Update on Rhinovirus and Coronavirus Infections

Stephen B. Greenberg, M.D., M.A.C.P.1

ABSTRACT

Rhinoviruses and coronaviruses cause significant morbidity in immunocompetent people of all ages and in patients with underlying chronic medical or immunosuppressed conditions. Newer diagnostic tests, such as polymerase chain reaction (PCR), have expanded our understanding of these respiratory viruses in clinical infections. These sensitive diagnostic tests have been used to describe new members of these virus families, such as human rhinovirus C (HRVC) and human coronavirus NL-63 (HCoV-NL63). The epidemiology of these newly described viruses will help us develop better intervention strategies.

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

More than 50% of all common colds are caused by rhinoviruses and coronaviruses.1–3 Clinically, the common cold includes rhinitis and pharyngitis, as well as sneezing, hoarseness, and nonproductive 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 employing PCR technologies have increased the percentage of respiratory illnesses attributable to these viruses.14 Currently, there are no approved antiviral agents for rhinovirus or coronavirus infections. This review updates recent advances in our knowledge of these two virus groups and their importance in respiratory viral infections.15

VIROLOGY

Rhinoviruses

Rhinoviruses are members of the Picornaviridae family (Table 1), are positive-sense, single-stranded ribonucleic acid (RNA) viruses with icosahedral symmetry. The capsid is composed of four proteins: VP1, VP2, VP3, and VP4. Proteins VP1, VP2, and VP3 are responsible for antigenic diversity and the host immune response following infection.16 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. Many serotypes of HRV-A attach to cells by the intercellular adhesion molecule 1 (ICAM-1).17 A small number of serotypes use the low density lipoprotein receptor for attachment and entry into cells.18 One serotype, HRV-87, requires the presence of sialic acid on cellular receptors, unlike the major and minor group serotypes.19 Currently, human rhinoviruses are divided into two approved species, human rhinovirus A (HRVA) and human rhinovirus B (HRVB) and a third, human rhinovirus C (HRVC), is awaiting ratification as a separate species20 (Table 2). In 2003, a distinct and previously undefined clade of HRVs were reported and labeled HRVC.21 These newly identified HRVCs have been circulating for at least 10 years.22,23 Recent studies have shown that specimens passed through tissue culture and then tested by PCR would have missed HRVCs.24

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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). They are divided into three genera: group I includes both human (HCoV-229E and HCoV-NL63) and animal pathogens; group II includes both human [HCoV-OC43, HCoV-HKU1, and severe acute respiratory syndrome (SARS)] 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. Upon SARS-coronavirus infection, ACE2 expression in the lungs is markedly downregulated, and this finding helps explain SARS pathogenesis and progression to acute respiratory distress syndrome (ARDS). HCoV-NL63 is the only group I coronavirus known to use ACE2 as its receptor. The receptors for HCoV-OC43 and HCoV-HKU1 remain unknown. Carcinoembryonic antigen (CEA) is the receptor for mouse hepatitis virus, a group II coronavirus. Group III coronaviruses contain the avian infectious bronchitis virus.

Table 1 Coronaviruses: Virology

<table>
<thead>
<tr>
<th>Virology</th>
<th>Rhinoviruses</th>
<th>Coronaviruses</th>
</tr>
</thead>
<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>
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<td>Helical</td>
</tr>
<tr>
<td>Genome size (Kb)</td>
<td>~8</td>
<td>~30</td>
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</table>

Table 2 Coronaviruses: Classification

<table>
<thead>
<tr>
<th>Group</th>
<th>Species</th>
<th>Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinovirus</td>
<td>HRVA</td>
<td>Tissue culture, PCR</td>
</tr>
<tr>
<td></td>
<td>HRVB</td>
<td>Tissue culture, PCR</td>
</tr>
<tr>
<td></td>
<td>HRVC</td>
<td>PCR only</td>
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Coronavirus

Group I

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<thead>
<tr>
<th>Species</th>
<th>Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>229E</td>
<td>Organ culture, PCR</td>
</tr>
<tr>
<td>NL63</td>
<td>PCR, animal models</td>
</tr>
</tbody>
</table>

Group II

<table>
<thead>
<tr>
<th>Species</th>
<th>Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>OC43</td>
<td>Organ culture, PCR</td>
</tr>
<tr>
<td>HKU1</td>
<td>PCR, animal models</td>
</tr>
<tr>
<td>SARS</td>
<td>PCR, animal models</td>
</tr>
</tbody>
</table>

Group III (Only avian)

<table>
<thead>
<tr>
<th>Species</th>
<th>Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Only avian)</td>
<td>Organ culture</td>
</tr>
</tbody>
</table>

PATHOGENESIS

Rhinoviruses

The pathogenesis of rhinovirus infections is through infection of the upper respiratory tract. After deposition of rhinovirus in the eye or nose, there is attachment to host cell epithelium. 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, 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.

