

Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

## Infectious triggers of asthma

Ana L. MacDowell, MD, Leonard B. Bacharier, MD\*

*Department of Pediatrics, Division of Allergy and Pulmonary Medicine,  
Washington University School of Medicine and St. Louis Children's Hospital,  
One Children's Place, St. Louis, MO 63110, USA*

The rise in the incidence of atopic disease, including asthma, over the past several decades has not been limited to a particular geographic area and has occurred in developed and developing countries. Several factors influence the development and severity of asthma, including atopy, environmental exposures, genetic predisposition, gene–environment interactions, stress, obesity, diet, socio-economic status, and infection. The “Hygiene Hypothesis” [1,2] has focused attention on the role of infection in the development of allergic disease. This hypothesis suggests that infections in early life can have a protective effect on the development of asthma and atopy. Other researchers have suggested, however, that infection may be a cause for the onset and persistence of asthma. In this “Hit and Run Hypothesis,” a pathogen promotes dysregulation of the immune system, leading to prolonged inflammatory responses even after the pathogen has been cleared [3]. Thus, the role of infectious agents in the development of asthma is complex: Evidence implicates infections as causal and protective with respect to asthma development.

In addition to the potential role of infection in the inception of asthma, infection has been implicated as the most common precipitant of asthma exacerbations. Several clinical observations have indicated that most asthma episodes are precipitated by factors other than allergen exposure. Many asthma episodes are preceded by upper respiratory tract symptoms and may last several days to weeks, in contrast with allergen-induced asthma exacerbations, where exposure often leads to a rapid onset of symptoms with a recovery time of approximately 24 hours [4,5]. Infections have been linked to asthma exacerbations since the 1950s, and over the past several decades there has been extensive investigation

---

\* Corresponding author.

E-mail address: [Bacharier\\_L@kids.wustl.edu](mailto:Bacharier_L@kids.wustl.edu) (L.B. Bacharier).

of infectious agents as they relate to asthma development and exacerbations. In this article, we examine infections as triggers of asthma, with a focus on asthma exacerbations.

## **Epidemiology of respiratory infections leading to asthma exacerbations**

Respiratory tract infections (RTIs) are the most common cause of acute illness in adults and children, with upper respiratory infections (URIs) constituting the majority of such illnesses [6]. Adults typically experience two to four URIs per year, and children may have up to 12 URIs per year [7]. RTIs are the major cause of visits to primary care physicians [8] and are associated with significant work and school absenteeism, with an estimated 150 million lost workdays annually. Consequently, RTIs have great economic impact, with an estimated cost of \$40 billion annually in the United States [9]. Numerous viruses produce URIs (Table 1), and because the symptom patterns are common between many viruses, it is difficult to determine clinically the specific viral etiology of an acute illness (Table 2).

Viral infections commonly trigger asthma exacerbations, having been noted in nearly half of asthma exacerbations in adults [10] and in an even greater percentage of exacerbations in children. This was demonstrated in a 13-month study investigating the role of viral infections in asthma exacerbations in 114 children 9 to 11 years of age with asthma [11]. Peak expiratory flow (PEF) rate was performed twice daily, and upper and lower respiratory tract symptoms were recorded daily. Virologic samples were obtained within 48 hours of an increase in upper or lower respiratory symptoms, a fall in PEF by more than 50 L/min from the child's baseline, or if the parent subjectively felt that the child was developing a cold. Evidence of a viral infection was detected in 80% to 85% of episodes with respiratory tract symptoms, fall in PEF, or both. The highest detection rate occurred during reported episodes of wheeze, cough, and upper respiratory tract symptoms, together with a decline in PEF. In addition, the severity of a respiratory illness may influence the outcome of a URI because more severe viral infections seem more likely than mild infections to lead to exacerbations of asthma [5]. Viral infection has been noted more often during severe exacerbations of asthma than during milder exacerbations [12].

The advent of more sensitive diagnostic tools to detect specific infectious pathogens, such as detection of microbial DNA or RNA using the polymerase chain reaction (PCR), has strengthened the evidence for viruses as a primary triggering factor in asthma exacerbations [13]. A recent study confirmed a significant increase in the weighted average viral identification in patients of all ages with asthma exacerbation in studies that used PCR when compared with the pre-PCR studies [14]. The same study suggests that viral recovery occurs more often in asthmatic patients who are having an acute exacerbation than in asymptomatic asthmatics or nonasthmatic individuals.

Table 1  
 Characteristics of infectious agents associated with asthma exacerbations

Pathogen	Family	Type	Number of serotypes	Seasonality	Frequency of cause of common cold in adults [6]
Rhinovirus	Picornaviridae	RNA virus	100+	Year round with fall and spring peaks	45%
Coronavirus	Coronaviridae	Enveloped RNA virus	3	Year round with winter peak. Summer outbreaks have been described.	25%
Influenza virus	Orthomyxoviridae	Enveloped RNA virus	3	Annual epidemic in winter in temperate climates. In tropical climates there may be multiple outbreaks.	14%
Adenovirus	Adenoviridae	Double-stranded, non-enveloped DNA virus	49	Sporadic. Epidemics and endemic disease are more prevalent in the late winter, spring, and summer.	5%
Parainfluenza virus	Paramyxoviridae	Enveloped RNA virus	4	Winter peaks for Parainfluenza 1 and 2; summer peaks for Parainflunza 3	5%
Respiratory syncytial virus	Paramyxoviridae, but lacks neuraminidase and hemagglutinin surface glycoproteins	Enveloped RNA virus	2 (A and B)	Epidemics are mainly in winter and early spring but may be sporadic throughout the year.	1%
Human metapneumovirus	Paramyxoviridae	RNA virus	2	It was initially thought that epidemics occurred between December and April; however, it has been extended to all year round.	Unknown
<i>Mycoplasma pneumoniae</i>		Smallest free-living microorganisms	1	Pleomorphic and ubiquitous in animals and plants; prone to outbreaks throughout the world, at any season	
<i>Chlamydia pneumoniae</i>	Antigenically, genetically, and morphologically distinct from other Chlamydia species. A new name has been proposed: <i>Chlamydothila pneumoniae</i>	All isolates seem to be closely related serologically.	1	Worldwide distribution, with no evidence of seasonality or known animal reservoir	

Table 2  
Clinical characteristic of infectious agents triggering asthma

Pathogen	Clinical symptoms	Mode of transmission	Specific immunity
Rhinovirus	Most common virus causing upper respiratory illnesses (40% to 50%)	Person-to-person contact	Some type-specific immunity; of variable degree and brief duration; generally offers little protection against other serotypes
Coronavirus	A common cause of URI in adults and children; also implicated in lower respiratory tract infections. The superficial layers of the nasal mucosa temperature (32°–33°C) yields optimal growth.	Person-to-person via aerosol or fomites	Cellular and humoral immunity are required for virus clearance. Re-infections seem to occur throughout life (implying multiple serotypes [at least four are known] or antigenic variation).
Influenza virus	Systemic involvement differentiates from other viral illness, with fever being almost always present. The onset is abrupt with marked malaise and myalgias.	Person-to-person via droplets, direct contact or contaminated nasopharyngeal secretions	Specific antibodies confer immunity. Antigenic serotypes (A, B, and C) are subclassified by the presence of two surface antigens, hemagglutinin (HA) and neuroaminidase (NA). Antigenic shifts are determined by major changes in HA or NA with emergence of new virus strains, leading to epidemics or pandemics. Antigenic drifts are minor changes with variations within subtype, continuously resulting on variant viruses and leading to seasonal epidemics.
Adenovirus	Adenovirus most commonly causes respiratory illness, but, depending on the infecting serotype, other illnesses may occur; half of infections are asymptomatic.	Via respiratory secretions through person-to-person contact or via the oral-fecal route	There is a worldwide distribution, with a higher prevalence in developing countries and in lower socioeconomic groups. Generally, by school age, most children have been exposed to various serotypes.
Parainfluenza virus	Major cause of laryngotracheobronchitis (croup). Commonly causes URI, pneumonia, and bronchiolitis. Exacerbates symptoms of chronic lung disease.	Person-to-person via direct contact or contaminated nasopharyngeal secretions through respiratory tract droplets and fomites	Reinfection usually causes a mild illness limited to the upper respiratory tract. Most people have exposure to all serotypes by 5 y of age.

