

Spectrum of Clinical Illness in Hospitalized Patients with “Common Cold” Virus Infections

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The viruses associated most frequently with the “common cold” are rhinoviruses and coronaviruses. The first prospective cohort study to determine the prevalence of rhinovirus and coronavirus infections in patients of all ages hospitalized for acute respiratory illnesses is described. Hospital admissions for acute respiratory illnesses were identified, and cell culture for rhinovirus and serologic assays on paired sera for coronaviruses 229E and OC43 were performed. A total of 61 infections with rhinoviruses and coronaviruses were identified from 1198 respiratory illnesses (5.1%); in addition, 9 additional infections associated with ≥ 1 other respiratory viruses were identified. Of those infected with only rhinovirus or coronavirus, underlying cardiopulmonary diseases were present in 35% of the patients aged < 5 years, in 93% aged between 5 and 35 years, and in 73% aged > 35 years. The predominant clinical syndromes varied by age: pneumonia and bronchiolitis in children aged < 5 years; exacerbations of asthma in older children and young adults; and pneumonia and exacerbations of chronic obstructive pulmonary disease and congestive heart failure in older adults. Therefore, rhinovirus and coronavirus infections in hospitalized patients were associated with lower respiratory tract illnesses in all age groups.

Rhinoviruses and coronaviruses are the most frequently identified causes of the “common cold” syndrome [1–3]. Rhinoviruses are members of the *Picornaviridae* family and were first identified in 1956 [4]. Since then, > 100 different serotypes have been identified [5]. Human coronaviruses, members of the *Coronaviridae* family, were first identified in 1962 and have been particularly difficult to isolate by use of standard cell culture techniques [6, 7]. A self-limited upper respiratory tract illness, or “common cold” syndrome, is the usual clinical manifestation of infection with these viruses. However, over the past 3 decades, several studies have found these viruses to be associated with clinical syndromes that require hospital care [8–19]. We recently performed a prospective, cohort study to evaluate the association of respiratory virus infection with respiratory conditions identified in hospitalized patients [20]. In this article, we describe the demographics and clinical characteristics of hospitalized patients identified with recent rhinovirus or coronavirus infection.

Methods

Study design. This prospective study was conducted in an urban public teaching hospital (Ben Taub General Hospital), a chil-

dren’s hospital (Texas Children’s Hospital), and a community hospital (St. Luke’s Episcopal Hospital) in Houston, Texas, from 1991 through 1995 [20]. Patients with an admitting diagnosis suggestive of an acute respiratory condition or congestive heart failure (CHF) were visited in the hospital to confirm eligibility and to seek consent for participation. Acute respiratory disease diagnoses included the following: pneumonia, tracheobronchitis, bronchitis, croup, and exacerbations of asthma or chronic obstructive pulmonary disease (COPD). Patients with active tuberculosis or known HIV disease were excluded. On admission to the hospital, a nasal and/or throat swab and an acute serum specimen were obtained. A convalescent serum was collected ≥ 10 days after obtaining the acute serum. Patients’ inpatient medical records were reviewed. Information collected included sociodemographic data, symptoms, signs, acute respiratory diagnosis and other diagnoses, the location of admission (i.e., general ward or intensive care unit), the duration of hospitalization, the need for ventilatory support, and the chest radiograph interpretation.

Laboratory methods. Respiratory secretion specimens were inoculated on 4 cell culture lines, including human embryonic lung fibroblast cells (WI-38), continuous human epithelioid carcinoma cells (Hep-2), rhesus monkey kidney cells (LLC-MK2), and primary rhesus monkey kidney or Madin-Darby canine kidney (MDCK) cells. Rhinoviruses were identified initially by the characteristic cytopathic changes induced in cell culture. Rhinoviruses were differentiated from enteroviruses by use of acid lability or reverse transcriptase (RT)–PCR assays [21]. Coronavirus infections were identified serologically by use of paired serum samples, with the convalescent serum being collected at least 10 days after the acute serum collection. Antibody tests for coronavirus 229E were performed by use of a microneutralization assay, and infection was defined by the presence of a ≥ 4 -fold increase in antibody levels [22]. An ELISA was used to measure antibodies to coronavirus

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OC43, and infection was defined as a ≥ 4 -fold increase in ELISA IgG antibodies or by a ≥ 2.5 increase that was confirmed on a repeated test [23]. Coinfections with other respiratory viruses were identified by cell culture and serology, as described elsewhere [24].

Results

A total of 1068 patients were enrolled in the study, and these patients had 1198 illnesses evaluated. Of these illnesses, 408 (34.1%) had paired sera available for testing for coronavirus infection. Sixty-one illnesses were identified that were associated with a rhinovirus or coronavirus infection, but infection with no other respiratory viruses (table 1); 9 additional illnesses were associated with both a "common cold" virus (6 rhinoviruses and 3 coronavirus OC43) and an additional respiratory virus (influenza virus, respiratory syncytial virus [RSV], or parainfluenza virus). These patients with dual virus infections tended to be younger (5 of 9, aged < 5 years) and more likely to have had paired sera collected (6 of 9 versus 18 of 61, respectively) than the group identified to have only "common cold" virus infections. These illnesses were not considered further because of the potential confounding effect of the additional respiratory virus infection.

