# Rhinovirus and Coronavirus Infections

**Stephen B. Greenberg, M.D.**[1]

## ABSTRACT

Rhinoviruses and coronaviruses cause the majority of common colds and play a part in more serious respiratory illnesses that lead to increased morbidity and mortality. Patients who are infants or elderly, have asthma or chronic obstructive pulmonary disease (COPD), or are immunosuppressed have increased frequency of rhinovirus-related respiratory complications. Newer diagnostic tests such as reverse transcriptase polymerase chain reaction (RT-PCR) have greatly expanded our understanding of the importance of these respiratory viruses. Although there are no currently approved antiviral agents for clinical use, our increased understanding of the virus–host interaction should lead to new intervention strategies.

**KEYWORDS:** Rhinovirus, coronavirus, asthma, COPD, otitis media, sinusitis

Rhinoviruses and coronaviruses cause more than 50% of all common colds.[1–3] Clinically, the common cold includes rhinitis and pharyngitis, as well as sneezing, hoarseness, and cough.[4,5] Although self-limited in healthy people, the illness is associated with complications in individuals who suffer from heart or lung disease or who are immunosuppressed.[6–11] In infants and young children, rhinoviruses and coronaviruses are associated with many cases of otitis media and sinusitis.[12,13] Diagnostic tests have increased the percentage of respiratory illnesses attributable to these viruses. New studies have provided better understanding of the pathogenesis of these infections and should lead to more specific treatment modalities. However, as yet, there are no approved antiviral agents for rhinovirus or coronavirus infections. This review highlights recent advances in our knowledge of these two virus groups and their importance in respiratory viral infections.

## VIROLOGY

### Rhinoviruses

Rhinoviruses are members of the Picornaviridae family (Table 1). These small, positive-sense, single-stranded ribonucleic acid (RNA) viruses have icosahedral symmetry. The capsid is composed of four proteins. Proteins VP1, VP2, and VP3 are on the surface of the viral capsid. Variations in these surface proteins are responsible for antigenic diversity and the host immune response following infection.[14] VP4 is on the inside of the virus and anchors the RNA core to the viral capsid.

There are more than 100 serotypes of rhinoviruses. Over 90% of these serotypes attach to cells by the intercellular adhesion molecule 1 (ICAM-1).[15] A small number of serotypes use the low-density lipoprotein receptor for attachment and entry into cells.[16] One serotype, HRV-87, requires the presence of sialic acid

[1]Department of Medicine, Baylor College of Medicine, Houston, Texas.

Address for correspondence and reprint requests: Stephen B. Greenberg, M.D., Department of Medicine, Baylor College of Medicine, One Baylor Plaza, 523D, Houston, TX 77030 (e-mail: stepheng@bcm.edu).

Respiratory Viral Infections; Guest Editor, Edward E. Walsh, M.D.
Semin Respir Crit Care Med 2007;28:182–192. 
DOI 10.1055/s-2007-976490. ISSN 1069-3424.

**Table 1 Rhinoviruses and Coronaviruses: Virology and Pathogenesis**

| Virology | Rhinoviruses | Coronaviruses |
|---|---|---|
| Family | Picornaviridae | Coronaviridae |
| Type of RNA | +RNA | +RNA |
| Lipid envelope | No | Yes |
| Capsid symmetry | Icosahedral | Helical |
| Genome size (Kb) | ~8 | ~30 |
| Pathogenesis | 91 serotypes with ICAM-1 as specific receptor 10 serotypes use low-density lipoprotein receptor | 229E and OC-43 infect ciliated epithelial cells |

ICAM, intercellular adhesion molecule; RNA, ribonucleic acid.

on cellular receptors, unlike the major and minor group serotypes.[17]

### Coronaviruses

Coronaviruses are positive, single-stranded RNA viruses that replicate in the cytoplasm and bud into cytoplasmic vesicles from the endoplasmic reticulum (Table 1). Coronaviruses are divided into three genera: group I includes both human (HCoV-229E) and animal pathogens; group II includes both human (HCoV-OC43) and animal pathogens; and group III includes only avian pathogens. CD13 (Human aminopeptidase N) is the cellular receptor for most group I coronaviruses, including HCoV-229E.[18] Recent studies have shown that the newly reported group I coronavirus HCoV-NL63 does not use CD13 as the receptor cell entry.[19] HCoV-NL63, along with SARS-CoV, uses angiotensin-converting enzyme 2 (ACE2) as the entry receptor. ACE2 is found on the ciliated nasal and tracheobronchial epithelial cells.[20] The receptor for HCoV-OC43 is not known. Carcinoembryonic antigen (CEA) is the receptor for mouse hepatitis virus, a group II coronavirus.[21] Group III coronaviruses contain avian infectious bronchitis virus.[22] Phylogenetic relationships between coronaviruses have been based on deduced amino acid sequences of the coronavirus replicase *ORF1b* gene (see Fig. 1).[23]

## PATHOGENESIS

### Rhinoviruses

The pathogenesis of rhinovirus infections is through infection of the upper respiratory tract where minimal epithelial cell damage has been noted.[24] After deposition of rhinovirus in the eye or nose, there is attachment to host cell epithelium via virus-specific receptors. Infection of nasal epithelial cells results in increased neutrophils detectable in the nasal mucosa and secretions.[25] Inflammatory mediators, including kinins, leukotrienes, interleukin (IL)-1, IL-6, IL-8,

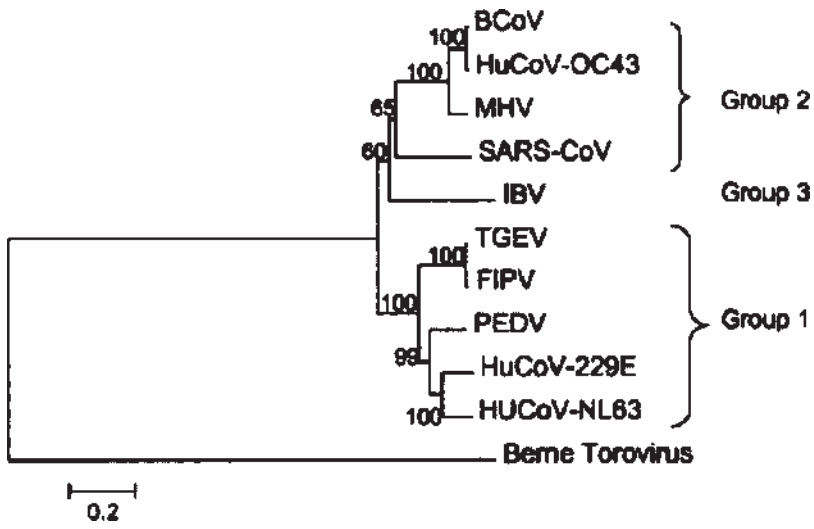


**Figure 1** Phylogenetic tree based on deduced amino acid sequence of the coronavirus replicase ORF1b gene for bovine coronavirus (BCoV), human coronavirus 22E (HuCoV-OC43), mouse hepatitis virus (MHV), severe acute respiratory syndrome coronavirus (SARS-CoV), infectious bronchitis virus (IBV), transmissible gastroenteritis virus (TGEV), feline infectious peritonitis virus (FIPV), porcine epidemic diarrhea virus (PEDV), human coronavirus 229E (HuCoV-229E), human coronavirus NL63 (HuCoV-NL63) and Berne Torovirus (used as an outgroup). Reprinted with permission from Haagmans, Osterhaus.[23]

tumor necrosis factor-α (TNF-α) and RANTES (regulated upon activation normal T cell expressed and secreted), are released following rhinovirus infection and are partially responsible for the common respiratory symptoms.[26–28]

