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

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

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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. Recent studies have shown that the newly reported group I coronavirus HCoV-NL63 does not use CD13 as the receptor cell entry. 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. The receptor for HCoV-OC43 is not known. Carcinoembryonic antigen (CEA) is the receptor for mouse hepatitis virus, a group II coronavirus. Group III coronaviruses contain avian infectious bronchitis virus. Phylogenetic relationships between coronaviruses have been based on deduced amino acid sequences of the coronavirus replicase ORF1b gene (see Fig. 1).

PATHOGENESIS

Rhinoviruses

The pathogenesis of rhinovirus infections is through infection of the upper respiratory tract where minimal epithelial cell damage has been noted. 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. Inflammatory mediators, including kinins, leukotrienes, interleukin (IL)-1, IL-6, IL-8,

Table 1 Rhinoviruses and Coronaviruses: Virology and Pathogenesis

<table>
<thead>
<tr>
<th>Virology</th>
<th>Rhinoviruses</th>
<th>Coronaviruses</th>
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<tbody>
<tr>
<td>Family</td>
<td>Picornaviridae</td>
<td>Coronaviridae</td>
</tr>
<tr>
<td>Type of RNA</td>
<td>+ RNA</td>
<td>+ RNA</td>
</tr>
<tr>
<td>Lipid envelope</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Capsid symmetry</td>
<td>Icosahedral</td>
<td>Helical</td>
</tr>
<tr>
<td>Genome size (Kb)</td>
<td>~8</td>
<td>~30</td>
</tr>
<tr>
<td>Pathogenesis</td>
<td>91 serotypes with ICAM-1 as specific receptor 10 serotypes use low-density lipoprotein receptor</td>
<td>229E and OC-43 infect ciliated epithelial cells</td>
</tr>
</tbody>
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ICAM, intercellular adhesion molecule; RNA, ribonucleic acid.

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.
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. Polypeptides 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

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.

**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

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
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. 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-OC43, 53 were positive for HCoV-NL63, 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-OC43 infections occurred in early summer and fall but not in the winter.

In a recent prospective study of respiratory viral infections among hospitalized patients, 5.7% had coronaviruses identified. 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. 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. 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.

### Table 3 Diagnostic Tests for Rhinoviruses and Coronaviruses

<table>
<thead>
<tr>
<th>Rhinoviruses</th>
<th>Coronaviruses</th>
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<tbody>
<tr>
<td>1. Cell culture isolation: routine</td>
<td>1. Organ-culture isolation*: not readily available</td>
</tr>
<tr>
<td>2. Polymerase chain reaction: sensitive; not readily available</td>
<td>2. Polymerase chain reaction: sensitive; not readily available</td>
</tr>
<tr>
<td>3. Serum antibody tests are type specific but not readily available</td>
<td>3. Serum antibody tests are not readily available</td>
</tr>
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</table>

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

### DIAGNOSIS

Standard tissue culture methods for isolation are useful for detecting rhinoviruses but are insensitive for coronavirus (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. 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. Several other studies have found increased sensitivity of RT–PCR compared with viral culture techniques. Coronaviruses have also been detected by RT–PCR with greater sensitivity than standard culture techniques.

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. Therefore, serologic tests for antibody specific responses are mainly reserved for research or epidemiological studies.

### INFECTIONS IN PATIENTS WITH ASTHMA

Asthma exacerbations in children and adults are frequently associated with respiratory virus infections, especially rhinoviruses and coronaviruses. Wark et al found viruses in sputum of 76% of admitted adults with asthma exacerbation. 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.
Experimental rhinovirus 16 (RV16) infection in volunteers with mild atopic asthma led to significantly reduced forced expiratory volume in 1 second (FEV1) in home recordings. In allergic subjects, RV16 infection potentiated airway inflammation after bronchoprovocation. During other experimental rhinovirus infections, significant increases in submucosal CD3+ lymphocytes and eosinophils were detected in bronchial mucosal biopsies. 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. In situ hybridization studies demonstrated the replicative strand of rhinovirus in the lower airways.

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. 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. 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.

Several recent studies have reported deficient induction of IFN-λ by rhinovirus in bronchial epithelial cells for asthmatic patients. Recently, type III IFNs, IFN-λ1 and IFN-λ2/3, have been discovered with many similarities to type I IFNs. Contoli et al has found that IFN-αs are induced by rhinovirus infection of human bronchial epithelial cells, monocytes, and macrophages. 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.

Multiple longitudinal studies have documented the importance of respiratory viral infections in acute exacerbations of chronic bronchitis. Early studies reported on the role of rhinoviruses in COPD exacerbations. In a more recent longitudinal study of both COPD patients and normal controls, 27% of acute respiratory illnesses were associated with respiratory viruses. Rhinoviruses accounted for 43% of the viral infections. In an updated study using PCR techniques, additional rhinovirus or coronavirus infections were demonstrated. 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 (FEV1 < 50% of predicted) than in COPD patients with mild COPD (FEV1 > 50% and < 70% of predicted), 3.0 versus 1.8 respiratory illnesses per year, respectively.

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. Rohde et al also found that rhinoviruses were the most common virus detected in virus-associated exacerbations in a cohort of COPD patients.

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. Rhinoviruses have also been recovered from the lower airways. Inflammatory mediators, especially IL-8, have been found in increased levels from respiratory secretions obtained from stable COPD patients.

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. Evidence has demonstrated an increase in Staphylococcus aureus and Streptococcus pneumoniae adherence to respiratory epithelial cells infected with rhinovirus. 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. 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 76% 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.\(^{108-111}\) 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 ipratropium or antihistamines could be used for the commonly reported symptom, rhinorrhea. Anticholinergic nasal sprays have been reported to reduce rhinorrhea by \sim 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.\textsuperscript{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.\textsuperscript{117}

Using our understanding of the cellular changes following rhinovirus infection and replication, several antiviral agents and treatment strategies have been tested.\textsuperscript{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 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.\textsuperscript{119,120} However, local side-effects limited its use when tested in natural rhinoviral infections.\textsuperscript{121–123} One volunteer study with IFN-α given prior to coronavirus challenge did demonstrate an antiviral and anti-illness effect.\textsuperscript{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.\textsuperscript{125,126}

Viral capsid-binding compounds, such as pleconaril, block virus uncoating in vitro.\textsuperscript{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 on oral contraceptives. Enviroxime inhibited the 3A-coding region of picornavirus RNA in vitro, but clinical trials revealed intolerance to oral dosing.\textsuperscript{63} Several low molecular weight compounds inhibit the 3C protease, which is essential for viral replication and assembly.\textsuperscript{128} In volunteer trials, a 3C-protease inhibitor, rupintrivir was found to reduce virus shedding but was associated with blood-tinged mucus and irritation of the nasal passages.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.

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