

Respiratory infections and asthma

Clinical and experimental evidence suggests an important role for respiratory infections in the development of asthma attacks. Viral upper respiratory infections have been associated with 80% of asthma exacerbations in children and 50% of all asthma episodes in adults. Human rhinovirus has been implicated as the principal virus associated with asthma episodes. Separate studies indicate that atypical bacteria such as *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* may precipitate asthma symptoms. Although not completely clarified, the intricate pathogenetic mechanisms by which viral infections promote asthma attacks have been extensively investigated in recent years. By contrast, it has not yet been established whether atypical bacterial infections are an epiphenomenon or a pathogenic event in asthma.

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Asthma is a chronic inflammatory disorder of the airways in which many genetic and environmental factors contribute to the expression of the phenotype. In recent years, a growing number of observations have highlighted the importance of respiratory infections in acute asthma exacerbations.

The use of highly sensitive techniques, in combination with comprehensive standard methods, has enabled an accurate evaluation of the incidence of respiratory infection in the development of asthma symptoms. Recent investigations identify respiratory viruses as a major trigger of acute asthma exacerbations in both adults and children. In addition there is evidence that atypical bacteria such as *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* may cause asthma symptoms. However, it remains controversial whether common bacterial infections play a role in asthma episodes.

Despite this clinicoepidemiologic evidence, the pathogenetic events underlying the association between respiratory infections and asthma exacerbations are not completely understood.

Respiratory viruses

Acute viral respiratory infections are the most frequent illness of the human host, causing much morbidity and days lost from school and work. Risk factors for the

increased incidence and/or severity of viral respiratory infections include age of the host; overcrowding; sex; environmental pollution; anatomical, metabolic, genetic, or immunologic disorders; and malnutrition (1).

Respiratory viruses that usually affect the upper airway can infect lower airway tissues and induce relevant biologic and pathophysiologic changes within the lower respiratory tract (2).

There is a large body of evidence that viral infections are a potent trigger of asthma symptoms. The first associations between viral infections and asthma exacerbations were observed more than two decades ago, although technical difficulties in the detection of respiratory viruses underestimated the impact of respiratory viral infections on asthma episodes (3, 4).

Since the introduction of reverse transcription polymerase chain reaction (RT-PCR), which is a more sensitive method for viral detection, an accurate estimation of the incidence of viral infections in the development of asthma symptoms has been reported. Prospective epidemiologic studies show that over 80% of childhood asthma exacerbations and about 50% of all adult asthma attacks are associated with viral upper respiratory infections (5, 6). Other observations report a strong linkage between patterns of viral respiratory infections and hospitalization for severe asthma episodes (7).

More recently, a close temporal relationship between the peak in seasonal asthma deaths and subjective/objective evidence of respiratory viral infection has been demonstrated (8).

Several pathophysiologic mechanisms have been implicated in the development of virus-induced airway dysfunction:

- Viruses can induce alterations in neural control of the airway. Indeed, viral infections potentially induce bronchoconstriction and increased airway responsiveness by enhancing parasympathetic bronchoconstrictive responses via stimulation of reflex bronchospasm or neuropeptide release from sensory C fibers, or interference with the function of nonadrenergic-noncholinergic neurons, which produce the potent bronchodilator nitric oxide (9).
- Viral respiratory infection produces increased sensitivity of the lower airway to nonspecific stimuli such as bronchoprovocation with histamine or methacholine. During viral infections, allergic individuals experience greater changes in airway responsiveness than nonallergic control subjects, suggesting that host factors influence the effect of viral infections on lower airway function (10, 11).
- Viral infections induce relevant changes in small-airway function, even in the absence of marked alterations in the usual parameters of airway obstruction and responsiveness (9).
- Viruses produce increased airway inflammation (9).

Much still remains to be learned about the importance of pre-existing airway inflammation in influencing the development and outcome of acute viral infections. As human rhinoviruses (HRV) are responsible for the majority of viral infections associated with asthma exacerbations, a great deal of scientific interest has been recently focused on this family of viruses.

Human rhinovirus (HRV)

HRV are RNA-containing viruses belonging to the Picornavirus family. Rhinovirus infection, the most common upper respiratory infection of man, is self-limiting in healthy subjects (12).

There is evidence that HRV contribute to more severe respiratory diseases; in particular, HRV has been implicated as the most common virus precipitating asthma episodes. Recent investigations indicate that HRV infections precede as many as 50% of all exacerbations of childhood asthma and also contribute critically to the morbidity of asthma in adults (5–7).

The initial steps in rhinovirus pathogenesis consist of viral entry into the nose, mucociliary transport of the virus to the posterior pharynx, and initiation of infection in ciliated and nonciliated epithelial cells (EC) of the upper airway. Once the infection is

established, viral concentrations in nasal secretions increase progressively, peaking at 48 h on average. Subsequently, viral titers fall, but viral shedding continues for up to 3 weeks (12).

Ninety percent of the approximately 100 HRV serotypes use a single common cell-surface receptor (the major rhinovirus receptor) for viral attachment and subsequent cellular entry: intercellular adhesion molecule 1 (ICAM-1) (13–16). The remaining 10% of rhinovirus serotypes engage members of the low-density lipoprotein receptor (LDLR) family together with an α_2 -macroglobulin receptor/LDLR-related protein (α_2 MR/LRP) for viral attachment and subsequent viral internalization (17).