### Coronaviruses

Coronaviruses attach to cellular receptors by the spike proteins on their surface.[20] Internalization into host cells occurs by direct fusion with the plasma membrane or by endocytosis. Posttranslational proteolytic processes are important regulatory mechanisms. Polyproteins are cleaved by viral proteases, facilitating assembly of subunit protein complexes that are responsible for replication and transcription.[29,30] There is little information on the host response to coronavirus replication. Humoral immune responses are detectable following natural infection, but the role of cell-mediated immunity is largely unknown.[31,32]

## EPIDEMIOLOGY

### Rhinoviruses

Rhinoviruses cause respiratory illnesses throughout the world in all age groups and throughout the year (Table 2). However, rhinoviruses are most prevalent in the fall and spring in temperate climates.[33] In a study using polymerase chain reaction (PCR) techniques, rhinoviruses accounted for 50% of common colds in one prospective study.[34] They infect children in early childhood and into adulthood. As a frequent cause of the common cold, these viruses are responsible for millions of lost work days, school absenteeism, and physician visits. Most rhinovirus infections are symptomatic. Upper respiratory tract infections caused by respiratory viruses such as rhinoviruses are a frequent reason for inappropriate antibiotic use.[35]

**Table 2 Epidemiology of Rhinovirus and Coronavirus Illness**

| | Rhinoviruses | Coronaviruses* |
|---|---|---|
| "Common cold" illnesses | 25–50% | 7–30% |
| Worldwide distribution | + | + |
| Acquisition in childhood | + | + |
| Spread | Direct contact, hand-to-hand contact, or aerosol | Droplets |
| Prevalence | Peak in early fall and spring | Late fall, winter, and early spring |

*Not including severe acute respiratory syndrome coronavirus (SARS-CoV).

The home is the principal location for transmission of rhinovirus.[36] School-aged children are frequently the introducer of the infection. Secondary attack rates range from 25 to 70%. Day care centers and schools are important locations for the spread of rhinovirus. Transmission of rhinoviruses can occur by close contact, autoinoculation, fomites, or aerosols.

### Coronaviruses

Coronaviruses were detected as agents of respiratory infections ~40 years ago.[37,38] They were later identified as coronaviruses, labeled OC43 and 229E, and accepted as a new genus in 1975.[39] In epidemiological studies in adults, coronaviruses were estimated to cause ~15% of adult common colds.[40] Coronaviruses were found to cause epidemics every 2 to 3 years, with reinfections being common.[41] All ages are susceptible. From epidemiological studies, coronaviruses were found associated with respiratory illnesses, usually in the upper respiratory tract, but occasionally causing pneumonia. In temperate climates, HCoV-OC43 and HCoV-229E are transmitted primarily during the winter. They have been linked to asthma and COPD exacerbations in children and adults, respectively.[42,43] The elderly are also prone to these infections in day care and as cause for hospitalization.[44,45]

Besides HCoV-OC43 and HCoV-229E, other coronavirus strains have been recently identified. A new coronavirus causing severe acute respiratory syndrome (SARS) was reported in 2003. It was different from known human and animal coronaviruses by DNA sequencing.[46] This new coronavirus was cultured from Himalayan palm civets, but it is now thought that bats are the primary reservoir. SARS infected over 8000 people resulting in over 700 deaths. The SARS agent is reviewed by Drs. Muller and McGeer elsewhere in this issue.

In 2004 and 2005, three closely related coronavirus species were reported.[47–49] NL63 was isolated from a 7-month-old girl with coryza, conjunctivitis, fever, and bronchiolitis.[47] Sequencing the entire genome enabled these investigators to place this virus in the group I coronaviruses. After screening over 600 previously collected respiratory specimens, seven individuals were positive for HCoV-NL63. Four additional respiratory specimens obtained between 2000 and 2002 were positive for HCoV-NL63. From other additional epidemiological studies, patients with HCoV-NL63 have ranged in age from 1 month to 100 years, with the highest infection rate occurring before age 5 years. Using molecular probes that targeted conserved regions of the coronavirus genome, a related coronavirus (HCoV-NH) was found in 79 of 895 young children tested by RT-PCR on respiratory specimens.[49]

**Table 3 Diagnostic Tests for Rhinoviruses and Coronaviruses**

| Rhinoviruses | Coronaviruses |
|---|---|
| 1. Cell culture isolation: routine | 1. Organ-culture isolation*; not readily available |
| 2. Polymerase chain reaction: sensitive; not readily available | 2. Polymerase chain reaction: sensitive; not readily available |
| 3. Serum antibody tests are type specific but not readily available | 3. Serum antibody tests are not readily available |

*Severe acute respiratory syndrome coronavirus (SARS-CoV) grows in African green monkey kidney (Vero E6) cells.

A newly identified group II human coronavirus, HCoV-HKU1, was found in a respiratory specimen of a 71-year-old Chinese man with fever and cough.[50] This HCoV-HKU1 coronavirus was genetically distinct from OC43 and could not be propagated in cell culture.

In a prospective study in Hong Kong, coronaviruses were detected in 2.1% of patients admitted to the hospital with signs and symptoms of acute respiratory illness. Of the 87 infected patients, 13 were positive for HCoV-HKU1, 17 were positive for HCoV-NL63, 53 were positive for HCoV-OC43, and four were positive for 229E. HCoV-HKU1 and HCoV-OC43 peaked in the winter months. Upper respiratory tract illness was the most common presentation for HCoV-HKU1 infections. HCoV-NL63 infections occurred in early summer and fall but not in the winter.[51]

In a recent prospective study of respiratory viral infections among hospitalized patients, 5.7% had coronaviruses identified.[52] The 47 coronavirus infections represent 10.5% of all the respiratory viral infections. In 14 patients, coronaviruses were associated with another respiratory virus. Lower respiratory tract infections (bronchitis, bronchiolitis, pneumonia) were far more common than upper respiratory tract (rhinitis, pharyngitis, laryngitis), 75% versus 25%, respectively. Over half of the infections were due to OC43-like strains. Approximately 20% were due to 229E-like strains and ~20% were due to NL63 strains. Three patients were infected by untypeable coronaviruses. Coronavirus infections in the first year of life were associated predominantly with OC43-like strains. Coinfections with human coronavirus appear to be associated with severe lower respiratory tract illnesses.