Respiratory syncytial virus	Causes acute respiratory illness in patients of all ages. It is the most common cause of bronchiolitis and pneumonia in infants.	Humans are the only source of infection. Transmission occurs by direct or close contact with contaminated secretions. Good hygiene habits are important because the virus may persist in environmental surfaces for many hours and on the hands for 30 min or more.	Almost 100% of children are infected with RSV by 2 y of age.
Human metapneumovirus	Varied — includes cough, coryza, fever, irritability, anorexia, wheezing, pharyngitis, vomiting, or diarrhea	Unknown	By 5 y of age nearly 100% individuals have been infected
<i>Mycoplasma pneumoniae</i>	Most commonly causes respiratory illnesses such as acute bronchitis, including pharyngitis, and occasionally otitis media, which may be bullous. Ten percent of infected individuals develop pneumonia within a few days that may last for 3–4 wk.	Causes disease only in humans; it is highly transmissible by droplets. The long incubation period (ranging from 1–4 wk) along with long asymptomatic carriage (for weeks to months) facilitates familial spread, which may continue for months.	Epidemics occur every 4–7 y because immunity is not long lasting.
<i>Chlamydia pneumoniae</i>	Responsible for a variety of respiratory diseases including pneumonia, acute bronchitis, and, less commonly, pharyngitis, laryngitis, otitis media, and sinusitis. Many infected patients are asymptomatic or mild to moderately ill. A prolonged illness may be present with cough persisting for 2–6 wk, sometimes with a biphasic course.	Assumed transmission is person-to-person, via infected respiratory secretions.	Recurrent infection is common, especially in adults. In tropical, less-developed areas, infection seems to occur earlier in life. In the United States, 50% of adults have antibodies by 20 y of age, with initial infection peaking between 5 and 15 y of age.

Another important observation that links viral infection with asthma exacerbation is the seasonal pattern of distribution of viral infections and asthma exacerbations, especially severe cases requiring hospitalization. In a 2-year study comparing asthma exacerbations due to seasonal allergens, other environmental triggers, and viral infections, a strong relationship was found between the seasonal incidence of asthma and viral infection, although there was no correlation with pollen and spore counts [15]. Similarly, viral infections were the major identifiable risk factor for autumnal asthma exacerbations [16].

In addition to viral infections, RTIs with atypical organisms, such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, precipitate a significant proportion of acute episodes of wheezing, contribute to the severity and persistence of asthma, and may serve as the initial insult that leads to development of asthma [17–19].

### **Specific infectious agents associated with asthma exacerbations**

#### *Rhinovirus*

Human rhinovirus (RV) causes nearly half of all upper respiratory illnesses. Although RV infection was initially believed to be limited to the upper airways [20], lower airway epithelial RV infection has been demonstrated [21]. Although infection of the lower respiratory tract may occur, the mechanisms through which viral infections, including RV, provoke asthma are unclear but may include direct extension of upper RTIs to the lower respiratory tract. The mechanism may be indirect and involve effects on airway responsiveness independent of the direct epithelial damage and inflammation associated with lower RTIs (LRTIs). RV infection can enhance the immediate and late-phase responses to allergen [22], potentially augmenting the allergic inflammation within the airway and precipitating asthma exacerbations.

RV infection can lead to profound exacerbation of asthma and is responsible for the majority of hospitalizations for childhood asthma, although less so in adults [20]. RV infections are associated with declines in lung function in asthmatics compared with normal subjects within 2 days after development of a RV infection [23]. RV infection augments airways hyper-responsiveness 4 days after experimental RV infection, an effect that was more pronounced in those with a severe cold [24]. The rise in airways hyper-responsiveness was accompanied by an increase in nasal interleukin (IL)-8 in the RV-infected group at days 2 and 9; the increase in nasal IL-8 at day 2 correlated significantly with the change in airway responsiveness at day 4.

#### *Coronavirus*

Coronavirus is the second most common virus associated with asthma episodes in children and adults. Infections due to coronavirus may be associated

with less severe lower respiratory tract symptoms than infections with other viruses. This is suggested by the finding that coronavirus-associated asthma episodes in asthmatic school-age children were associated with smaller median declines in PEF (56 L/min) compared with episodes triggered by other viruses (85.5 L/min) [11]. In a study of elderly adults, coronavirus was associated with lower respiratory illness in more than 40% of patients, and one quarter of patients consulted a medical practitioner and received antibiotics. More impressive was the observation that coronavirus infection produced a greater disease burden value than influenza or respiratory syncytial virus [25].

### *Influenza virus*

Influenza virus triggers asthma exacerbations in all age groups [11,26]. In addition, asthmatic individuals seem to be more susceptible to death associated with influenza infections, as observed in the Asian pandemic in 1957 [27]. The time course of influenza-induced asthma exacerbations was examined retrospectively in 20 asthmatic children 8 to 12 years of age with acute respiratory symptoms [28]. Fifteen of 20 patients had decreases in FEV<sub>1</sub> >20% from baseline during the acute stage, beginning from onset of symptoms in all but one subject, whose FEV<sub>1</sub> decreased during the incubation period. FEV<sub>1</sub> decreased maximally on the second day of illness by an average of 30%. Improvement began on the third day, and FEV<sub>1</sub> returned to within 10% of normal between the seventh and tenth day.

### *Adenovirus*

The rate of adenoviral infection declines with age until 9 years and then increases. The exception to this pattern is infection with serotype 7, whose infection rate increases with age [29]. Infection is frequently associated with wheezing, as demonstrated in a retrospective chart review study [30] where wheezing was noted in 58.3% of nonasthmatic children under 2 years of age admitted to an intensive care unit with adenoviral acute LRTI. In this study, the mortality rate was 16.7%, generally in the setting of infection with adenoviral serotype 7. Adenoviral infection has been demonstrated during acute asthma episodes, but the frequency of adenoviral infection is substantially lower than the frequency for rhinovirus and coronavirus [31].

Latent adenoviral infection may have a role in the genesis of asthma. Furthermore, adenoviral shedding may be prolonged, lasting up to 906 days. When nasopharyngeal swabs from 50 asymptomatic asthmatic children and 20 healthy control subjects were examined by PCR, adenovirus DNA was found in 78.4% of asthmatic children, compared with only 5% of healthy control subjects [32]. Adenovirus has been recovered from bronchoalveolar lavage (BAL) in children with asthma 12 months or more after acute infection [33]. In this study, BAL was performed in 34 children (mean age of 5 years) with unfavorable responses to standard corticosteroid and bronchodilator therapy. Adenoviral



antigens were detected in BAL fluid (BALF) from 94% of subjects. Repeat studies within 1 year showed that six of eight subjects were positive for adenovirus on two occasions and that three were positive when sampled three times. Cultures of the BALF were positive for adenovirus in all cultures performed, indicating that the virus was capable of replication. Similar studies performed in control patients without persistent asthma failed to detect evidence of adenovirus.