Coronaviruses

Coronaviruses attach to cellular receptors by the spike proteins on their surface. 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. 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.

EPIDEMIOLOGY

Rhinoviruses

Rhinoviruses cause respiratory illnesses throughout the world, in all age groups, and throughout the year (Table 3). However, rhinoviruses are most prevalent in the fall and spring in temperate climates. In a study using PCR techniques, rhinoviruses accounted for 50% of common colds in one prospective study. 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.

The home is the principal location for transmission of rhinovirus. 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 spread of rhinovirus. Transmission of rhinoviruses can occur by close contact, autoinoculation, fomites, or aerosols.
Coronaviruses were detected as agents of respiratory infections ~40 years ago.72–74 They were later identified as coronaviruses, labeled OC43 and 229E, and accepted as a new genus in 1975. In epidemiological studies in adults, coronaviruses were estimated to cause ~15% of adult common colds.75 Coronaviruses were found to cause epidemics every 2 to 3 years, with reinfections being common.76 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.77,78 The elderly are also prone to these infections and are a cause of hospitalization.79,80

Besides HCoV-OC43 and HCoV-229E, other coronavirus strains have been recently identified. A new coronavirus causing SARS was reported in 2003. It was different from known human and animal coronaviruses by DNA sequencing.81 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.

In 2004 and 2005, three closely related coronavirus species were reported.82–84 NL63 was isolated from a 7-month-old girl with coryza, conjunctivitis, fever, and bronchiolitis.82 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.84

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.85 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 4 were positive for

### Table 3 Epidemiology of Rhinovirus and Coronavirus Illness

<table>
<thead>
<tr>
<th></th>
<th>Rhinoviruses</th>
<th>Coronaviruses*</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Common cold’ illnesses</td>
<td>25-50%</td>
<td>7-30%</td>
</tr>
<tr>
<td>Worldwide distribution</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Acquisition in childhood</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Spread</td>
<td>Direct contact, hand-to-hand contact, or aerosol</td>
<td>Droplets</td>
</tr>
<tr>
<td>Prevalence</td>
<td>Peak in early fall and spring</td>
<td>Late fall, winter, and early spring</td>
</tr>
</tbody>
</table>

*Not including severe acute respiratory syndrome (SARS)-CoV.
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 winter.86

Using newer molecular assays, the group at Vanderbilt reassessed the role of the newly described coronaviruses in a large cohort of healthy children who had been followed prospectively for 20 years.87 Of the LRI (lower respiratory infection) samples available for screening, 8.4% had positive results for HCo-V and all were under 2 years of age. Acute otitis media was found in half the HCo-V-infected children, but none of the children were hospitalized. Of the URI (upper respiratory infection) samples tested, 4.7% had detectable HCo-V RNA. Of these positive children, 51% were diagnosed with acute otitis media. The burden of URI attributable to HCo-V had significant year-to-year variation.

In a prospective study of respiratory viral infections among hospitalized patients, 5.7% had coronaviruses identified.88 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) infections, 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. Co-infections 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.89 The most frequently identified isolates were HCoV-OC43 in 12, followed by HCoV-229E in seven, HCoV-NL63 in 6, and HCoV-HKU1 in four specimens. Many patients had high-risk underlying conditions. In several recent studies evaluating multiplex PCR assays, HRV and HCoVs were detected in 3 to 8% of hospitalized children <5 years of age with acute respiratory illnesses.90–92

A recent study has provided evidence for genetic variability in OC43 strains.93 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. 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 increased significantly. Detection of rhinovirus in respiratory specimens was enhanced by reverse transcription PCR (RT-PCR), involving the use of hybridization probes or double-stranded DNA binding dye. Several other studies have found increased sensitivity of RT-PCR compared with viral culture techniques.94–99 Coronaviruses have also been detected by RT-PCR with greater sensitivity than standard culture techniques.100

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 and enzyme-linked immunosorbent assay (ELISA) antibody assays for coronaviruses 229E and OC43 have been published, but are not available in clinical laboratories.101,102 Therefore, serological 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.103–109 It was reported 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.110

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.111 In allergic subjects, RV16 infection potentiated airway inflammation after bronchoprovocation.112 During other experimental rhinovirus infections, significant increases in submucosal CD4+ CD25+ lymphocytes and eosinophils were detected in bronchial mucosal biopsies.113 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, immunological, or neurogenic mechanisms in the upper airway and thereby impacting the lower airways. Papadopoulos
et al 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. 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-α (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 found that IFN-λs are induced by rhinovirus infection of human bronchial epithelial cells, monocytes, and macrophages. Induction of IFN-λ1 and IFN-λ2/3 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.