HCoV was identified in 5.4% of specimens from 279 hospitalized adult patients with lower respiratory tract infections.[53] The most frequently identified isolates were HCoV-OC43 in 12, followed by HCoV-229E in seven, HCoV-NL63 in six, and HCoV-HKU1 in four specimens. Many patients had high-risk underlying conditions.

A recent study has provided evidence for genetic variability in OC43 strains.[54] The complete nucleotide sequence of two contemporary OC43 strains compared with the prototype strain (ATCC VR 759) demonstrated important amino acid substitutions in the potential cleavage site sequence of the spike protein.

## DIAGNOSIS

Standard tissue culture methods for isolation are useful for detecting rhinoviruses but are insensitive for coronaviruses (Table 3). Rhinoviruses can be differentiated from other picornaviruses, such as enteroviruses because of their acid lability. Coronaviruses require special cell lines or organ culture for detection by cultivation methods.[39] These cell or organ culture techniques are labor intensive, time consuming, and relatively insensitive.

With the development of PCR techniques, the ability to detect respiratory viruses has improved. Detection of rhinovirus in respiratory specimens was enhanced by reverse transcriptase PCR (RT-PCR), involving the use of hybridization probes or double-stranded DNA-binding dye. Dagher et al reported significant increases in sensitivity for the detection of rhinovirus in nasal aspirates compared with conventional PCR.[55] Several other studies have found increased sensitivity of RT-PCR compared with viral culture techniques.[56–60] Coronaviruses have also been detected by RT-PCR with greater sensitivity than standard culture techniques.[61]

Antibody assays are reported for both rhinoviruses and coronaviruses but are not readily available or helpful clinically. Because there is no common antigen for rhinoviruses, serotype-specific neutralizing antibody assays are necessary to detect rises in serum antibodies following acute infections, and the large number of rhinovirus serotypes makes this approach impractical. Complement-fixing assays and enzyme-linked immunosorbent assay (ELISA) for coronaviruses 229E and OC43 have been published but are not available in clinical laboratories.[32,62] Therefore, serologic tests for antibody specific responses are mainly reserved for research or epidemiological studies.[63]

## INFECTIONS IN PATIENTS WITH ASTHMA

Asthma exacerbations in children and adults are frequently associated with respiratory virus infections, especially rhinoviruses and coronaviruses.[64–66] Wark et al found viruses in sputum of 76% of admitted adults with asthma exacerbation.[67] Severity of the exacerbation was associated with elevated LDH (lactic dehydrogenase) levels. Corne et al recently found that naturally occurring rhinovirus infections led to more severe and longer-lasting lower respiratory tract symptoms and changes in peak flow rate in asthmatic versus normal subjects.[68]

Experimental rhinovirus 16 (RV16) infection in volunteers with mild atopic asthma led to significantly reduced forced expiratory volume in 1 second ($FEV_1$) in home recordings.[69] In allergic subjects, RV16 infection potentiated airway inflammation after bronchoprovocation.[70] During other experimental rhinovirus infections, significant increases in submucosal CD3+ lymphocytes and eosinophils were detected in bronchial mucosal biopsies.[71] These studies have shown that airway obstruction, airway inflammation, and airway responsiveness are induced following rhinovirus infections in asthmatic subjects.

Lower airway dysfunction following rhinovirus infection can be triggered by direct infection of the lower airway or by stimulating inflammatory, immunologic, or neurogenic mechanisms in the upper airway and thereby impacting the lower airways. Papadopoulos et al have detected rhinovirus in the columnar and basal cell layers of the lower airways following intranasal inoculation.[72] In situ hybridization studies demonstrated the replicative strand of rhinovirus in the lower airways.[73]

Experimental rhinovirus infections in asthmatic subjects have demonstrated (1) long-lasting airway narrowing; (2) sputum markers of eosinophil activation, IL-8, and neutrophils; (3) bronchial infiltration with eosinophils, CD4 cells, CD8 cells; (4) activation of prostaglandin and leukotriene pathways; and (5) induction of nitric oxide.[74–80] Recently, innate immune responses were found to be defective in bronchial epithelial cells obtained from asthmatic subjects. Following RV16 infections, asthmatic bronchial epithelial cells were found to have impaired production of interferon and apoptosis, leading to increased rhinovirus replication.[77] There is also evidence of impaired acquired immune responses in asthmatic patients. Impaired Th1 responses to rhinovirus were found in peripheral blood mononuclear cells as reflected in significantly lower levels of interferon (IFN)-α and IL-12 and higher levels of IL-10 from asthmatic patients compared with normal healthy volunteers.[81]

Several recent studies have reported deficient induction of IFN-λ by rhinovirus in bronchial epithelial cells for asthmatic patients.[76] Recently, type III IFNs, IFN-λ1 and IIFN-λ2/3, have been discovered with many similarities to type I IFNs.[82] Contoli et al has found that IFN-λs are induced by rhinovirus infection of human bronchial epithelial cells, monocytes, and macrophages.[83] Induction of IFN-λ1 and IFN-λ2/3 messenger RNAs (mRNAs) was significantly reduced in asthmatic compared with normal subjects. Bronchoalveolar cells in asthma patients were deficient in IFN-λ after rhinovirus was added. These studies support the view that innate immune responses in asthmatic subjects have deficiencies in two IFN families, in several lung cell types, and in response to rhinovirus infection.

## INFECTIONS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS

Multiple longitudinal studies have documented the importance of respiratory viral infections in acute exacerbations of chronic bronchitis.[7,84] Early studies reported on the role of rhinoviruses in COPD exacerbations.[85] In a more recent longitudinal study of both COPD patients and normal controls, 27% of acute respiratory illnesses were associated with respiratory viruses.[7] Rhinoviruses accounted for 43% of the viral infections. In an updated study using PCR techniques, additional rhinovirus or coronavirus infections were demonstrated.[61] There was no evidence of more frequent viral infections in the COPD group compared with control subjects, but use of medical care including hospitalization was only observed in the COPD patients. Acute respiratory illness occurred more frequently in COPD patients with moderate to severe COPD ($FEV_1 < 50\%$ of predicted) than in COPD patients with mild COPD ($FEV_1 > 50\%$ and $< 70\%$ of predicted), 3.0 versus 1.8 respiratory illnesses per year, respectively.[7]

Other recent studies using PCR techniques for respiratory virus detection have also found $> 40\%$ of COPD exacerbations associated with respiratory viruses, especially rhinoviruses. Seemungal et al found 58% of the virus-associated exacerbations to be due to rhinoviruses, and 11% were due to coronaviruses.[84] Rohde et al also found that rhinoviruses were the most common virus detected in virus-associated exacerbations in a cohort of COPD patients.[86]

There are several possible mechanisms of rhinovirus-induced exacerbations in COPD patients. This may reflect the role of receptor upregulation, new sites for viral infections, or the role of inflammatory mediators. Upregulation of ICAM-1 in the bronchial mucosa of patients with COPD has been reported in one study.[84] Rhinoviruses have also been recovered from the lower airways.[85] Inflammatory mediators, especially IL-8, have been found in increased levels from respiratory secretions obtained from stable COPD patients.[87]

The role of bacteria in COPD exacerbations is complex and the interaction between bacterial and viral infection of the respiratory tract is not well understood.[88] Evidence has demonstrated an increase in *Staphylococcus aureus* and *Streptococcus pneumoniae* adherence to respiratory epithelial cells infected with rhinovirus.[89,90] In a recent in vitro study using primary differentiated human cell culture lines, a strain of nontypeable *Haemophilus influenzae* was found to potentiate airway epithelial cell responses to rhinovirus by increasing ICAM-1 and TLR3 (toll-like receptor 3) expression.[91] However, it remains to be determined whether the interaction of respiratory virus with bacterial pathogens is a common cause of exacerbations or whether respiratory viruses, such as rhinovirus and coronavirus, cause these pulmonary complications alone.

