Respiratory Consequences of Rhinovirus Infection

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Rhinoviruses, a genus of the family Picornaviridae, are the cause of more than 50% of respiratory tract infections. Complications of rhinovirus infections, which include otitis media, sinusitis, exacerbations of asthma, and other pulmonary diseases, can be significant in certain populations. Reverse transcriptase–polymerase chain reaction has allowed the identification of rhinoviruses and led to a greater appreciation of the role of this pathogen in upper and lower respiratory tract disease. Furthermore, antiviral agents with broad activity against rhinoviruses have recently been developed, have undergone clinical trials, but have not been approved for clinical use. By altering the clinical course of picornavirus infections, it may be possible to minimize their potential adverse consequences.

The picornaviruses are a diverse family of human pathogens and include the genera Enterovirus and Rhinovirus. They are responsible for many common infections, including viral respiratory infections (VRIs), which are known as the common cold, and several rare but potentially life-threatening infections, including viral meningitis and encephalitis, myocarditis, and neonatal sepsis–like syndrome (Table). Because rhinoviruses cause more than 50% of viral respiratory infections, this article will focus on rhinoviruses.

PICORNAVIRUS (RHINOVIRUS) STRUCTURE

The Picornaviridae family includes more than 100 serotypes of rhinovirus. These viruses are small, generally 24 to 30 nm in diameter, and they contain a simple viral capsid and a single strand of positive-sense RNA. The capsid contains 4 proteins, designated VP1, VP2, VP3, and VP4, which are arranged in 60 repeating protomerous icosahedral units. Proteins VP1, VP2, and VP3 are found on the surface of the viral capsid and have antigenic sites that are important for the host immune response. Variations in VP1, VP2, and VP3 on the viral surface are responsible for the antigenic diversity of these viruses. The other protein, VP4, is found inside the virus, where it anchors the RNA core to the viral capsid.

The human rhinoviruses are divided into 2 groups based on cellular receptors. More than 90% of rhinovirus serotypes attach to the host cell via intercellular adhesion molecule 1 (ICAM-1) to gain cell entry and initiate infection. The remainder attach via the low-density lipoprotein receptor.

EPIDEMIOLOGY AND IMPACT OF RHINOVIRUS INFECTION

Rhinoviruses are the most frequent pathogen associated with the symptoms of VRI, or a cold, which are most commonly rhinorrhea, sore throat, nasal congestion, sneezing, cough, and headache. Worldwide, rhinovirus infection occurs among all age groups and during all seasons. In temperate climates, however, rhinovirus infections are most prevalent in the fall (September and October) and spring (March and April).

In 1996, the common cold was responsible for almost 20 million days of missed work, 22 million days of missed school, and 27 million physician visits in the United States. A more recent article by Gonzales et al reported that 76 million visits were made to primary care providers in 1998 for acute respiratory tract infections.
infections. Moreover, upper respiratory tract infections are the most common reason for inappropriate antibiotic use in children and adults, contributing to the emergence of resistant bacterial strains.8-10

RHINOVIRUS INFECTIONS IN PATIENTS WITH ASTHMA

Asthma attacks are most often preceded by a VRI. Studies confirm the association of VRIs and asthma attacks. Johnston et al11 reported on schoolchildren 9 to 11 years of age who had exacerbations of asthma during a 13-month study period. Viruses were detected in 80% of episodes with reduced peak expiratory flow, in 80% of reported episodes of wheezing, and in 85% of reported incidences of upper respiratory symptoms, cough, wheeze, and fall in peak expiratory flow. Rhinoviruses were the most commonly identified virus; they were found in 147 episodes (65%) in which viruses were identified.

Although data regarding VRIs as precipitators of asthma attacks in adults have been less clear, Nicholson et al12 found that VRIs are as commonly linked to exacerbations in adults as they are in children. Colds were reported in 80% (223/280) of episodes in adults who had symptoms of wheeze, chest tightness, or breathlessness, and 86% (223/259) of colds were associated with asthma symptoms in 138 adults who had a long history of asthma. Almost 25% of acute nonbacterial infections (viral and chlamydial) were associated with reduced peak expiratory flow rates. Respiratory pathogens were implicated in almost 50% of the most severe exacerbations; 64% of viruses identified by reverse transcriptase–polymerase chain reaction (RT-PCR) were rhinoviruses.