### *Respiratory syncytial virus*

Respiratory syncytial virus (RSV) infects almost 100% of children by 2 years of age and is the most common cause of bronchiolitis and pneumonia in infants [34]. In addition to causing acute LRTI, RSV serves as a trigger for exacerbations of asthma and other chronic lung diseases.

Infants who experience severe RSV bronchiolitis seem to have increased frequencies of wheeze and asthma later in life. A comparison of several retrospective studies of children admitted for bronchiolitis found that the post-bronchiolitis group had a significantly higher frequency of bronchial obstructive symptoms 2 to 10 years later and, when pulmonary function studies were performed, diminished FEV<sub>1</sub> or increased bronchial reactivity compared with healthy control subjects [35]. These findings were confirmed in a prospective study when children hospitalized with confirmed RSV bronchiolitis were evaluated at 7.5 years of age and compared with age- and gender-matched control subjects [36]. By 7.5 years of age, the cumulative prevalence of asthma was 30% in the RSV group versus 3% in the control group, and current asthma was present in 23% of the RSV group versus 2% of the control group. However, the duration of the effect of RSV infection on asthma-related symptoms appears to be limited. In a prospective study of 1246 children enrolled at birth, 207 developed an RSV LRTI not requiring hospitalization during the first 3 years of life [37]. When compared with a control group of children with no LRTI documented during the first 3 years of life, the group with mild RSV LRTI had a substantially increased risk of frequent wheeze at 6 years of age (odds ratio [OR] 4.3), and the risk for frequent wheeze remained significantly increased at 11 years of age (OR 2.4), at which time prebronchodilator FEV<sub>1</sub>, but not postbronchodilator FEV<sub>1</sub>, was significantly lower in the RSV group. By age 13 years, there were no significant between-group differences in terms of increased risk for frequent or infrequent wheezing. These studies demonstrate that RSV bronchiolitis is a significant independent risk factor for subsequent frequent wheezing, although this effect seems to decrease with age and may be dependent upon the severity of the RSV infection.

Similar to adenoviral infection, the persistence of RSV may underlie in part the sequelae of severe RSV disease. Infection may lead to alteration in the patterns of local interferon, chemokine, and cytokine production [38], potentially leading to chronic inflammation [39]. Furthermore, the age at first viral infection may direct the pattern of disease later in life by generating a Th2-biased memory

response to RSV, which may direct responses to other antigens in the lung toward an allergic phenotype. This is suggested by a study in which mice infected with RSV at different ages (1, 7, 28, or 56 days) demonstrated stronger Th2 responses in the group primed at the youngest age when reinfected with RSV at 12 weeks of age [40].

### *Parainfluenza virus*

The parainfluenza viruses (PIV) cause a spectrum of respiratory illness similar to that caused by RSV but result in fewer hospitalizations [41,42]. Most illnesses are limited to the upper respiratory tract [41], although approximately 15% involve the lower respiratory tract, and 2.8 of every 1000 children with such infections required hospitalization [42]. Although less common than RV or coronavirus infection, PIV was detected in 14% of episodes of increased symptoms or decreased PEF in school-aged children [11]. More frequent and severe wheezing has been correlated with elevated levels of IgE antibody to RSV and PIV in nasal secretions of children with bronchiolitis due to RSV and PIV [43].

### *Human metapneumovirus*

Human metapneumovirus (hMPV) was identified in 2001 in respiratory samples from children with respiratory disease in the Netherlands [44]. The clinical symptoms experienced by infected individuals are diverse and may consist of upper or lower respiratory tract symptoms ranging from otitis media to bronchiolitis, croup, pneumonia, and possibly exacerbations of asthma [45]. hMPV is responsible worldwide for community-acquired acute RTIs affecting children and other age groups, with a mean age of illness of 11.6 months and a male predominance (male/female ratio 1.8:1). The broad epidemic seasonality and the evidence of genetic variability suggest that there may be more than one serotype of hMPV [44].

Wheezing is part of the clinical symptomatology associated with hMPV infection. More than half of otherwise healthy children presenting with acute respiratory illness and evidence of hMPV infection experienced wheezing in one study [45]. In series of 19 children with evidence of hMPV infection, bronchiolitis was the most common diagnosis, and 50% of patients had wheezing [46]. Both of these studies evaluated specimens collected from previously healthy children during an acute respiratory illness during which no other pathogen was identified and detected evidence of hMPV in 6.4% [46] and 20% [45] of the previously negative samples.

Although hMPV infection is often accompanied by wheezing, there have been conflicting reports linking hMPV infections and asthma exacerbations [47,48]. Nevertheless, bronchiolitis is a common cause for hospitalization, and given the increasing hospitalization rates over the past two decades [49], it is possible that hMPV may be responsible for a portion of hospitalizations in children with

bronchiolitis and wheezing unrelated to RSV infection [46]. Furthermore, co-infection with RSV and hMPV may augment the severity of bronchiolitis [47].

### *M pneumoniae* and *C pneumoniae*

Initial evidence suggested that infection with *M pneumoniae* and *C pneumoniae* was associated with asthma chronicity. Several case reports suggest associations between infections with atypical organisms with decreased expiratory flow rates and increased airway hyper-responsiveness in nonasthmatic individuals [50] and the onset of asthma symptoms in previously healthy nonasthmatic adults [51,52]. Most of these individuals present with complaints of malaise, shortness of breath of gradual onset, and wheezing, which typically resolve after treatment with macrolide antibiotics or oral corticosteroids [51]. Symptoms may progress and persist, as illustrated by an adult male with fever, severe cough, shortness of breath, consolidation on chest radiograph, and evidence of *M pneumoniae* infection based on a rise in serum antibody titers who subsequently developed wheezing episodes with reversible airway obstruction and airway reactivity to methacholine [52]. Infections with these organisms can persist for months, and animal studies show that *M pneumoniae* can be detected by PCR for up to 200 days after infection, even though the animals become antibody and culture negative by 70 days [53]. These reports suggest that *M pneumoniae* may serve as a cause of acute wheezing and a triggering factor for the onset of asthma.

The most comprehensive evaluation of the role of *M pneumoniae* and *C pneumoniae* infections in patients with chronic asthma evaluated 55 adult patients with chronic asthma and 11 control subjects by using PCR, culture, and serology to detect *M pneumoniae* species, *C pneumoniae* species, and viruses from the nasopharynx, lung, and blood [54]. Fifty-six percent of the asthmatic patients had positive PCR studies for *M pneumoniae* ( $n = 25$ ) or *C pneumoniae* ( $n = 7$ ), which were mainly found in BALF or biopsy samples. Only 1 of 11 control subjects had a positive PCR finding for *M pneumoniae*. Cultures for these organisms were negative in all patients. A distinguishing feature between PCR-positive and PCR-negative patients was a significantly greater number of tissue mast cells in the group of patients who were PCR positive.