## RHINOVIRUS AND CORONAVIRUS IN ACUTE OTITIS MEDIA

Viral respiratory infections are important cofactors in predisposing children to acute otitis media (AOM).[92,93] Viruses, especially rhinoviruses, result in an inflammatory reaction that results in mucociliary damage, impaired middle ear ventilation, and increased mucus in the eustachian tube. This leads to superinfection of the middle ear by bacteria and fluid accumulation (effusion). Chantzi et al detected rhinoviruses in 40% of children with otitis media with effusion.[94] Rhinoviruses were cultured in 24% of nasopharyngeal specimens. Pitkäranta et al detected rhinovirus by RT-PCR in 24% of middle ear fluid specimens and 30% of nasopharyngeal specimens.[95] In the same study, coronaviruses were found in 8% of middle ear fluid specimens. In a recently reported prospective study of 121 otitis-prone children, nasopharyngeal swabs were assayed by PCR for respiratory viruses and by culture for bacterial pathogens.[95] Rhinovirus was found at baseline in 30% of specimens. Positive PCR tests for rhinovirus correlated with culturing *Moraxella catarrhalis* and *S. pneumoniae* but not nontypeable *Hemophilus influenzae*. Rhinoviruses and bacterial pathogens were found in otitis-prone children, even in the absence of clinical symptoms. Using in situ hybridization of adenoid tissue removed from 56 children with histories of recurrent otitis media or adenoid hypertrophy, rhinovirus RNA was detected in 45% of specimens.[96]

Middle ear abnormalities are commonly observed with rhinovirus infections. In 91 subjects with documented rhinovirus colds, major middle ear pressure abnormalities were found in 50%.[97] The middle ear pressure changes were not associated with earache or severity of rhinovirus infection. Similar eustachian tube abnormalities were observed within 2 days of experimentally induced rhinovirus infection and resolved within 2 weeks.[98]

The presence of rhinovirus in middle ear fluid was associated with an antibiotic failure rate in 78% of AOM cases.[99,100]

## RHINOVIRUS INFECTIONS IN RHINOSINUSITIS

Most patients with the common cold syndrome have sinus abnormalities detectable by computed tomography.[101,102] Abnormalities were most frequently detected in the maxillary and ethmoid sinuses and resolved without antibiotics in 80% of patients followed over several weeks.

Less than 20% of cases of viral rhinosinusitis are complicated by bacteria infection.[103] However, most cases of bacterial sinusitis are thought to complete a preceding viral infection. In a study of 20 adults with acute rhinosinusitis, 15% had virus cultures positive for rhinovirus, but 50% were positive using RT-PCR on maxillary sinus aspirates or nasal swabs.[104] Intranasal pressure increases following nose blowing, sneezing, and coughing. This increased pressure is high enough to propel virus-infected nasal secretions into the sinuses.[105] However, it is unclear from these studies whether virus replication occurs in the sinus mucosa.

## RHINOVIRUS INFECTION IN PATIENTS WITH CYSTIC FIBROSIS

There have been a few studies examining the role of respiratory viral infections in cystic fibrosis patients. Collinson et al detected picornavirus in over 40% of upper respiratory tract infections in children with underlying cystic fibrosis.[106] There was no difference in pulmonary function in those children with proven rhinovirus infection versus other respiratory viruses. Smyth et al followed 108 patients with cystic fibrosis for 1 year and detected rhinovirus in 16% of exacerbations. Those patients with proven rhinovirus infection did not show deterioration in clinical activity but did receive more days of intravenous antibiotics.[107]

## RHINOVIRUS INFECTIONS IN IMMUNOCOMPROMISED HOSTS

Respiratory virus infections are common causes of acute respiratory illness in patients after solid organ transplantation or following bone marrow transplantation.[108–113] In these immunocompromised patients, rhinovirus was the number one detected respiratory virus by PCR assays. Ghosh et al reported on seven of 22 hematopoietic stem cell transplant (HSCT) recipients who developed fatal pneumonia attributable to rhinovirus infection.[114] Ison et al found an 83% (5/6) fatality rate in HSCT patients with bronchoalveolar lavage (BAL) positive samples for rhinovirus.[111] For a complete discussion of respiratory virus infections in immunocompromised hosts, see the article in this issue by Kim, Boeckh, and Englund.

## TREATMENT OF RHINOVIRUS AND CORONAVIRUS UPPER RESPIRATORY INFECTIONS

Because there are currently no approved antiviral medications for rhinovirus or coronavirus respiratory tract infections, symptomatic treatment should be considered.[115] Anticholinergic medications, such as ipratroprium or antihistamines could be used for the commonly reported symptom, rhinorrhea. Anticholinergic nasal sprays have been reported to reduce rhinorrhea by ~30%. Nasal congestion can be alleviated by nasal and systemic decongestants. Several studies

have suggested that heated, humidified steam may reduce nasal congestion in common colds, but the data are not conclusive.[116] Cough is a common accompanying problem in respiratory viral infections and can be suppressed with nonprescription cough suppressants. Other symptoms such as sore throat, myalgias, fever, or headache can be controlled with nonsteroidal antiinflammatory drugs. Antibiotics are inappropriate for treating viral infections, although they are frequently prescribed by physicians.[117]

Using our understanding of the cellular changes following rhinovirus infection and replication, several antiviral agents and treatment strategies have been tested.[118] Compounds targeting cell susceptibility, virus attachment, receptor blockage, virus uncoating, RNA replication, and viral protein synthesis have been evaluated. Although several agents have demonstrated both in vitro and in vivo success, none has received Food and Drug Administration (FDA) approval because of poor bioavailability, side-effect profile, or limited potency.