There is long-standing speculation that children and possibly adults with allergies and asthma get more respiratory infections than normal healthy populations do. However, a definite connection and evidence supporting increased susceptibility to respiratory infections have been questioned.13 Minor et al14 showed in a small study that children with asthma had a greater frequency of VRIs than their nonasthmatic siblings.

Importantly, a time-trend analysis by Johnston et al15 showed that hospital admissions for asthma were significantly correlated with seasonal patterns for upper respiratory tract infections in both children and adults. Among children, both hospital admissions and infection were more common during periods of school attendance than during school holidays, a finding that is consistent with viral transmission in the school setting. Moreover, rhinovirus was the most common pathogen during all 4 peaks of viral infection and hospital admissions during the 1-year analysis period. However, the authors could not account for other possible confounding variables, such as allergen exposure, because those data were not available. It was stated that those factors could have been associated with hospital admissions.13 Of adults who presented to an urban emergency center for care of asthma exacerbations, more than 50% had a respiratory virus detected, with rhinoviruses being the most frequent virus identified.16

In addition to the epidemiological evidence, studies of experimental rhinovirus infection provide clinical evidence that these viral infections can worsen many features of asthma. Experimental rhinovirus 16 infection significantly reduced forced expiratory volume in 1 second in home recordings by patients with mild atopic asthma.17 The maximum reduction in forced expiratory volume in 1 second was observed 2 days after infection, and it correlated significantly with both the cold symptom score and the asthma symptom score.

Also, rhinovirus 16 potentiated airway inflammation after segmental antigen bronchoprovocation in allergic subjects, as reflected by higher histamine and tumor necrosis factor α levels in bronchoalveolar lavage fluid and greater eosinophil recruitment into the airways.18 It should be noted that in rhinovirus illness viral shedding occurs naturally for up to 21 days but predominantly for 3 to 4 days.

Bronchial mucosal biopsy specimens showed that submucosal CD3+ lymphocytes and epithelial eosinophils were significantly increased during experimental rhinovirus infection.19 The increase in airway inflammation correlated with an increase in histamine responsiveness. The numbers of lymphocytes in biopsy specimens declined during the subsequent convalescence period, but the increased number of eosinophils persisted in the airways of patients with asthma. These studies indicate that rhinovirus produces airway obstruction, promotes airway inflammation, and enhances airway hyperresponsiveness, all of which are clinical features of asthma. These changes are associated with an increased number of asthma symptoms.

Rhinovirus may produce lower airway dysfunction and trigger asthma exacerbations in 2 different ways, either directly by infecting the lower airways or indirectly by infecting the upper airways and stimulating inflammatory, immunologic, or neurogenic mechanisms that have an adverse impact on the lower airways (Figure). Rhinovi-
Potential mechanisms by which rhinovirus may trigger asthma exacerbations. IL indicates interleukin; ICAM-1, intercellular adhesion molecule 1.

Rhinovirus 16 has been detected in the columnar epithelial and basal cell layers of the lower airways after intranasal inoculation. Moreover, in situ hybridization for the replicative strand of the rhinovirus provided evidence of viral replication in the lower airways.

Rhinoviral infection of epithelial cells also leads to production of numerous proinflammatory cytokines and chemokines, including interleukin (IL)-1, IL-6, and IL-8, which correlate with the severity of respiratory symptoms during infection. These products promote further airway inflammation, but they may also cause other adverse effects in the lung. For example, expression of IL-1 in airway smooth muscle enhances contractile responses to bronchoprostaglandins and attenuates relaxation responses to bronchodilators.