Of additional significance is the link of atypical infectious organisms with asthma exacerbations. In a serologically based prospective study, 100 adult patients hospitalized with exacerbations of asthma were compared with hospitalized surgical patients with no history of lung disease at any time or URI in the month before admission [55]. In this series, *M pneumoniae* was identified more often than any other pathogen in the asthmatic group (18 *M pneumoniae*, eight *C pneumoniae*, 11 Influenza A, five Influenza B, three PIV-1, two PIV-2, one PIV-3, six adenovirus, two RSV, three *S. pneumoniae*, and five *Legionella* spp.) and in the control group (three *M pneumoniae*). However, only 8 of the 18 patients had *M pneumoniae* identified as the sole infectious agent, making it difficult to ascertain the culpability of *M pneumoniae* as the cause of hospitalization. A study of 71 children with acute wheezing and 80 age-matched

healthy children detected *M pneumoniae* in 22.5% and *C pneumoniae* in 15.5% of children with wheezing compared with 7.5% and 2.5%, respectively, in healthy control subjects [56]. When the children who were infected with either organism were treated with clarithromycin, improvement in the course of the disease was observed, further supporting the role of these atypical organisms in the exacerbation of asthma. These findings were recently confirmed in a French series, where *M pneumoniae* infection was found in 20% and *C pneumoniae* infection was found in 3.4% of children during an acute asthma exacerbation [19]. Acute *M pneumoniae* infection was confirmed in 50% and *C pneumoniae* in 8.3% of patients experiencing their first wheezing episode. Further studies are needed to confirm the association between infection and asthma exacerbation, to determine the prevalence of such infections in patients with acute exacerbations of asthma, and to examine if infection with these organisms modifies the severity of the exacerbation or the response to therapy.

### **Phenotypes of wheezing associated with respiratory tract infections**

Viral-induced wheeze (VIW) is characterized by brief episodes of lower respiratory symptoms and decreased pulmonary function in the setting of an acute viral URI, interspersed with longer asymptomatic periods with normal pulmonary function [11,57]. This differs from classic childhood asthma, which is characterized by chronic symptoms, with atopy being a major risk factor [58]. Classic asthma and VIW were considered two different entities until 1969, when a report suggested that the two groups have similar characteristics [59] and benefited similarly from the same prophylactic treatment [60]. In the 1990s, there was a division of the wheezing phenotypes, especially in children [58]. Patients with VIW alone seem to outgrow the symptoms by age 6; however, in some patients, the pattern of VIW may continue into adulthood with less severe symptoms, negative methacholine challenges, and pulmonary functions that remain normal [61]. The inability to reliably differentiate between VIW and asthma, especially in young children, complicates the evaluation of the influence of viral infections on exacerbations of wheezing. Furthermore, this heterogeneity in wheezing phenotypes has implications in terms of the efficacy of therapies used to treat such episodes.

### **Immunopathology and mechanism of disease**

Viruses typically enter the body through contact with mucosal surfaces. The cell-specific distribution of viral receptors determines the viral tropism. Once the viral particles are internalized, nucleic acids are released, and transcription and production of viral proteins starts. The viral genome is replicated, and virions are

released, propagating the infection. The immune system is activated through several mechanisms when a viral infection is noted: (1) through cell surface receptor (ie, EBV activates B cells by stimulating CD21), (2) viral proteins may interact with intracellular proteins and signaling molecules activating the host cell, and (3) activation of epithelial cells leading to production of cytokines (interferon [IFN]- $\alpha$  and - $\beta$ ) and chemokines (IL-8; RANTES; MIP-1, -2, and -3; and MCP-3). This culminates in the generation of responses in an attempt to control infection.

One of the earliest responses to viral infection is the production of IFNs by different cell types; IFN- $\alpha$  is produced by leukocytes, IFN- $\beta$  is produced by fibroblasts, and INF- $\gamma$  is produced by Th1 cells and natural killer (NK) cells. IFNs induce transcription of many genes, including two with direct antiviral activity, and lead to increased expression of MHC class I and II genes. Interferons are potent activators of antiviral effector cells such as NK cells, CD8 T lymphocytes, and macrophages.

Although the inflammatory process generated by virus infection is generally viewed as a TH1 pattern with a predominance of interferons, especially INF- $\gamma$ , in atopy there is a predominance of the TH2 cytokine profile. However, viral infections promote increased cytokine-mediated inflammation through direct induction of specific cytokines produced by different viral agents [62]. The ability of certain pathogens to stimulate the production of TH2 cytokines [63] may explain why certain pathogens are more strongly associated with asthma exacerbation than others.

Viruses have been implicated in the inception of asthma because viral infections with a propensity for lower airway involvement during infancy have been associated with chronic lower respiratory tract symptoms and asthma [64]. This seems to be particularly relevant to RSV bronchiolitis, which has been demonstrated to be a significant independent risk factor for subsequent frequent wheezing [37]. The sequelae of severe RSV disease could be explained in part by viral persistence [39]. This has been supported by a recent study demonstrating the persistence of viral genomic and messenger RNA in lung homogenates of BALB/c mice up to 100 days post RSV infection, whereas virus could no longer be detected in BALF after day 14 post-infection [65].

Another possible mechanism by which a virus could promote asthma is by generating changes in patterns of pro-inflammatory cytokine production, which could facilitate virus persistence, as demonstrated with RSV [38]. Viral infection may exert direct effects on airway cells. An increase in the production of IL-10 by nonspecifically stimulated peripheral blood mononuclear cells during acute and convalescent phases of RSV infection requiring hospitalization has been demonstrated [66]. In animal studies, it was suggested that IL-10 may have a direct effect in airway smooth muscle and in the regulation of airway tone [67].

Although there is evidence supporting the role of viral infections in the development of asthma, further investigation is necessary to confirm this hypothesis because the mechanisms that could allow persistency or latency of viral infection are poorly understood.

## Interactions between infectious agents and allergy

It has been hypothesized that asthmatic individuals have increased susceptibility to viral infections. Some researchers have found an increased incidence of viral infections in asthmatic children when compared with nonasthmatics [14,26], a pattern that could be explained by the increased expression of ICAM-1, the receptor for RV, in asthmatic subjects [68]. However, this finding was not confirmed in a study that followed cohabitating couples consisting of an atopic asthmatic and a healthy nonatopic, nonasthmatic individual [23]. In this study, subjects completed daily diary cards of upper and lower respiratory tract symptoms and measured PEF twice daily. Nasal aspirates were taken and examined for rhinovirus every 2 weeks. Rhinovirus was detected in 10.1% of samples from the asthmatics and 8.5% of samples from the nonasthmatic participants. After adjustment for confounding factors, asthma did not significantly increase the risk of infection with rhinovirus in asthmatic individuals (OR 1.15).

The effect of atopic status on the rate of viral infection is unclear; evidence exists suggesting no difference between the rate of viral infection between atopic and nonatopic individuals [69] or an even lower rate of viral infections among atopic individuals [15,70], although these studies did not have adequate statistical power to confirm this trend. There is an increased risk of acute wheezing when atopy is combined with viral infection when compared with atopy or virus infection alone [70], and infants with a family history of atopy seem more likely to develop bronchiolitis with a higher rate of hospitalization [71].

Even if asthmatics do not experience more frequent infections than nonasthmatics, it is possible that asthmatics have a higher incidence of symptoms when experiencing viral infections. During rhinoviral infection, there is a greater incidence of symptoms in asthmatics compared with nonasthmatics [72]. This is further suggested by a report that asthmatics experienced seroconversion to influenza A virus at the time of asthma exacerbation even in the absence of signs of respiratory infection [5].

Although there is evidence supporting the role of infection in the genesis of asthma and allergy, a protective effect of infections in the development of atopy has also been postulated. An inverse relationship between infection and allergy was first noted when a study comparing white families with Native Americans reported that IgE levels and the prevalences of asthma and eczema were higher in the white population, whereas helminthic, viral, and bacterial infections were more prevalent in the Native Americans [1]. It was observed that increased family size, often associated with more frequent infections in early childhood, had an inverse relationship with the prevalence of allergic rhinitis [2] and asthma [73]. This was further supported by studies reporting an inverse relationship between the age of day care entry and the diagnosis of asthma [74,75]. One potential explanation for this pattern is that at birth there is a predominant TH2 response, and, as exposure to infections occurs, there is a gradual shift toward a TH1-dominant response. However, if the skewing of the immune response to TH1, which regulates response to viral infection, is impaired, a TH2 response would

predominate, favoring the development of allergy. Ex vivo studies have shown that asthmatics exposed to viral infections lack the capacity to mount a strong TH1 response [76,77].