Intranasal IFN-α2 had significant antiviral and anti-illness effect in several volunteer challenge studies.[119,120] However, local side-effects limited its use when tested in natural rhinoviral infections.[121–123] One volunteer study with IFN-α given prior to coronavirus challenge did demonstrate an antiviral and anti-illness effect.[124] ICAM-1 blockage has been tried using soluble ICAM-1 in volunteers, and inhibition of ICAM-1 upregulation by clarithromycin or proton pump inhibitors has been demonstrated in vitro.[125,126]

Viral capsid-binding compounds, such as pleconaril, block virus uncoating in vitro.[127] Clinical trials demonstrated significant reduction in duration of respiratory symptoms in individuals receiving pleconaril for naturally occurring colds, but the drug was not approved because of pregnancy in women on oral contraceptives. Enviroxime inhibited the 3A-coding region of picornavirus RNA in vitro, but clinical trials revealed intolerance to oral dosing.[63] Several low molecular weight compounds inhibit the 3C protease, which is essential for viral replication and assembly.[128] In volunteer trials, a 3C-protease inhibitor, ruprintrivir was found to reduce virus shedding but was associated with blood-tinged mucus and irritation of the nasal passages.[129]

Alternative medications, such as *Echinacea angustifolia* or zinc lozenges, have been tested in several volunteer trials but are not currently thought to be clinically effective.[130–132] A recent study in children with "common cold" reported to show shorter mean duration of symptoms in those taking zinc sulfate compared with placebo.[133] All of these studies suffer from poor control groups or incomplete virology. However, most reports show few side-effects from taking alternative therapies.

## PREVENTION

Spread of rhinovirus from the respiratory tract to susceptible individuals may occur by aerosol or directly by contact spread or fomites.[134] Rhinovirus can be recovered from the hands of ~40% of adults with colds. Hand-to-hand transmission of rhinovirus has led to evaluation of disinfectants that will eliminate virus on human skin and that are thought to be clinically nontoxic. A study using 2% aqueous iodine decreased transmission in family members who were exposed to rhinovirus-infected individuals. A recent in vivo evaluation of virucidal hand treatments has confirmed the prevention of rhinovirus infections by organic acids but not ethanol.[135] Several of the tested organic acids were found in commercially dispensed hand lotions and could prove to be clinically useful if proven to be effective when used under natural conditions.

## SUMMARY

Newer, more sensitive diagnostic tests such as PCR have given us a greater appreciation of the role rhinoviruses and coronaviruses play in respiratory illnesses, especially in patients with underlying lung disease or with immunocompromised host responses. Recent studies have demonstrated newer strains of coronaviruses causing respiratory infections. Although there are no approved antiviral agents for these respiratory viruses, our current understanding of the pathogenesis of these infections should motivate us to develop specific antiviral agents that could be used to treat these specific viruses. It is unlikely that vaccines will be forthcoming for rhinoviruses because of the numerous prevalent serotypes.

## REFERENCES

1. Greenberg SB. Respiratory consequences of rhinovirus infection. Arch Intern Med 2003;163:278–284
2. Wat D. The common cold: a review of the literature. Eur J Intern Med 2004;15:79–88
3. Larson HE, Reed SE, Tyrrell DA. Isolation of rhinoviruses and coronaviruses from 38 colds in adults. J Med Virol 1980;5:221–229
4. Gwaltney JM Jr, Winther B, Patrie JT, Hendley JO. Combined antiviral-antimediator treatment for the common cold. J Infect Dis 2002;186:147–154
5. Gwaltney JM Jr, Phillips CD, Miller RD, Riker DK. Computed tomographic study of the common cold. N Engl J Med 1994;330:25–30
6. Whimbey E, Champlin RE, Couch RB, et al. Community respiratory virus infections among hospitalized adult bone marrow transplant recipients. Clin Infect Dis 1996;22:778–782
7. Greenberg SB, Allen M, Wilson J, Atmar RL. Respiratory viral infections in adults with and without chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000;162:167–173

8. El-Sahly HM, Atmar RL, Glezen WP, Greenberg SB. Spectrum of clinical illness in hospitalized patients with "common cold" virus infections. Clin Infect Dis 2000; 31:96–100
9. Wedzicha JA. Role of viruses in exacerbations of chronic obstructive pulmonary disease. Proc Am Thorac Soc 2004; 1:115–120
10. 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;310:1225–1229
11. Hiatt PW, Grace SC, Kozinetz CA, et al. Effects of viral lower respiratory tract infection on lung function in infants with cystic fibrosis. Pediatrics 1999;103:619–626
12. Chonmaitree T, Howie VM, Truant AL. Presence of respiratory viruses in middle ear fluids and nasal wash specimens from children with acute otitis media. Pediatrics 1986;77:698–702
13. Pitkäranta A, Virolainen A, Jero J, Arruda E, Hayden FG. Detection of rhinovirus, respiratory syncytial virus, and coronavirus infections in acute otitis media by reverse transcriptase polymerase chain reaction. Pediatrics 1998; 102:291–295
14. Hayden FG. Rhinovirus and the lower respiratory tract. Rev Med Virol 2004;14:17–31
15. Greve JM, Davis G, Meyer AM, et al. The major human rhinovirus receptor is ICAM-1. Cell 1989;56:839–847
16. Marlovits TC, Abrahamsberg C, Blaas D. Soluble LDL minireceptors: minimal structure requirements for recognition of minor group human rhinovirus. J Biol Chem 1998;273:33835–33840
17. Uncapher CR, DeWitt CM, Colonno RJ. The major and minor group receptor families contain all but one human rhinovirus serotype. Virology 1991;180:814–817
18. Yeager CL, Ashmun RA, Williams RK, et al. Human aminopeptidase N is a receptor for human coronavirus 229E. Nature 1992;357:420–422
19. Hofmann H, Pyrc K, van der Hoek L, Geier M, Berkhout B, Pohlmann S. Human coronavirus NL63 employs the severe acute respiratory syndrome coronavirus receptor for cellular entry. Proc Natl Acad Sci USA 2005;102:7988–7993
20. van der Hoek L, Pyrc K, Berkhout B. Human coronavirus NL63, a new respiratory virus. FEMS Microbiol Rev 2006;30:760–773
21. Williams RK, Jiang GS, Holmes KV. Receptor for mouse hepatitis virus is a member of the carcinoembryonic antigen family of glycoproteins. Proc Natl Acad Sci USA 1991;88: 5533–5536
22. Lai MM, Holmes KV. Coronaviridae: the viruses and their replication. In: Knipe DM, Howley PM, eds. Fields Virology. Philadelphia, PA: Lippincott-Raven; 2001:641–663
23. Haagmans BL, Osterhaus AD. Coronaviruses and their therapy. Antiviral Res 2006;71:397–403
24. Johnston SL. Overview of virus-induced airway disease. Proc Am Thorac Soc 2005;2:150–156
25. Jarjour NN, Gern JE, Kelly EA, Swenson CA, Dick CR, Busse WW. The effect of an experimental rhinovirus 16 infection on bronchial lavage neutrophils. J Allergy Clin Immunol 2000;105:1169–1177
26. Johnston SL, Papi A, Bates PJ, Mastronarde JG, Monick MM, Hunninghake GW. Low grade rhinovirus infection induces a prolonged release of IL-8 in pulmonary epithelium. J Immunol 1998;160:6172–6181
27. Griego SD, Weston CB, Adams JL, Tal-Singer R, Dillon SB. Role of p38 mitogen-activated protein kinase in rhinovirus-induced cytokine production by bronchial epithelial cells. J Immunol 2000;165:5211–5220
28. Laza-Stanca V, Stanciu LA, Message SD, Edwards MR, Gern JE, Johnston SL. Rhinovirus replication in human macrophages induces NF-kappaB-dependent tumor necrosis factor alpha production. J Virol 2006;80:8248–8258
29. Blau DM, Holmes KV. Human coronavirus HCoV-229E enters susceptible cells via the endocytic pathway. Adv Exp Med Biol 2001;494:193–198
30. Pyrc K, Jebbink MF, Berkhout B, van der Hoek L. Genome structure and transcriptional regulation of human coronavirus NL63. Virol J 2004;1:7
31. Callow KA, Parry HF, Sergeant M, Tyrrell DA. The time course of the immune response to experimental coronavirus infection of man. Epidemiol Infect 1990;105: 435–446
32. Schmidt OW, Kenny GE. Immunogenicity and antigenicity of human coronaviruses 229E and OC43. Infect Immun 1981;32:1000–1006
33. Arruda E, Pitkäranta A, Witek TJ Jr, Doyle CA, Hayden FG. Frequency and natural history of rhinovirus infections in adults during autumn. J Clin Microbiol 1997;35:2864–2868
34. Makela MJ, Puhakka T, Ruuskanen O, et al. Viruses and bacteria in the etiology of the common cold. J Clin Microbiol 1998;36:539–542
35. Gonzales R, Malone DC, Maselli JH, Sande MA. Excessive antibiotic use for acute respiratory infections in the United States. Clin Infect Dis 2001;33:757–762
36. Hendley JO, Gwaltney JM Jr. Mechanisms of transmission of rhinovirus infections. Epidemiol Rev 1988;10:243–258
37. Tyrrell DA, Bynoe ML. Cultivation of viruses from a high proportion of patients with colds. Lancet 1966;1:76–77
38. Hamre D, Procknow JJ. A new virus isolated from the human respiratory tract. Proc Soc Exp Biol Med 1966; 121:190–193
39. McIntosh K, Dees JH, Becker WB, Kapikian AZ, Chanock RM. Recovery in tracheal organ cultures of novel viruses from patients with respiratory disease. Proc Natl Acad Sci USA 1967;57:933–940
40. McIntosh K, Kapikian AZ, Turner HC, Hartley JW, Parrott RH, Chanock RM. Seroepidemiologic studies of coronavirus infection in adults and children. Am J Epidemiol 1970;91:585–592
41. Monto AS. Medical reviews: coronaviruses. Yale J Biol Med 1974;47:234–251
42. McIntosh K, Ellis EF, Hoffman LS, Lybass TG, Eller JJ, Fulginiti VA. The association of viral and bacterial respiratory infections with exacerbations of wheezing in young asthmatic children. J Pediatr 1973;82:578–590
43. Monto AS. Epidemiology of respiratory viruses in persons with and without asthma and COPD. Am J Respir Crit Care Med 1995;151:1653–1658
44. Falsey AR, McCann RM, Hall WJ, et al. The "common cold" in frail older persons: impact of rhinovirus and coronavirus in a senior daycare center. J Am Geriatr Soc 1997;45:706–711
45. Falsey AR, Walsh EE, Hayden FG. Rhinovirus and coronavirus infection-associated hospitalizations among older adults. J Infect Dis 2002;185:1338–1341