As rhinovirus replicates in the respiratory mucosa, it elicits specific and nonspecific T-cell-dependent immune responses, with enhanced production of interferon γ and increased numbers of cytotoxic CD8+ T cells. These responses are directed at controlling the viral infection, but nonspecific T-cell activation would be expected to contribute to airway dysfunction in asthma patients. The balance of T helper cell types 1 and 2 is likely to be an important factor in regulating the immune response to rhinovirus, inasmuch as weak T helper cell type 1 responses were associated with more severe respiratory symptoms and longer periods of viral shedding. In asthma, the balance is shifted in favor of T helper cell type 2.

RHINOVIRUS INFECTION IN ACUTE RHINOSINUSITIS

Sinusitis is an inherent part of the common cold syndrome. Sinus abnormalities have been detected by computed tomography in approximately 87% of patients with a common cold. The computed tomographic study involved patients who presented within 2 to 4 days of naturally acquiring a common cold. Notably, these patients did not have a history of allergy, nasal polyps, or recurrent or chronic sinusitis. Sinus abnormalities were most frequently detected in the maxillary and ethmoid sinuses, but some patients also had abnormalities in the sphenoid and frontal sinuses. Occlusion of the infundibulum was also commonly seen. The sinus abnormalities were not associated with symptoms of acute sinusitis, and 80% resolved without antibiotic or symptomatic treatment.

In a magnetic resonance imaging study, ethmoid or antral sinus abnormalities were observed in 4 of 18 patients after experimental infection with rhinovirus. Two of 10 infected volunteers who had technically satisfactory, normal sinus magnetic resonance imaging findings before infection subsequently developed sinus abnormalities during the period of acute infection. Two additional subjects with technically unsatisfactory preinfection scans also developed sinus abnormalities during the acute infection. In 3 of these subjects, sinus mucosal thickening was evident, whereas in the fourth subject an air-fluid level was present. Notably, rhinorrhea scores and nasal secretion weight were significantly higher among the subjects with sinus abnormalities than among those who had normal magnetic resonance imaging findings.

Only a small proportion of cases of viral rhinosinusitis are complicated by bacterial infection (0.5% to 2%). These findings suggest a role of rhinoviruses in viral sinusitis, in particular because the common cold can be considered a “rhinosinusitis.” Most cases of bacterial sinusitis are believed to result from a viral infection. However, the role of rhinovirus in sinusitis has not been clear, owing to the difficulty of isolating the pathogen. The use of RT-PCR has clarified the role of rhinoviruses in sinusitis. In a study of 20 adults who had acute community-acquired sinusitis, rhinovirus was detected in 50% of patients by RT-PCR of maxillary sinus aspirates or nasal swabs, but it was detected in only 15% of patients when these specimens were cultured. Patients who had positive culture results all presented within 8 days of symptom onset, whereas most of the subjects who had positive RT-PCR findings but negative culture findings presented later. Although these observations show that rhinovirus is detectable in the sinus cavities of patients with acute sinusitis, it remains to be determined whether active viral replication occurs in the sinus mucosa.

There is evidence that personal behaviors during a cold can be responsible for a viral sinusitis. Gwaltney et al reported that the intranasal pressure created by nose blowing, sneezing, and coughing is great enough to propel nasal secretions into the sinuses. Because rhinoviruses are present in nasal secretions, nose blowing may be an important factor in in...
introducing rhinoviruses into the sinuses during colds.

ACUTE OTITIS MEDIA AND RHINOVIRUS INFECTION

Acute otitis media (AOM) is generally considered a bacterial disease; however, VRIs are an important factor predisposing individuals to AOM. Viruses are considered to play a role in the pathogenesis of AOM because the disease occurs concurrently with or just after a VRI.30 Viruses induce an inflammatory response that leads to mucociliary damage and dysfunction, impaired middle ear ventilation, and increased mucus and debris in the eustachian tube. These events lead to an invasion of the middle ear by viruses and bacteria. Once the pathogens reach the middle ear, another inflammatory cascade is initiated, leading to middle ear fluid accumulation (effusion), symptoms of AOM, and further opportunity for bacterial invasion.30 Acute otitis media with effusion can persist for weeks.