## Treatment

There is no clinically effective treatment for the common cold. As the mechanisms of viral-induced wheezing and asthma are elucidated, new forms of treatment may emerge. The involvement of many inflammatory pathways suggests that antiviral and anti-inflammatory therapies have potential roles for intervention after onset of symptoms; however, a combination of both therapeutic approaches may have the greatest impact. Prophylaxis for the acquisition of viral infections, in the form of vaccination or pharmacologic therapy, offers the best hope of disease control.

The major obstacle for treatment is the wide variety of organisms associated with URIs, including viral and bacterial agents (Table 2). In addition, accurate and timely diagnosis is essential for the appropriate targeting of specific anti-infective therapies. The rapid rate of mutation of viruses leads to the emergence of resistant strains. In addition, there are difficulties with the delivery, expense, and efficacy of drugs [78]. Treatment for viral RTIs remains symptomatic, although future approaches will likely be directed toward reducing the inflammatory response elicited by the virus.

Vaccination remains the mainstay of prophylaxis against infections. However, with the exception of influenza, vaccine development for respiratory viruses has been slow and disappointing. Influenza vaccine contains three strains (two A and one B) of inactivated virus, one or two of which are modified yearly based upon predictions of the upcoming viral strains. They are produced in embryonated hen eggs and are highly immunogenic, conferring protection in 70% to 80% of the vaccine recipients with minimal adverse effects. Whole-cell influenza vaccine is no longer available, and the current vaccines consist of subvirion (prepared by disrupting the lipid membrane) or purified surface antigen. Recently, a live-attenuated, cold-adapted, trivalent, intranasal influenza vaccine (FluMist) has been introduced, but it is contraindicated in asthmatics [79].

A long-standing concern that influenza vaccination may trigger exacerbations of asthma was addressed in a multicenter, randomized, double-blind, placebo-controlled, crossover trial in 2032 patients with asthma (age range 3–64 years). This study confirmed the safety of the influenza vaccine in asthmatics by demonstrating that the frequency of exacerbations of asthma was similar in the 2 weeks after vaccination with the active influenza vaccine or placebo (28.8% and 27.7%, respectively) [80].

Although yearly influenza vaccination is recommended as a routine element of asthma management [81], a recent study generated concern about the usefulness of influenza vaccine in preventing influenza-related asthma exacerbations. This randomized, double-blind, placebo-controlled trial showed that the number, se-

verity, and duration of influenza-related asthma exacerbation was similar between the group receiving influenza vaccination and the group receiving placebo over the course of one influenza virus season [82]. Vaccinated children tended to have shorter exacerbations (by approximately 3 days) than nonvaccinated children.

Antiviral therapy targets the source of infection directly, decreasing the number of infectious agents and therefore reducing inflammatory process. The only licensed antiviral therapies are directed against influenza A (amantadine and rimantadine), influenza A and B (zanamivir and oseltamivir), and RSV (ribavirin). The neuraminidase inhibitors, zanamivir and oseltamivir, have an advantage over adamantanes, amantadine, and rimantadine because they have a broader spectrum and are effective against the A and B strains of influenza virus. The inhibition of neuraminidase, whose active site consists of 11 amino acids conserved in all naturally occurring influenza virus [83], prevent cleavage of sialic acid from newly acquired membrane, leaving emerging virus inactive and thereby decreasing infectivity [84]. Both neuraminidase inhibitors improve respiratory outcomes in patients with asthma and acute influenza infections [78] and have the added benefit of being effective in the prophylaxis against influenza infections [85]. Although it is generally well tolerated, there are case reports of bronchospasm after treatment with inhaled zanamivir [86]; however, it is difficult to separate these symptoms from the effects of the influenza infection. The disadvantage of current antiviral therapy is the specificity for influenza and the need for initiation of treatment within 48 hours of onset of infection. The toxicity profile of ribavirin, approved for use in severe RSV infections, limits its clinical use except in settings of severe illness in immunocompromised hosts.

Antibiotic use is appropriate if there is evidence of bacterial infection contributing to asthma exacerbations, although pyogenic lung infections rarely exacerbate asthma and are rarely associated with wheezing. Although some macrolide antibiotics have been reported to have antiviral effects in vitro against rhinoviruses [87], these effects have not been confirmed in vivo, and a recent Cochrane review does not support the use of antibiotics for the treatment of the common cold [88]. The anti-inflammatory effects of macrolide antibiotics are not limited to their ability to interfere with corticosteroid metabolism [89], as evidenced by inhibition of the neutrophil oxidative burst [90], reduction of cytokine formation [91], and reduction of ICAM-1 production [92]. Asthmatic patients infected with *M pneumoniae* or *C pneumoniae* may benefit from prolonged treatment with clarithromycin, as evidenced by significant improvement in FEV<sub>1</sub> [18,93]. Furthermore, in a double-blind, randomized, crossover study, 17 patients with stable mild or moderate asthma not evaluated for *M pneumoniae* or *C pneumoniae* received 200 mg of clarithromycin or placebo twice daily for 8 weeks. Methacholine responsiveness improved in all the patients after 8 weeks of clarithromycin treatment [94]. Improvement in airway hyper-responsiveness after 8 weeks of clarithromycin treatment was confirmed in a group of patients with asthma receiving concomitant therapy with inhaled corticosteroids who were not selected on the basis of infection with *M pneumoniae* or *C pneumoniae* [95]. It remains unclear as to the mechanism by which macro-



lide antibiotics improve airway hyper-responsiveness in patients with asthma, but possibilities may include treatment of occult or chronic infection, interference with steroid metabolism, or the anti-inflammatory properties of this class of antimicrobials.

Although there are international guidelines for the management of asthma [81,96], there is a relative paucity of evidence regarding therapeutic strategies specifically for VIW in asthmatics or healthy subjects. Because most acute exacerbations of asthma are induced by viral infections and because many forms of asthma therapy, especially inhaled corticosteroids, reduce the frequency and severity of exacerbations, one would presume that the current treatment for chronic asthma would be efficacious in preventing VIW. However, the varying phenotypes of wheezing, especially in childhood, seem to respond differently to such management approaches. This is particularly true for RSV-associated wheezing, which does not consistently respond to medications often used to treat asthma exacerbations, including bronchodilators and corticosteroids [97]. Thus, despite the efficacy of inhaled corticosteroids in the control of asthma and reduction of exacerbations, patients continue to experience exacerbations, particularly in the setting of viral RTIs.

Several treatment approaches have been investigated in an attempt to reduce the morbidity associated with wheezing associated with RTIs. Brunette et al [98] examined the effect of a short course of oral corticosteroid administered in an unblinded manner at onset of URI symptoms in a group of children with histories of recurrent wheezing in the setting of viral infections. Over a 1-year period, the group receiving oral corticosteroids at the early signs of RTIs experienced reductions in the frequencies of wheezing, emergency room visits, and hospitalizations. However, a recent double-blind, placebo-controlled trial evaluating the use of parent-initiated oral corticosteroids at the early signs of an episode of presumed viral-induced wheezing did not detect a difference between oral corticosteroid therapy and placebo in terms of symptom scores and rate of hospitalization [99]. Thus, the role for the use of oral corticosteroids at the early signs of illness in children with recurrent viral wheezing is unclear, and additional investigation is required to determine the efficacy of this approach in the management and attenuation of wheezing episodes.