46. Peiris JS, Lai ST, Poon LL, SARS Study Group. Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet 2003;361:1319–1325
47. van der Hoek L, Pyrc K, Jebbink MF, et al. Identification of a new human coronavirus. Nat Med 2004;10:368–373
48. Fouchier RA, Hartwig NG, Bestebroer TM, et al. A previously undescribed coronavirus associated with respiratory disease in humans. Proc Natl Acad Sci USA 2004; 101:6212–6216
49. Esper F, Weibel C, Ferguson D, Landry ML, Kahn JS. Evidence of a novel human coronavirus that is associated with respiratory tract disease in infants and young children. J Infect Dis 2005;191:492–498
50. Woo PC, Lau SK, Chu CM, et al. Characterization and complete genome sequence of a novel coronavirus, coronavirus HKU1, from patients with pneumonia. J Virol 2005; 79:884–895
51. Esper F, Weibel C, Ferguson D, Landry ML, Kahn JS. Coronavirus HKU1 infection in the United States. Emerg Infect Dis 2006;12:775–779
52. Gerna G, Campanini G, Rovida F, et al. Genetic variability of human coronavirus OC43-, 229E-, and NL63-like strains and their association with lower respiratory tract infections of hospitalized infants and immunocompromised patients. J Med Virol 2006;78:938–949
53. Garbino J, Crespo S, Aubert JD, et al. A prospective hospital-based study of the clinical impact of non-severe acute respiratory syndrome (non-SARS)-related human coronavirus infection. Clin Infect Dis 2006;43:1009–1015
54. Vijgen L, Keyaerts E, Lemey P, et al. Circulation of genetically distinct contemporary human coronavirus OC43 strains. Virology 2005;337:85–92
55. Dagher H, Donninger H, Hutchinson P, Ghildyal R, Bardin P. Rhinovirus detection: comparison of real-time and conventional PCR. J Virol Methods 2004;117:113–121
56. van Kraaij MG, van Elden LJ, van Loon AM, et al. Frequent detection of respiratory viruses in adult recipients of stem cell transplants with the use of real-time polymerase chain reaction, compared with viral culture. Clin Infect Dis 2005;40:662–669
57. Vuorinen T, Vainionpaa R, Hyypia T. Five years' experience of reverse-transcriptase polymerase chain reaction in daily diagnosis of enterovirus and rhinovirus infections. Clin Infect Dis 2003;37:452–455
58. Loens K, Goossens H, de Laat C, et al. Detection of rhinoviruses by tissue culture and two independent amplification techniques, nucleic acid sequence-based amplification and reverse transcription-PCR, in children with acute respiratory infections during a winter season. J Clin Microbiol 2006;44:166–171
59. Lee BE, Robinson JL, Khurana V, Pang XL, Preiksaitis JK, Fox JD. Enhanced identification of viral and atypical bacterial pathogens in lower respiratory tract samples with nucleic acid amplification tests. J Med Virol 2006;78:702–710
60. van de Pol AC, Wolfs TF, Jansen NJ, van Loon AM, Rossen JW. Diagnostic value of real-time polymerase chain reaction to detect viruses in young children admitted to the paediatric intensive care unit with lower respiratory tract infection. Crit Care 2006;10:R61
61. Beckham JD, Cadena A, Lin J, et al. Respiratory viral infections in patients with chronic, obstructive pulmonary disease. J Infect 2005;50:322–330
62. Schmidt OW. Antigenic characterization of human coronaviruses 229E and OC43 by enzyme-linked immunosorbent assay. J Clin Microbiol 1984;20:175–180
63. Kahn JS, McIntosh K. History and recent advances in coronavirus discovery. Pediatr Infect Dis J 2005; 24(Suppl 11):S223–S227
64. 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;310:1225–1229
65. Atmar RL, Guy E, Guntupalli KK, et al. Respiratory tract viral infections in inner-city asthmatic adults. Arch Intern Med 1998;158:2453–2459
66. Nicholson KG, Kent J, Ireland DC. Respiratory viruses and exacerbations of asthma in adults. BMJ 1993;307:982–986
67. Wark PA, Johnston SL, Moric I, Simpson JL, Hensley MJ, Gibson PG. Neutrophil degranulation and cell lysis is associated with clinical severity in virus-induced asthma. Eur Respir J 2002;19:68–75
68. Corne 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;359:831–834
69. Grunberg K, Timmers MC, de Klerk EP, Dick EC, Sterk PJ. Experimental rhinovirus 16 infection causes variable airway obstruction in subjects with atopic asthma. Am J Respir Crit Care Med 1999;160:1375–1380
70. Calhoun WJ, Dick EC, Schwartz LB, Busse WW. A common cold virus, rhinovirus 16, potentiates airway inflammation after segmental antigen bronchoprovocation in allergic subjects. J Clin Invest 1994;94:2200–2208
71. Fraenkel DJ, Bardin PG, Sanderson G, Lampe F, Johnston SL, Holgate ST. Lower airways inflammation during rhinovirus colds in normal and in asthmatic subjects. Am J Respir Crit Care Med 1995;151:879–886
72. Papadopoulos NG, Bates PJ, Bardin PG, et al. Rhinoviruses infect the lower airways. J Infect Dis 2000;181:1875–1884
73. Gern JE, Galagan DM, Jarjour NN, Dick EC, Busse WW. Detection of rhinovirus RNA in lower airway cells during experimentally induced infection. Am J Respir Crit Care Med 1997;155:1159–1161
74. Zhu Z, Tang W, Gwaltney JM Jr, Wu Y, Elias JA. Rhinovirus stimulation of interleukin-8 in vivo and in vitro: role of NF-kappaB. Am J Physiol 1997;273:L814–L824
75. Zhu Z, Tang W, Ray A, et al. Rhinovirus stimulation of interleukin-6 in vivo and in vitro: evidence for nuclear factor kappa B-dependent transcriptional activation. J Clin Invest 1996;97:421–430
76. Wark PA, Johnston SL, Bucchieri F, et al. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. J Exp Med 2005; 201:937–947
77. Cheung D, Dick EC, Timmers MC, de Klerk EP, Spaan WJ, Sterk PJ. Rhinovirus inhalation causes long-lasting excessive airway narrowing in response to methacholine in asthmatic subjects *in vivo*. Am J Respir Crit Care Med 1995;152:1490–1496
78. Smart JM, Horak E, Kemp AS, Robertson CF, Tang ML. Polyclonal and allergen-induced cytokine responses in adults

