvement persisted after rhinovirus infection, even though budesonide did not significantly affect the accumulation of T cells seen after rhinovirus infection in both groups.

The utility of antiinflammatory agents against RSV is equivocal. Sixteen weeks of antiinflammatory therapy (budesonide or cromolyn sodium) given to 89 infants under 2 years of age hospitalized for RSV infection with wheezing had no effect on the occurrence of asthma 3 years later. Conversely, in a study of 117 infants with a mean age of 2.6 months who were hospitalized for RSV bronchiolitis, prevalence of asthma at 2 years was inversely related to the duration of budesonide therapy: asthma developed in 37% of children who did not receive budesonide at initial hospitalization, in 18% of those who received 7 days of therapy, and in 12% of those who received 2 months of therapy.

Conclusions
Epidemiologic data indicate that viral respiratory tract infection in infancy may cause transient asthma symptoms or may trigger the development of persistent asthma in children with a predisposition to atopy but does not directly induce allergic sensitization itself. For medical management purposes, in either case, effective therapies to prevent or suppress infection by viruses linked to AHR are desirable. Treatment would also be desirable in asthma patients of all ages to reduce the high burden of virus-induced exacerbations. Whether certain pathogens may play a beneficial role in protecting against AHR remains unclear, and medical strategies for AHR based on the hygiene hypothesis would be premature.

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