The repeated use of systemic corticosteroids for such episodes remains a clinical concern. Given the efficacy of inhaled corticosteroids (ICS) in the daily management of asthma and their favorable safety profile when compared with systemic corticosteroids, the use of ICS in the management of VIW has been explored. Although ICS are effective in the management of persistent asthma, current evidence suggests a lack of efficacy in the regular use of ICS in patients with mild VIW [100,101]. A recent meta-analysis concluded that the use of ICS episodically for viral-triggered wheezing in children not using them as maintenance may decrease the rate of oral corticosteroid requirement [101]. In patients receiving daily ICS therapy, the common clinical practice of doubling the dose of ICS at the onset of an asthma exacerbation has been shown to be ineffective in preventing symptom progression [102]. However, a recent study in

adults demonstrated the valuable effects of quadrupling the ICS dose with acute asthma exacerbations [103]. These data suggest that corticosteroids, taken orally or inhaled, may be used as treatment and preventive therapy for asthma exacerbations in the setting of RTIs.

The cysteinyl leukotrienes (cysLTs) have been identified as important mediators in the complex pathophysiology of asthma. CysLTs are detectable in the blood, urine, nasal secretions, sputum, and BALF of patients with chronic asthma. Elevated cysLTs have been detected in respiratory secretion of children with viral induced wheezing [104]. Similar to elevated levels in asthmatics, 20 infants with prolonged or persistent wheeze (mean 14.9 months) and a history of viral illness at wheeze onset had significant elevations of leukotrienes in BAL despite the fact that 12 of 20 infants were receiving daily ICS therapy ( $\leq 450 \mu\text{g/d}$ ) [105]. These findings suggest that, similar to asthma pathophysiology, cysLTs play a role in the pathophysiology of viral-induced wheeze. Additionally, based on the above study, the cysLTs are not fully suppressed by the preferred standard anti-inflammatory therapy, inhaled corticosteroids. Thus, antagonism of the effects of cysLT using the leukotriene receptor antagonists may provide clinical benefit to patients with VIW.

The relative efficacies of these intervention strategies aimed at reduction of wheezing and asthma in the setting of RTIs depend upon the wheezing phenotype and probably the timing of the initiation of therapy. Investigation of other therapeutic approaches to VIW is ongoing and may provide insight as to the optimal treatment approach for this challenging condition.

## Summary

Infections have been implicated in asthma exacerbations and in the inception of asthma. Several studies support the concept that viruses and atypical infectious agents may induce asthma exacerbations and contribute to the chronicity of asthma. The further elucidation of the mechanisms that underlie the interaction between infectious agents and asthma will lead to improvements in treatment and prevention of such exacerbations. Studies are needed to explore the vast domain of infectious triggered asthma exacerbations.

## References

- [1] Gerrard J, Geddes C, Regin P, et al. Serum IgE levels in white and metis communities in Saskatchewan. *Ann Allergy* 1976;37:91–100.
- [2] Strachan D. Hay fever, hygiene, and household size. *BMJ* 1989;299:1259–60.
- [3] Walter MJ, Morton JD, Kajiwara N, et al. Viral induction of a chronic asthma phenotype and genetic segregation from the acute response. *J Clin Invest* 2002;110:165–75.
- [4] Mertsola J, Ziegler T, Ruuskanen O, et al. Recurrent wheezy bronchitis and viral respiratory infections. *Arch Dis Child* 1991;66:124–9.

- [5] Roldaan A, Masural N. Viral respiratory infections in asthmatic children staying in a mountain resort. *Eur J Respir Dis* 1982;63:140–50.
- [6] Myint S. Microbiology and epidemiology of upper respiratory tract infections. In: Johnson SL, Papadopoulos NG, editors. *Respiratory infections in allergy and asthma*. 1st edition. New York: Marcel Dekker; 2003. p. 13–41.
- [7] Monto AS, Sullivan KM. Acute respiratory illness in the community: frequency of illness and the agents involved. *Epidemiol Infect* 1993;110:145–60.
- [8] Davey P, Rutherford D, Graham B, et al. Repeat consultations after antibiotic prescribing for respiratory infection: a study in one general practice. *Br J Gen Pract* 1994;44:509–13.
- [9] Fendrick AM, Monto AS, Nightengale B, et al. The economic burden of non-influenza-related viral respiratory tract infection in the United States. *Arch Intern Med* 2003;163:487–94.
- [10] Nicholson KG, Kent J, Hammersley V, et al. Risk factors for lower respiratory complications of rhinovirus infections in elderly people living in the community: prospective cohort study. *BMJ* 1996;313:1119–23.
- [11] Johnston SL, Pattemore PK, Sanderson G, et al. Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. *BMJ* 1995;310:1225–9.
- [12] Beasley R, Coleman E, Hermon Y, et al. Viral respiratory tract infections and exacerbations of asthma in adult patients. *Thorax* 1988;43:679–83.
- [13] Pattemore P, Johnston S, Bardin P. Viruses as precipitants of asthma symptoms. I: epidemiology. *Clin Exp Allergy* 1992;22:325–36.
- [14] Pattemore P. Epidemiology and diagnosis of virus-induced asthma. In: Johnston S, Papadopoulos N, editors. *Respiratory infections in allergy and asthma*. New York: Marcel Dekker; 2003. p. 43–89.
- [15] Carlsen K, Orstavik I, Leegard J, et al. Respiratory virus infections and aeroallergens in acute bronchial asthma. *Arch Dis Child* 1984;59:310–5.
- [16] Dales R, Schweitzer I, Toogood J, et al. Respiratory infections and the autumn increase in asthma morbidity. *Eur Respir J* 1996;9:72–7.
- [17] Cunningham AF, Johnston SL, Julious SA, et al. Chronic Chlamydia pneumoniae infection and asthma exacerbations in children. *Eur Respir J* 1998;11:345–9.
- [18] Kraft M, Cassell GH, Henson JE, et al. Detection of Mycoplasma pneumoniae in the airways of adults with chronic asthma. *Am J Respir Crit Care Med* 1998;158:998–1001.
- [19] Biscardi S, Lorrot M, Marc E, et al. Mycoplasma pneumoniae and asthma in children. *Clin Infect Dis* 2004;38:1341–6.
- [20] Johnston S, Holgate S. Epidemiology of viral respiratory tract infections. In: Myint S, Taylor-Robinson D, editors. *Viral and other infections of the human respiratory tract*. London: Chapman & Hall; 1996. p. 1–38.
- [21] Papadopoulos NG, Bates PJ, Bardin PG, et al. Rhinoviruses infect the lower airways. *J Infect Dis* 2000;181:1875–84.
- [22] Lemanske Jr RF, Dick EC, Swenson CA, et al. Rhinovirus upper respiratory infection increases airway hyperreactivity and late asthmatic reactions. *J Clin Invest* 1989;83:1–10.
- [23] Come JM, Marshall C, Smith S, et al. Frequency, severity, and duration of rhinovirus infections in asthmatic and non-asthmatic individuals: a longitudinal cohort study. *Lancet* 2002;359:831–4.
- [24] Grunberg K, Timmers MC, Smits HH, et al. Effect of experimental rhinovirus 16 colds on airway hyperresponsiveness to histamine and interleukin-8 in nasal lavage in asthmatic subjects in vivo. *Clin Exp Allergy* 1997;27:36–45.
- [25] Nicholson K, Kent J, Hammersley V, et al. Acute viral infections of upper respiratory tract in the elderly people living in the community: comparative, prospective, population based study of disease burden. *BMJ* 1997;315:1060–4.
- [26] Minor T, Dick E, DeMeo A, et al. Viruses as precipitants of asthmatic attacks in children. *JAMA* 1974;227:292–8.
- [27] Quarles van Ufford W, Savelberg P. Asiatic influenza in allergic patients with bronchial asthma. *Int Arch Allergy Appl Immunol* 1959;227:292–8.