with asthma: resolution of asthma is associated with normalization of IFN-gamma responses. J Allergy Clin Immunol 2002;110:450–456
79. Seymour ML, Gilby N, Bardin PG, et al. Rhinovirus infection increases 5-lipoxygenase and cyclooxygenase-2 in bronchial biopsy specimens from nonatopic subjects. J Infect Dis 2002;185:540–544
80. de Gouw HW, Grunberg K, Schot R, Kroes AC, Dick EC, Sterk PJ. Relationship between exhaled nitric oxide and airway hyperresponsiveness following experimental rhinovirus infection in asthmatic subjects. Eur Respir J 1998; 11:126–132
81. Papadopoulos NG, Stanciu LA, Papi A, et al. A defective type 1 response to rhinovirus in atopic asthma. Thorax 2002;57:328–332
82. Sheppard P, Kindsvogel W, Xu W, et al. IL-28, IL-29 and their class II cytokine receptor IL-28R. Nat Immunol 2003;4:63–68
83. Contoli M, Message SD, Laza-Stanca V, et al. Role of deficient type III interferon-lambda production in asthma exacerbations. Nat Med 2006;12:1023–1026
84. Seemungal T, Harper-Owen R, Bhowmik A, et al. Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001; 164:1618–1623
85. Smith CB, Golden CA, Kanner RE, Renzetti AD Jr. Association of viral and *Mycoplasma pneumoniae* infections with acute respiratory illness in patients with chronic obstructive pulmonary diseases. Am Rev Respir Dis 1980; 121:225–232
86. Rohde G, Wiethege A, Borg I, et al. Respiratory viruses in exacerbations of chronic obstructive pulmonary disease requiring hospitalisation: a case-control study. Thorax 2003;58:37–42
87. Keatings VM, Collins PD, Scott DM, Barnes PJ. Differences in interleukin-8 and tumor necrosis factor-alpha in induced sputum from patients with chronic obstructive pulmonary disease or asthma. Am J Respir Crit Care Med 1996;153:530–534
88. Bandi V, Apicella MA, Mason E, et al. Nontypeable *Haemophilus influenzae* in the lower respiratory tract of patients with chronic bronchitis. Am J Respir Crit Care Med 2001;164:2114–2119
89. Ishizuka S, Yamaya M, Suzuki T, et al. Effects of rhinovirus infection on the adherence of *Streptococcus pneumoniae* to cultured human airway epithelial cells. J Infect Dis 2003; 188:1928–1939
90. Passariello C, Schippa S, Conti C, et al. Rhinoviruses promote internalisation of *Staphylococcus aureus* into non-fully permissive cultured pneumocytes. Microbes Infect 2006;8:758–766
91. Sajjan US, Jia Y, Newcomb DC, et al. *H. influenzae* potentiates airway epithelial cell responses to rhinovirus by increasing ICAM-1 and TLR3 expression. FASEB J 2006; 20:2121–2123
92. Nokso-Koivisto J, Raty R, Blomqvist S, et al. Presence of specific viruses in the middle ear fluids and respiratory secretions of young children with acute otitis media. J Med Virol 2004;72:241–248
93. Heikkinen T, Chonmaitree T. Importance of respiratory viruses in acute otitis media. Clin Microbiol Rev 2003;16: 230–241
94. Chantzi FM, Papadopoulos NG, Bairamis T, et al. Human rhinoviruses in otitis media with effusion. Pediatr Allergy Immunol 2006;17:514–518
95. Pitkäranta A, Roivainen M, Blomgren K, et al. Presence of viral and bacterial pathogens in the nasopharynx of otitis-prone children: a prospective study. Int J Pediatr Otorhinolaryngol 2006;70:647–654
96. Rihkanen H, Carpen O, Roivainen M, Vaheri A, Pitkäranta A. Rhinovirus in adenoid tissue. Int J Pediatr Otorhinolaryngol 2004;68:903–908
97. Elkhatieb A, Hipskind G, Woerner D, Hayden FG. Middle ear abnormalities during natural rhinovirus colds in adults. J Infect Dis 1993;168:618–621
98. McBride TP, Doyle WJ, Hayden FG, Gwaltney JM Jr. Alterations of the eustachian tube, middle ear, and nose in rhinovirus infection. Arch Otolaryngol Head Neck Surg 1989;115:1054–1059
99. Sung BS, Chonmaitree T, Broemeling LD, et al. Association of rhinovirus infection with poor bacteriologic outcome of bacterial-viral otitis media. Clin Infect Dis 1993; 17:38–42
100. Bulut Y, Guven M, Otlu B, et al. Acute otitis media and respiratory viruses. Eur J Pediatr 2007;166:223–228
101. Gwaltney JM Jr, Phillips CD, Miller RD, Riker DK. Computed tomographic study of the common cold. N Engl J Med 1994;330:25–30
102. Turner BW, Cail WS, Hendley JO, et al. Physiologic abnormalities in the paranasal sinuses during experimental rhinovirus colds. J Allergy Clin Immunol 1992;90:474–478
103. Gwaltney JM Jr. Acute community-acquired sinusitis. Clin Infect Dis 1996;23:1209–1223
104. Pitkäranta A, Arruda E, Malmberg H, Hayden FG. Detection of rhinovirus in sinus brushings of patients with acute community-acquired sinusitis by reverse transcription-PCR. J Clin Microbiol 1997;35:1791–1793
105. Gwaltney JM Jr, Hendley JO, Phillips CD, Bass CR, Mygind N, Winther B. Nose blowing propels nasal fluid into the paranasal sinuses. Clin Infect Dis 2000;30:387–391
106. Collinson J, Nicholson KG, Cancio E, et al. Effects of upper respiratory tract infections in patients with cystic fibrosis. Thorax 1996;51:1115–1122
107. Smyth AR, Smyth RL, Tong CY, Hart CA, Heaf DP. Effect of respiratory virus infections including rhinovirus on clinical status in cystic fibrosis. Arch Dis Child 1995;73: 117–120
108. Kumar D, Erdman D, Keshavjee S, et al. Clinical impact of community-acquired respiratory viruses on bronchiolitis obliterans after lung transplant. Am J Transplant 2005;5: 2031–2036
109. Garbino J, Gerbase MW, Wunderli W, et al. Respiratory viruses and severe lower respiratory tract complications in hospitalized patients. Chest 2004;125:1033–1039
110. Whimbey E, Champlin RE, Couch RB, et al. Community respiratory virus infections among hospitalized adult bone marrow transplant recipients. Clin Infect Dis 1996;22:778–782
111. Ison MG, Hayden FG, Kaiser L, Corey L, Boeckh M. Rhinovirus infections in hematopoietic stem cell transplant recipients with pneumonia. Clin Infect Dis 2003;36:1139–1143
112. Hassan IA, Chopra R, Swindell R, Mutton KJ. Respiratory viral infections after bone marrow/peripheral stem-cell