In a 1-year prospective study of 363 children with AOM, viruses were detected by culture of nasopharyngeal specimens in 42% of the patients.31 Rhinovirus (24%) and respiratory syncytial virus (13%) were the most common viruses associated with AOM, but their presence did not have a significant impact on the rate of recurrent otitis media or on the frequencies of adenoidectomy or insertion of tympanostomy tubes.

Pitkäranta et al32 found that rhinovirus was more prevalent in AOM when RT-PCR was used: overall, it was detected in 24% of middle-ear fluid specimens, in 30% of nasopharyngeal specimens, and in 35% of both types of specimens from children aged 3 months to 7 years. In their study, rhinovirus was detected in the middle ear fluid more often than respiratory syncytial virus (18%) or human coronavirus (8%). The presence of rhinovirus in middle ear fluid was somewhat more common in children older than 2 years (59%) than in younger children (41%); however, it did not substantially increase the risk of treatment failure, recurrence of otitis, or development of otitis with effusion.

Although AOM is less common in adults than in children, middle ear abnormalities are commonly seen during rhinoviral infections. Elkhatieh et al33 described a total of 91 subjects who had symptoms of nasal obstruction and a documented rhinovirus cold. More than 50% of their subjects developed major middle ear pressure abnormalities as assessed by digital tympanometry, whereas 75% had at least mild changes. The changes were especially evident after 2 to 3 days of infection. These abnormalities usually resolved by 2 weeks; however, in 1 patient with a history of middle ear infections during childhood, a major abnormality in middle ear pressure persisted in 1 ear at 4 weeks. Interestingly, middle ear pressure abnormalities were not clearly associated with complaints of earache or pressure or with the severity of the rhinoviral infection. Similarly, experimentally induced rhinovirus infection produced eustachian tube dysfunction and middle ear pressure abnormalities in adults that were detected within 2 days of infection and resolved within 2 weeks.34,35

Finally, and perhaps most importantly, the presence of virus in middle ear fluid of patients with AOM predisposes them to antibiotic failure. In a study of infants and children who had AOM associated with a viral-bacterial combination, antibiotic therapy failed to eradicate the bacteria in 30% of the cases. Notably, the presence of rhinovirus in middle ear fluid was associated with a significantly higher antibiotic failure rate (78%) than that associated with many other viruses, including respiratory syncytial virus (30%), enterovirus (17%), influenza virus (11%), and parainfluenza virus (10%).36 Similar findings have been reported in other studies.37,38

RHINOVIRUS INFECTION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Rhinoviruses have been implicated in 40% of acute infectious exacerbations in patients with chronic bronchitis.3 However, because of the difficulty in sampling, involvement of the lower respiratory tract by viruses has been difficult to prove.30 As with other complications of rhinovirus infection, identification and prevalence of viruses in studies of patients with chronic obstructive pulmonary disease (COPD) may have been underestimated because of limitations in sensitivity of available diagnostic technology and the methods used. More advanced techniques such as RT-PCR have clarified the role.

Greenberg et al40 reported on the role of VRI in elderly adults with and without COPD in a longitudinal cohort study conducted from September 1991 to April 1994. Their study defined the pathogenesis, frequency, and severity of illness and the use of medical care services. Picornaviruses were the most common viral pathogens identified, followed by parainfluenza viruses and coronaviruses; 75% of the picornaviruses were rhinoviruses. Rhinoviruses and coronaviruses were the cause of 35% of the virus infections in the control group and 43% of the virus infections in the group with COPD. Acute respiratory illness occurred more frequently in the subjects with moderate to severe COPD (3.0 acute respiratory illnesses per year) than in subjects with mild COPD (1.8 acute respiratory illnesses per year) or controls (1.3 acute respiratory illnesses per year) (P<.001).