- [28] Kondo S, Abe K. The effects of influenza virus infection on FEV1 in asthmatic children: the time-course study. *Chest* 1991;100:1235–8.
- [29] Fox J, Hall C, Cooney M. The Seattle Virus Watch. VIII: observations of adenovirus infections. *Am J Epidemiol* 1977;105:362–86.
- [30] Carballal G, Videla C, Misirlian A, et al. Adenovirus type 7 associated with severe and fatal acute lower respiratory infections in Argentine children. *BMC Pediatr* 2002;2:6–12.
- [31] Tan WC, Xiang X, Qiu D, et al. Epidemiology of respiratory viruses in patients hospitalized with near-fatal asthma, acute exacerbations of asthma, or chronic obstructive pulmonary disease. *Am J Med* 2003;115:272–7.
- [32] Marin J, Jeler-Kacar D, Levstek V, et al. Persistence of viruses in upper respiratory tract of children with asthma. *J Infect* 2000;41:69–72.
- [33] Macek V, Sorli J, Kopriva S, et al. Persistent adenoviral infection and chronic airway obstruction in children. *Am Rev Respir Dis* 1994;150:7–10.
- [34] Mufson M, Levine H, Wasil R, et al. Epidemiology of respiratory syncytial virus infection among infants and children in Chicago. *Am J Epidemiol* 1973;98:88–95.
- [35] Sigurs N. Epidemiologic and clinical evidence of a respiratory syncytial virus-reactive airway disease link. *Am J Respir Crit Care Med* 2001;163:S2–6.
- [36] Sigurs N, Bjarnason R, Sigurbergsson F, et al. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. *Am J Respir Crit Care Med* 2000;161:1501–7.
- [37] Stein RT, Sherrill D, Morgan WJ, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999;354:541–5.
- [38] Guerrero-Plata A, Ortega E, Gomez B. Persistence of respiratory syncytial virus in macrophages alters phagocytosis and pro-inflammatory cytokine production. *Viral Immunol* 2001;14:19–30.
- [39] Southern P, Oldstone MB. Medical consequences of persistent viral infection. *N Engl J Med* 1986;314:359–67.
- [40] Culley FJ, Pollott J, Openshaw PJ. Age at first viral infection determines the pattern of T cell-mediated disease during reinfection in adulthood. *J Exp Med* 2002;196:1381–6.
- [41] Knott AM, Long CE, Hall CB. Parainfluenza viral infections in pediatric outpatients: seasonal patterns and clinical characteristics. *Pediatr Infect Dis J* 1994;13:269–73.
- [42] Reed G, Jewett PH, Thompson J, et al. Epidemiology and clinical impact of parainfluenza virus infections in otherwise healthy infants and young children <5 years old. *J Infect Dis* 1997;175:807–13.
- [43] Welliver RC. Immunologic mechanisms of virus-induced wheezing and asthma. *J Pediatr* 1999;135:14–20.
- [44] Van den Hoogen B, De Jong J, Groen J, et al. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. *Nat Med* 2001;7:719–24.
- [45] Williams J, Harris P, Tollefson S, et al. Human metapneumovirus and lower respiratory tract disease in otherwise healthy infants and children. *N Engl J Med* 2004;350:443–50.
- [46] Esper F, Boucher D, Weibel C, et al. Human metapneumovirus infection in the United States: clinical manifestations associated with a newly emerging respiratory infection in children. *Pediatrics* 2003;111:1407–10.
- [47] Greensill J, McNamara P, Dove W, et al. Human metapneumovirus in severe respiratory syncytial virus bronchiolitis. *Emerg Infect Dis* 2003;9:372–5.
- [48] Rawlinson W, Waliuzzaman Z, Carter I, et al. Asthma exacerbations in children associated with rhinovirus but not with human metapneumovirus infections. *J Infect Dis* 2003;187:1313–8.
- [49] Shay D, Holman R, Newman R, et al. Bronchiolitis-associated hospitalizations among US children, 1980–1996. *JAMA* 1999;282:1440–6.
- [50] Sabato AR, Martin AJ, Marmion BP, et al. *Mycoplasma pneumoniae*: acute illness, antibiotics, and subsequent pulmonary function. *Arch Dis Child* 1984;59:1034–7.
- [51] Shee CD. Wheeze and *Mycoplasma pneumoniae*. *J R Soc Med* 2002;95:132–3.

- [52] Yano T, Ichikawa Y, Komatu S, et al. Association of *Mycoplasma pneumoniae* antigen with initial onset of bronchial asthma. *Am J Respir Crit Care Med* 1994;149:1348–53.
- [53] Marmion BP, Williamson J, Worswick DA, et al. Experience with newer techniques for the laboratory detection of *Mycoplasma pneumoniae* infection: Adelaide, 1978–1992. *Clin Infect Dis* 1993;17(Suppl 1):S90–9.
- [54] Martin RJ, Kraft M, Chu HW, et al. A link between chronic asthma and chronic infection. *J Allergy Clin Immunol* 2001;107:595–601.
- [55] Lieberman D, Printz S, Ben-Yaakov M, et al. Atypical pathogen infection in adults with acute exacerbation of bronchial asthma. *Am J Respir Crit Care Med* 2003;167:406–10.
- [56] Esposito S, Blasi F, Arosio C, et al. Importance of acute *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* infections in children with wheezing. *Eur Respir J* 2000;16:1142–6.
- [57] Doull I, Lampe F, Smith S, et al. The effect of inhaled corticosteroid on episodes of viral associated wheezing in school age children. *BMJ* 1997;315:858–62.
- [58] Martinez F, Wright A, Taussig L, et al. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995;332:133–8.
- [59] Williams H, McNicol K. Prevalence, natural history and relationship of wheezy bronchitis and asthma in children: an epidemiologic study. *BMJ* 1969;iv:321–5.
- [60] Speight A, Lee D, Hey E. Underdiagnosis and treatment of asthma in childhood. *BMJ* 1983;286:1253–6.
- [61] Godden D, Ross S, Abdalla M, et al. Outcome of wheeze in childhood: symptoms and pulmonary function 25 years later. *Am J Respir Crit Care Med* 1994;149:106–12.
- [62] Noah T. Cytokine network in virus infection and asthma. In: Johnson SL PN, editor. *Respiratory infections in allergy and asthma*. New York: Marcel Dekker; 2003. p. 173–97.
- [63] Bendelja K, Gagro A, Bace A, et al. Predominant type-2 response in infants with respiratory syncytial virus (RSV) infection demonstrated by cytokine flow cytometry. *Clin Exp Immunol* 2000;121:332–8.
- [64] Castro-Rodriguez JA, Holberg CJ, Wright AL, et al. Association of radiologically ascertained pneumonia before age 3 yr with asthma-like symptoms and pulmonary function during childhood: a prospective study. *Am J Respir Crit Care Med* 1999;159:1891–7.
- [65] Schwarze J, O'Donnell DR, Rohwedder A, et al. Latency and persistence of respiratory syncytial virus despite T cell immunity. *Am J Respir Crit Care Med* 2004;169:801–5.
- [66] Bont L, Heijnen CJ, Kavelaars A, et al. Monocyte IL-10 production during respiratory syncytial virus bronchiolitis is associated with recurrent wheezing in a one-year follow-up study. *Am J Respir Crit Care Med* 2000;161:1518–23.
- [67] Makela MJ, Kanehiro A, Dakhama A, et al. The failure of interleukin-10-deficient mice to develop airway hyperresponsiveness is overcome by respiratory syncytial virus infection in allergen-sensitized/challenged mice. *Am J Respir Crit Care Med* 2002;165:824–31.
- [68] Gern J, Busse W. Association of rhinovirus infection with asthma. *Clin Microbiol Rev* 1999;12:9–18.
- [69] Huhti E, Mokka T, Nikoskelainen J, et al. Association of viral and mycoplasma infections with exacerbations of asthma. *Ann Allergy* 1974;33:145–9.
- [70] Rakes G, Arruda E, Ingram J, et al. Rhinovirus and respiratory syncytial virus in wheezing children requiring emergency care. IgE and eosinophil analyses. *Am J Respir Crit Care Med* 1999;159:785–90.
- [71] Trefny P, Stricker T, Baerlocher C, et al. Family history of atopy and clinical course of RSV infection in ambulatory and hospitalized infants. *Pediatr Pulmonol* 2000;30:302–6.
- [72] Horn M, Gregg I. Role of viral infection and host factors in acute episodes of asthma and chronic bronchiolitis. *Chest* 1973;63(Suppl):44S–8S.
- [73] Rona RJ, Duran-Tauleria E, Chinn S. Family size, atopic disorders in parents, asthma in children, and ethnicity. *J Allergy Clin Immunol* 1997;99:454–60.
- [74] Ball T, Castro-Rodriguez J, Griffith K, et al. Siblings, day care attendance and the risk of asthma and wheezing during childhood. *N Engl J Med* 2000;343:538–43.
- [75] Kramer U, Heinrich J, Wjst M, et al. Age of entry to day nursery and allergy in later childhood. *Lancet* 1999;353:450–4.