transplantation: the Christie Hospital experience. Bone Marrow Transplant 2003;32:73–77
113. Ljungman P, Ward KN, Crooks BN, et al. Respiratory virus infections after stem cell transplantation: a prospective study from the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant 2001;28:479–484
114. Ghosh S, Champlin R, Couch R, et al. Rhinovirus infections in myelosuppressed adult blood and marrow transplant recipients. Clin Infect Dis 1999;29:528–532
115. Eccles R. Efficacy and safety of over-the-counter analgesics in the treatment of common cold and flu. J Clin Pharm Ther 2006;31:309–319
116. Singh M. Heated, humidified air for the common cold. Cochrane Database Syst Rev 2006, Issues. Art no: CD001728. DOI:1002/14651858. CDC001728 pub
117. Rotbart HA. Antiviral therapy for enteroviruses and rhinoviruses. Antivir Chem Chemother 2000;11:261–271
118. Edwards MR, Kebadze T, Johnson MW, Johnston SL. New treatment regimes for virus-induced exacerbations of asthma. Pulm Pharmacol Ther 2006;19:320–334
119. Samo TC, Greenberg SB, Couch RB, et al. Efficacy and tolerance of intranasally applied recombinant leukocyte A interferon in normal volunteers. J Infect Dis 1983;148:535–542
120. Hayden FG, Gwaltney JM Jr. Intranasal interferon-alpha 2 treatment of experimental rhinoviral colds. J Infect Dis 1984;150:174–180
121. Hayden FG, Gwaltney JM Jr. Intranasal interferon alpha 2 for prevention of rhinovirus infection and illness. J Infect Dis 1983;148:543–550
122. Douglas RM, Albrecht JK, Miles HB, et al. Intranasal interferon-alpha 2 prophylaxis of natural respiratory virus infection. J Infect Dis 1985;151:731–736
123. Monto AS, Shope TC, Schwartz SA, Albrecht JK. Intranasal interferon-alpha 2b for seasonal prophylaxis of respiratory infection. J Infect Dis 1986;154:128–133
124. Higgins PG, Phillpotts RJ, Scott GM, Wallace J, Bernhardt LL, Tyrrell DA. Intranasal interferon as protection against experimental respiratory coronavirus infection in volunteers. Antimicrob Agents Chemother 1983;24:713–715
125. Sasaki T, Yamaya M, Yasuda H, et al. The proton pump inhibitor lansoprazole inhibits rhinovirus infection in cultured human tracheal epithelial cells. Eur J Pharmacol 2005;509:201–210
126. Jang YJ, Kwon HJ, Lee BJ. Effect of clarithromycin on rhinovirus-16 infection in A549 cells. Eur Respir J 2006;27:12–19
127. Hayden FG, Herrington DT, Coats TL, et al; Pleconaril Respiratory Infection Study Group. Efficacy and safety of oral pleconaril for treatment of colds due to picornaviruses in adults: results of 2 double-blind, randomized, placebo-controlled trials. Clin Infect Dis 2003;36:1523–1532
128. Patick AK, Brothers MA, Maldonado F, et al. In vitro antiviral activity and single-dose pharmacokinetics in humans of a novel, orally bioavailable inhibitor of human rhinovirus 3C protease. Antimicrob Agents Chemother 2005;49:2267–2275
129. Hayden FG, Turner RB, Gwaltney JM, et al. Phase II randomized, double-blind, placebo-controlled studies of ruprintrivir nasal spray 2-percent suspension for prevention and treatment of experimentally induced rhinovirus colds in healthy volunteers. Antimicrob Agents Chemother 2003;47:3907–3916
130. Schoop R, Klein P, Suter A, Johnston SL. Echinacea in the prevention of induced rhinovirus colds: a meta-analysis. Clin Ther 2006;28:174–183
131. Sperber SJ, Shah LP, Gilbert RD, Ritchey TW, Monto AS. *Echinacea purpurea* for prevention of experimental rhinovirus colds. Clin Infect Dis 2004;38:1367–1371
132. Turner RB. Ineffectiveness of intranasal zinc gluconate for prevention of experimental rhinovirus colds. Clin Infect Dis 2001;33:1865–1870
133. Kurugöl Z, Akilli M, Bayram N, Koturoglu G. The prophylactic and therapeutic effectiveness of zinc sulphate on common cold in children. Acta Paediatr 2006;95:1175–1181
134. Turner RB, Hendley JO. Virucidal hand treatments for prevention of rhinovirus infection. J Antimicrob Chemother 2005;56:805–807
135. Turner RB, Biedermann KA, Morgan JM, Keswick B, Ertel KD, Barker MF. Efficacy of organic acids in hand cleansers for prevention of rhinovirus infections. Antimicrob Agents Chemother 2004;48:2595–2598