HRV infections are a major cause of wheezing illnesses in young children. Wheezing episodes in infancy that are virus-induced are often harbingers of later asthma. HRV infections that resulted in hospitalization during infancy were recently implicated as early predictors of subsequent development of asthma. Almost 90% of wheezing children in year 3 of the study had asthma at 6 years of age. Outpatient HRV wheezing illnesses during infancy were also found to be predictors of wheezing through 3 years of age.

HRV infections as well as other respiratory viruses can induce the synthesis of factors that regulate airway remodeling and alveolar development. These factors include vascular endothelial growth factor (VEGF), nitric oxide (NO), transforming growth factor-β (TGF-β), and fibroblast growth factor (FGF). These infections may also upregulate neutrophine, which can cause airway remodeling and promote airway responsiveness. The relationship of viral respiratory tract infections, especially rhinovirus infections, in early childhood may contribute to early-onset childhood asthma (Fig. 1).

**Figure 1** Relationship of viral respiratory infections in early life to the development of asthma. From Gern. VIRI, viral respiratory infection. (Reproduced with permission from Wolters Kluwer Health/Lippincott, Williams & Wilkins, Inc.)

**INFECTIONS IN PATIENTS WITH COPD**

Multiple longitudinal studies have documented the importance of respiratory viral infections in acute exacerbations of chronic obstructive pulmonary disease (COPD). 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. Two recent studies have found both rhinoviruses and coronaviruses in hospitalized patients with acute exacerbation of COPD.

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, and/or the role of inflammatory mediators. Upregulation of intercellular adhesion molecule-1 (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. Studies have demonstrated an increase in Staphylococcus aureus and Streptococcus pneumoniae adherence to respiratory epithelial cells infected with rhinovirus. In an 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 Toll-like receptor-3 (TLR3) expression. However, it is unclear 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. 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. 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. 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. Rhinovirus was found at baseline in 30% of specimens. Positive PCR tests for rhinovirus correlated with culturing Moraxella catarrhalis and Streptococcus pneumoniae but not nontypeable Haemophilus influenzae. Rhinoviruses and bacterial pathogens were found in otitis-prone children even in the absence of clinical symptoms. Most new otitis media episodes are coincident with an HRV URI. The absence of clinical symptoms. Most new otitis media episodes are coincident with an HRV URI. The presence of rhinovirus in middle ear fluid was associated with an antibiotic failure rate in 78% of acute otitis media cases. 

RHINOVIRUS INFECTIONS IN RHINOSINUSITIS

Most patients with the common cold syndrome have sinus abnormalities detectable by computed tomography. 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 bacterial infection. In a study of 20 adults with acute rhinosinusitis, 15% had virus cultures positive for rhinovirus, but 50% were positive using reverse transcription PCR on maxillary sinus aspirates or nasal swabs. Intranasal pressure increases following nose blowing, sneezing, and coughing. This increased pressure is high enough to propel virus-infected nasal reactions into the sinuses. However, it is unclear from these studies whether virus replication occurs in the sinus mucosa.

RHINOVIRUS AND CORONAVIRUS IN COMMUNITY-ACQUIRED PNEUMONIA AND BRONCHIOLITIS

Until recently, rhinovirus and coronaviruses have not been thought to be important causes of community-acquired pneumonia (CAP). However, several studies using polymerase chain reaction (PCR) assays have shown that both these virus groups do cause CAP in children and adults. Five studies in children have reported a range of 11 to 29% positive specimens for rhinovirus. One study reported 6.7% positive specimens for coronavirus 229E in children (Table 4). In studies testing for respiratory viruses in adults with CAP, rhinoviruses were detected in 2 to 18% of cases. Coronavirus were detected in 2 to 17% of CAP cases in five published studies. Many cases of CAP had mixed infections with either a second respiratory virus or a bacterial pathogen. Therefore, it is difficult to be sure how important the rhinovirus- or coronavirus-positive result was in contributing to CAP. Nevertheless, there are sufficient cases where either rhinoviruses or coronaviruses were detected as single viruses to be confident that they do cause CAP.