- [76] Papadopoulos NG, Stanciu LA, Papi A, et al. A defective type 1 response to rhinovirus in atopic asthma. *Thorax* 2002;57:328–32.
- [77] Gern JE, Vrtis R, Grindle KA, et al. Relationship of upper and lower airway cytokines to outcome of experimental rhinovirus infection. *Am J Respir Crit Care Med* 2000;162:2226–31.
- [78] Creer D, Gelder C, Johnston S. Treatment of common colds. In: Sebastian L, Johnston NGP, editors. *Respiratory infections in allergy and asthma*. New York: Marcel Dekker; 2003. p. 675–710.
- [79] American Academy of Pediatrics Committee on Infectious Diseases. Recommendations for influenza immunization of children. *Pediatrics* 2004;113:1441–7.
- [80] American Lung Associations Asthma Clinical Research Centers. The safety of inactivated influenza vaccine in adults and children with asthma. *N Engl J Med* 2001;345:1529–36.
- [81] National Asthma Education and Prevention Program. Expert Panel Report II: guidelines for the diagnosis and management of asthma. Bethesda (MD): US Department of Health and Human Services; 1997.
- [82] Bueving HJ, Bernsen RM, de Jongste JC, et al. Influenza vaccination in children with asthma: randomized double-blind placebo-controlled trial. *Am J Respir Crit Care Med* 2004; 169:488–93.
- [83] Govorkova EA, Leneva IA, Golubeva OG, et al. Comparison of efficacies of RWJ-270201, zanamivir, and oseltamivir against H5N1, H9N2, and other avian influenza viruses. *Antimicrob Agents Chemother* 2001;45:2723–32.
- [84] Klenk HD, Rott R. The molecular biology of influenza virus pathogenicity. *Adv Virus Res* 1988;34:247–81.
- [85] Hayden F, Gubareva L, Monto A, et al. Inhaled zanamivir for the prevention of influenza in families. Zanamivir Family Study Group. *N Engl J Med* 2000;343:1282–9.
- [86] Williamson J, Pegram P. Respiratory distress associated with zanamivir. *N Engl J Med* 2000;342:661–2.
- [87] Suzuki T, Yamaya M, Sekizawa K, et al. Erythromycin inhibits rhinovirus infection in cultured human tracheal epithelial cells. *Am J Respir Crit Care Med* 2002;165:1113–8.
- [88] Arroll B, Kenealy T. Antibiotics for the common cold. *Cochrane Database Syst Rev* 2002;3:CD000247.
- [89] Shimuzu T, Kato M, Mochizuki H, et al. Roxithromycin reduces the degree of bronchial hyperresponsiveness in children with asthma. *Chest* 1994;106:458–61.
- [90] Anderson R. Erythromycin and roxithromycin potentiate human neutrophil locomotion in vitro by inhibition of leukoattractant activated superoxide generation and autooxidation. *J Infect Dis* 1989;5:966–72.
- [91] Takizawa H, Desaki M, Ohtoshi T, et al. Erythromycin suppresses interleukin 6 expression by human bronchial epithelial cells: a potential mechanism of its anti-inflammatory action. *Biochem Biophys Res Commun* 1995;210:781–6.
- [92] Khair O, Devalia J, Abdelaziz M, et al. Effect of erythromycin on Hemophilus influenzae endotoxin-induced release of IL-6, IL-8, and sICAM-1 by cultured human bronchial epithelial cells. *Eur Respir J* 1995;8:1451–7.
- [93] Kraft M, Cassell GH, Pak J, et al. Mycoplasma pneumoniae and Chlamydia pneumoniae in asthma: effect of clarithromycin. *Chest* 2002;121:1782–8.
- [94] Amayasu H, Yoshida S, Ebana S, et al. Clarithromycin suppresses bronchial hyperresponsiveness associated with eosinophilic inflammation in patients with asthma. *Ann Allergy Asthma Immunol* 2000;84:594–8.
- [95] Kostadima E, Tsioudras S, Alexopoulos EI, et al. Clarithromycin reduces the severity of bronchial hyperresponsiveness in patients with asthma. *Eur Respir J* 2004;23:714–7.
- [96] National Heart, Lung, and Blood Institute. Global Initiative for Asthma: global strategy for asthma management and prevention. Bethesda (MD): National Institutes of Health; 2002.
- [97] Milner AD. The role of corticosteroids in bronchiolitis and croup. *Thorax* 1997;52:595–7.
- [98] Brunette MG, Lands L, Thibodeau LP. Childhood asthma: prevention of attacks with short-term corticosteroid treatment of upper respiratory tract infection. *Pediatrics* 1988;81:624–9.

- [99] Oommen A, Lambert PC, Grigg J. Efficacy of a short course of parent-initiated oral prednisolone for viral wheeze in children aged 1–5 years: randomised controlled trial. *Lancet* 2003; 362:1433–8.
- [100] Wilson N, Sloper K, Silverman M. Effect of continuous treatment with topical corticosteroid on episodic viral wheeze in preschool children. *Arch Dis Child* 1995;72:317–20.
- [101] McKean M, du Charne F. Inhaled steroid for episodic viral wheeze of childhood. In: Review C, editor. *Cochrane Library*. Oxford: Update Software; 2000.
- [102] Garrett J, Williams S, Wong C, Holdaway D. Treatment of acute asthmatic exacerbations with an increased dose of inhaled steroid. *Arch Dis Child* 1998;79:12–7.
- [103] Foresi A, Morelli MC, Catena E. Low-dose budesonide with the addition of an increased dose during exacerbations is effective in long-term asthma control. *Chest* 2000;117:440–6.
- [104] van Schaik SM, Tristram DA, Nagpal IS, et al. Increased production of IFN-gamma and cysteinyl leukotrienes in virus-induced wheezing. *J Allergy Clin Immunol* 1999;103:630–6.
- [105] Krawiec ME, Westcott JY, Chu HW, et al. Persistent wheezing in very young children is associated with lower respiratory inflammation. *Am J Respir Crit Care Med* 2001;163:1338–43.