The subjects with COPD had more nonvirus-identified illnesses than virus-identified illnesses. Subjects with moderate to severe COPD accessed medical care more frequently than control subjects or subjects with mild COPD. Fifty-eight percent of the total COPD cohort and 31% of control subjects had at least 1 office visit for their VRI (P<.001). Six percent of the total COPD cohort were seen in emergency centers (12% of subjects with moderate to severe COPD), and 19% were hospitalized (35% of subjects with moderate to severe COPD). No control subjects required emergency care or hospitalization. Despite a similar rate of yearly occurrence of respiratory infections, there was a 2-fold increase in acute respiratory tract illness among the sub-

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jects with COPD compared with the control group. The cohort with moderate to severe COPD used significantly more medical resources, as reflected in the number of clinician visits, emergency center visits, and hospitalizations.

**RHINOVIRUS INFECTION IN PATIENTS WITH CYSTIC FIBROSIS**

Among children with cystic fibrosis, picornaviruses were detected by RT-PCR in 43% of upper respiratory tract infections41; of these, 41% were further identified as rhinoviruses. Declines in pulmonary function were comparable in children with rhinovirus or other picornavirus infections as well as in those with nonpicornavirus infections. These findings suggest that many respiratory viruses can adversely affect pulmonary function in cystic fibrosis.

**RHINOVIRUS INFECTION IN THE ELDERLY**

The impact of rhinovirus infections in the elderly was evaluated in a prospective community-based surveillance study conducted in England.42 Rhinovirus was identified as a cause of 107 respiratory tract infections in 96 people aged 60 to 90 years. The consequences of rhinovirus infection were significant. Nearly one fifth of the patients were confined to bed, and 26% were unable to perform routine household activities. The majority (63%) of patients had lower respiratory tract syndromes. The median duration of illness was 16 days overall, but it was 19 days among those with lower respiratory tract illness. The risk of lower respiratory tract illness was 40% higher among patients with chronic medical conditions and 47% higher among those who smoked. One patient died of COPD that was exacerbated by the rhinovirus infection.

**RHINOVIRUS INFECTION IN THE IMMUNOCOMPROMISED**

Among high-risk patients with cancer, rhinovirus infections are often fatal. In a study of 22 immunocompromised blood and marrow transplant recipients who were hospitalized with rhinovirus infections, 7 (32%) developed fatal pneumonia.43 The remaining patients had infections confined to the upper respiratory tract. In 6 of the 7 fatal cases, rhinovirus had been isolated in bronchoalveolar lavage fluid or an endotracheal aspirate before death.

In another study, rhinovirus was responsible for 25% of community-acquired VRIs among bone marrow transplant recipients.44 The investigators found that pneumonia occurred much more commonly among patients infected with respiratory syncytial virus or parainfluenza than among those with rhinovirus.

Nevertheless, these studies show that rhinovirus infections cause considerable pulmonary morbidity and mortality in high-risk patients with cancer.

**DIAGNOSIS AND TREATMENT**

**Diagnosis**

The specific diagnosis of rhinovirus infections has traditionally been made by virus isolation from appropriate patient specimens, using culture methods.3 In practice, however, rhinovirus culture requires several days and cannot yield results during the acute phase of the infection. Serologic testing is impractical, given the numerous rhinoviral or enteroviral genome, and accordingly they are capable of identifying most serotypes. One microarray-based colorimetric RT-PCR enterovirus kit can provide results in 5 hours.45 However, these assays use probes directed to conserved regions of the rhinoviral or enteroviral genome, and accordingly they are capable of identifying most serotypes. One microwell-based colorimetric RTPCR enterovirus kit can provide results in 5 hours.45 However, these assays are limited to the research setting; they are not available commercially. Therefore, the diagnosis is usually made clinically, based on signs and symptoms.

Rhinorrhea, nasal congestion, and sore or scratchy throat are very common symptoms. Arruda et al46 found that sore throat, nasal congestion, and rhinorrhea were the first symptoms noticed. The most bothersome symptoms were runny nose, stuffy nose, sore throat, and malaise. Coughing, sneezing, hoarseness, facial pressure, ear fullness, and headache are also typical symptoms. Less often, malaise, chills, and low-grade fever may occur.1 The median duration of rhinovirus colds is 1 week, but up to 25% last more than 2 weeks.1 Arruda and coworkers47 found that colds in rhinovirus-positive patients lasted 9.5 to 11 days and that symptom severity was highest on presentation and declined over the study period.