Bronchiolitis in children has been commonly reported in infants and young children. The most commonly reported virus recovered in acute cases has been respiratory syncytial virus (RSV). Three recent studies reported rhinoviruses in 2.5 to 19.5% of bronchiolitis
cases. In three published studies, coronaviruses were detected in 0.3 to 8% of bronchiolitis cases. As with CAP series, mixed infections with a second respiratory virus were common. The full impact of rhinoviruses and coronaviruses in both CAP and bronchiolitis has yet to be defined. The newer more sensitive detection assays have expanded the importance of these two virus groups in clinically severe lower respiratory tract illnesses in both children and adults.

**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. 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.

Olesen et al obtained sputum cultures in 75 children with cystic fibrosis, and 45 were virus positive. HRV infection did not appear to affect lung function. Having respiratory or "viral" symptoms had low positive predictive value, sensitivity, and specificity. The authors did not attempt to look for coronaviruses. Another study assayed for HRV in 71 patients with 165 episodes of URI. Forty percent were virus positive who had symptoms. URI symptoms correlated with positive virus detection independent of bacterial culture result. De Almeida et al reported infections by the novel rhinovirus species A2 and G in CF patients. There was a definite association between detecting these rhinoviruses and respiratory exacerbations.

**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. 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 infections.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Specimens Tested</th>
<th>Rhinovirus + (%)</th>
<th>Coronavirus + (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>168</td>
<td>Japan</td>
<td>118</td>
<td>–</td>
<td>2.5 (NL63)</td>
</tr>
<tr>
<td>169</td>
<td>United States</td>
<td>180</td>
<td>–</td>
<td>8</td>
</tr>
<tr>
<td>170</td>
<td>Italy</td>
<td>182</td>
<td>8.8</td>
<td>–</td>
</tr>
<tr>
<td>171</td>
<td>Scotland</td>
<td>11,661</td>
<td>–</td>
<td>0.3–0.85</td>
</tr>
<tr>
<td>172</td>
<td>France</td>
<td>NA</td>
<td>26.8– (hospital)</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19.5 (community)</td>
<td></td>
</tr>
</tbody>
</table>

NA, not assayed.
pneumonia attributable to rhinovirus infection. In a study of 215 patients with underlying HCT (human stem cell transplantation), 30% had infections at 100 days posttransplant. The incidence for HRV was 22.3% and 11.1% for HCo-V. Median duration of virus shedding was 3 weeks. HRV infection was associated with URI symptoms; however, HCo-V infection was not associated with respiratory symptoms. Two patients with HRV before 100 days developed an LRI, and one patient with HRV and one patient with HCo-V developed an LRI after 100 days.

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. 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 ~30%. Nasal congestion can be alleviated by nasal and systemic decongestants. Several studies have suggested that humidification with steam may reduce nasal congestion in common colds, but the data are not conclusive. Cough is a common accompanying problem in respiratory viral infections and can be controlled 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 physicians frequently prescribe them.

Using our understanding of the cellular changes following rhinovirus infection and replication, several antiviral agents and treatment strategies have been tested. Compounds targeting cell susceptibility, virus attachment, receptor blockade, 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 U.S. Food and Drug Administration approval because of poor bioavailability, side effect profile, or limited potency.

Viral capsid-binding compounds, such as pleconaril, block virus uncoating in vitro. 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. Several low molecular weight compounds inhibit the 3C protease, which is essential for viral replication and assembly. In volunteer trials, a 3C-protease inhibitor, ruaprintrivir, was found to reduce virus shedding but was associated with blood-tinged mucus and irritation of the nasal passages.

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. A recent study in children with “common cold” reported to show shorter mean duration of symptoms in those taking zinc sulfate compared with placebo. 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, directly by contact spread, or by fomite. 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. An evaluation of virucidal hand treatments confirmed the prevention of rhinovirus infections by organic acids but not ethanol. 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 expanded the role rhinoviruses and coronaviruses play in respiratory illnesses. The identification of HRVs has caused us to rethink the extent of these viruses in respiratory illnesses. In addition, newer strains of coronaviruses have extended the importance of these viruses in children. Although there are no approved antiviral agents for these respiratory viruses, our future understanding of the pathogenesis of these infections should guide us in developing antiviral agents and possibly new classes of vaccines.

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