A large body of interest has been recently concentrated on HRV–airway epithelium interactions. Airway EC are primary targets for viral agents and express the major group HRV receptor (ICAM-1). Studies report that HRV itself significantly upregulates surface ICAM-1 on EC, an effect which would facilitate viral cell attachment and entry (18, 19). Other investigations suggest that HRV may interfere with the ICAM-1/LFA-1 binding on leukocytes, with consequent disruption of the immune responses that are dependent on this interaction (20).

It has been recently demonstrated that the dynamic equilibrium of a number of cytokines within the local microenvironment plays a crucial role in the pathogenesis as well as the course of HRV infection (18, 21, 22).

In particular, it has been shown that IL-1 β , IL-6, IL-8, RANTES, and TNF- α induce a significant overexpression of ICAM-1 on EC. Interestingly, interferon (IFN)- γ , a known Th1 antiviral lymphokine, while increasing the level of ICAM-1 on uninfected cells, induces downregulation of membrane-bound ICAM-1 on *in vitro* HRV-infected EC (18).

There is growing scientific interest in the influence of pre-existing inflammation within the asthmatic airway on severity of susceptibility to HRV infections.

A peculiar feature of asthma inflammation is the Th2-cell predominance within the airway. Type-2 T cells, characterized by the ability to produce a specific cytokine profile (IL-4, IL-5, IL-6, IL-10, and IL-13), have been largely implicated in the pathogenesis of allergic inflammation through their ability to promote IgE synthesis, as well as differentiation, recruitment, and activation of eosinophils (23, 24). BAL cells and bronchial biopsies from asthmatic individuals exhibit high levels of mRNA expression of the Th2-associated cytokines IL-4, IL-5, IL-10, and IL-13, with a parallel reduced expression of IFN- γ (a Th1 lymphokine) and IL-12 (25–28).

Recent *in vitro* studies have investigated the influence of asthma-related Th2 cytokines on the EC major group HRV receptor (ICAM-1). It has been demonstrated that asthma-associated Th2 cytokines (IL-4, IL-5, IL-10, and particularly IL-13) produce a greater increase in

surface ICAM-1 expression than Th1-associated cytokines on both uninfected and HRV-infected EC. After prestimulation of EC with a combination of Th2 cytokines and IFN- γ , the levels of cell-surface ICAM-1 remain markedly elevated. These findings suggest that the presence of Th2 cytokines can influence the host cell–HRV interaction, inducing at the level of the target EC a pronounced and relatively IFN- γ -resistant increase in the receptor for most HRV serotypes (20, 21). Therefore, predominance of Th2-associated cytokines within the airway of asthmatic subjects would enhance the virus receptor, thereby facilitating viral entry into the cell, replication, and propagation of infection.

Chlamydia pneumoniae and *Mycoplasma pneumoniae*

While there is increasing evidence of the importance of atypical bacteria, such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, as a causal factor in asthma episodes, the role of common bacterial infections remains controversial.

C. pneumoniae is the causative infectious agent of respiratory illnesses such as rhinitis, pharyngitis, otitis, bronchitis, and atypical pneumonia. Both serologic detection of and culture positive for *C. pneumoniae* have also been associated with asthma (29, 30). Further evidence of a possible role of *C. pneumoniae* in asthma is derived from observations that some subjects treated with antichlamydial antibiotics reported improvement in their asthma symptoms (30, 31). Recently, *C. pneumoniae* has been found in 23% of asthma episodes in children; coinfection with other pathogens was reported in ~70% of the study population. In the same study, low levels of infection with *M. pneumoniae* (1–3%) were detected (33).

M. pneumoniae is a common respiratory pathogen that has been associated with asthma exacerbations. It causes both upper and lower respiratory infection in

man, tracheobronchitis being the most common clinical manifestation. In nonasthmatic individuals, infection with this organism can produce changes in lower airway physiology, such as decreased FEV₁ and airway hyperresponsiveness; these effects can persist for months (32). Recent investigations have demonstrated by PCR, but not by culture, that *M. pneumoniae* is present in more than 50% of the asthmatics studied (34).

These observations further support the importance of atypical bacteria in asthma. However, it is not yet clear whether the presence of atypical bacteria within the asthmatic airways should be considered an epiphenomenon or a pathogenic mechanism in asthma.

Conclusion

Much is known about the pathogenic events that characterize the host cell–virus interaction. Experimental studies performed both *in vitro* and *in vivo* with HRV as model have provided useful insights into the onset/outcome of respiratory viral infections. There is now a general consensus about the importance of biologic mediators within the airway in influencing the early pathogenic events as well as the course of viral infection. Accordingly, it appears that a Th1-associated cytokine-driven immune response is probably the most appropriate for eradication of viruses; conversely, the predominance of Th2-associated cytokines within the airway may facilitate replication and propagation of infection.

Despite the growing clinical observations that atypical bacterial infections are associated with asthma symptoms, the biologic mechanisms underlying this phenomenon have not yet been extensively defined. Further studies are needed to gain greater understanding of the intricate biologic events by which respiratory infections promote asthma.

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