**Treatment**

**Symptomatic.** The use of over-the-counter symptomatic treatments can reduce symptoms in some patients. Antihistamines and nonsteroidal anti-inflammatory drugs may relieve some symptoms, but they do not shorten the duration of illness.48 The sedative effects of these drugs may limit their use in some patients and may worsen blood pressure control in patients with hypertension.49 Other medications have been reported to be beneficial in hastening recovery from the common cold, but review of controlled trials has failed to provide incontrovertible evidence of benefit. These other medications include zinc lozenges, echinacea, and high-dose vitamin C.60-62 Nasal administration of buffered saline solution may give some temporary local relief.

**Antiviral Agents.** No antiviral drugs are currently approved for clinical use in picornaviral infections. Intra-nasal interferon alfa therapy was shown to be protective in early prophylactic trials, but it was not pursued for clinical use because of its local adverse effects.51-53 Antipicornaviral drugs have been developed that work at specific steps in the replication cycle. Soluble ICAM-1 works at the site of viral attachment and receptor binding, and it has in vitro activity against the major rhinovirus serotypes (>90%). In early studies, intravenously administered recombinant soluble ICAM-1 (tremacamra) appeared to reduce the severity of symptoms in patients with experimental rhinovirus colds. However, the compound has not been tested further.54
Human rhinovirus 3C protease inhibitors, such as AG7088, represent an alternative approach for rhinovirus infections because of their potent antiviral activity against rhinoviruses and enteroviruses. Although studies have shown that AG7088 did not prevent experimental rhinovirus infection, it modestly reduced illness severity when treatment was initiated before or within 1 day of infection, with administration 5 times per day. The most common drug-related adverse events (nausea and taste disturbance) were mild. Currently, the intranasal compound is being reformulated to optimize delivery of the active ingredient to the nasal cavity.

Capsid-function inhibitors bind to a hydrophobic pocket in VP4 at the site of viral attachment and uncoating, thereby inhibiting viral replication. Clinical trials have been conducted on one of these drugs, pleconaril.

Pleconaril was studied in an experimental challenge model using coxsackievirus A21 in normal adults. Pleconaril (200 mg) or placebo was administered twice a day for 7 days to 33 subjects infected with a safety-tested strain of coxsackievirus A21. The inoculation was done 14 hours after administration of the first dose of study treatment. Compared with placebo, pleconaril significantly reduced viral shedding in nasal secretion (P<.001), nasal mucus production (P=.004), and total respiratory illness (P=.02) scores.

In 2 randomized, double-blind, placebo-controlled studies of 2096 patients with self-diagnosed colds for 24 hours or less, pleconaril (400 mg twice a day) was compared with placebo. Time to alleviation of cold was reduced 1 day in the pleconaril group. A significant reduction from baseline symptom scores was observed by day 2. Adverse events profiles were similar. Pooled analysis of 2 pivotal trials showed that compared with placebo-treated patients, picornavirus-positive patients treated with 400 mg of pleconaril twice a day had a 1.5-day reduction in time to complete resolution of rhinorrhea, with all other symptoms absent or mild for 48 hours (median, 6.2 days for pleconaril vs 7.7 days for placebo; P=.001). Because of safety concerns centered on potential drug-drug interactions, the Food and Drug Administration did not approve pleconaril for use in treating the common cold. New formulations are being considered for clinical studies.

CONCLUSIONS

Viral respiratory infections caused by picornaviruses can have significant consequences in both children and adults, producing exacerbations of asthma and other pulmonary disorders as well as various respiratory tract abnormalities. New antiviral agents that have activity against rhinoviruses have been developed based on current understanding of virus replication and assembly. Antiviral therapy that is specifically targeted to rhinovirus infection and shortens the clinical course of picornavirus infections should reduce the likelihood of serious sequelae. Because of the need to reduce the morbidity and mortality associated with VRI, treatment studies should be performed in groups of high-risk patients, such as those who have asthma or are immunosuppressed.

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