Table 1. Sociodemographics and laboratory abnormalities in hospitalized patients with infections caused by rhinoviruses and coronaviruses.

Data	Age group, years		
	< 5	5–35	> 35
Total no. of illnesses evaluated	419	233	546
Total no. of illnesses with paired sera available	83	99	226
No. of patients with "common cold" virus infection ^a	20	15	26
Rhinovirus	18	14	13
Coronavirus	2	1	13 ^b
Male:Female	8:12	6:9	8:18
Race			
Black	4	7	14
Hispanic	15	4	4
White	1	3	8
Asian	0	1	0
History of smoking	0	2	18
History of asthma	5	13	18
Prior influenza vaccine	0	4	12
Prior pneumococcal vaccine	0	1	4
Mean no. in household	5.6	3.8	3.0
Mean WBC count, cells/ μ L	16,000	12,500	10,900
Positive blood cultures/total	2/9 ^c	0/3	2/7 ^d
Chest radiographic abnormalities	9/16	5/11	18/25

NOTE. RSV, respiratory syncytial virus.

^a Does not include 9 dual infections: 5 in age group < 5 years (2 rhinovirus/RSV, 1 rhinovirus/influenza A virus, 1 rhinovirus/RSV/influenza A virus, and 1 coronavirus OC43/influenza A virus coinfections), 3 in age group 5–35 years (2 rhinovirus/influenza A virus and 1 coronavirus OC43/influenza A virus coinfections), and 1 in age group > 35 years (coronavirus/influenza B virus/parainfluenza type 3 virus coinfection).

^b One dual infection (coronavirus OC43 and coronavirus 229E).

^c Two positive for *Staphylococcus* species.

^d Two positive for *Streptococcus pneumoniae*.

The racial/ethnic distribution of the patients with a "common cold" virus infection was similar to that of the overall study population: 41% ($n = 25$) versus 51% black; 38% ($n = 23$) versus 31% Hispanic; 17% ($n = 12$) versus 16% white; and 1% ($n = 1$) versus 1% Asian. In addition, the age distribution of patients with a rhinovirus or coronavirus infection was similar to that of the overall study population: 33% versus 37% aged < 5 years, 25% versus 19% aged 5–35 years, and 43% versus 44% aged > 35 years. Eighteen (90%) of the 20 patients aged < 5 years, 14 (93%) of 15 patients between the ages of 5 and 35 years, and 13 (50%) of 26 patients aged > 35 years had rhinovirus infections. The remaining 16 patients had coronavirus infections.

Illnesses associated with "common cold" viruses occurred throughout the year but were less frequent during summer months. The distribution of illnesses was as follows: 28% of cases occurred between January and March, 25% between April and June, 13% between July and September, and 34% between October and December. Fifty-eight percent of rhinovirus infections and 81% of coronavirus infections occurred between October and March; 8 of the 9 infections associated with other respiratory viruses also occurred during this period.

The patients' admitting diagnoses were tabulated (table 2). In the group aged < 5 years, the most common clinical diagnoses on admission were asthma ($n = 7$), bronchiolitis (5), possible sepsis (5), and pneumonia (4). For patients between the ages of 5 and 35 years, the primary reason for admission was for the treatment of asthma (14); 1 patient had pneumonia. For patients aged > 35 years, most clinical diagnoses on admission were for the treatment of pneumonia ($n = 8$) CHF (7), COPD (7), and asthma (5). Overall, a chronic cardiopulmonary disease diagnosis was present in 39 (64%) of 61 patients, with asthma being the most common illness, followed by CHF and COPD.

Hospital care took place on the wards in 66% of the cases; however, 34% of the cases were treated in the intensive care unit or the intermediate care unit. One patient aged < 35 years required mechanical ventilation compared with 2 patients aged > 35 years (table 3). Fever and an elevated WBC count were more common in patients aged < 5 years, and wheezing was seen in all age groups. Two of 9 cultures of blood obtained from patients aged < 5 years were positive for *Staphylococcus* species (probable contaminants). Two cultures of blood obtained from patients who were aged > 35 years and had pneumonia were positive for *Streptococcus pneumoniae*. Antibiotics were prescribed for the majority of patients. All patients survived, and the mean (median) length of stay was 3.4 (3) days for patients aged 0–5 years; 3.5 (2) days for patients aged 5–35 years; and 6.0 (6) days for patients aged > 35 years.

Changes seen on chest radiographs largely reflected the clinical diagnoses. For patients aged < 5 years, abnormalities were reported in 9 (56%) of 16 patients (infiltrates or pneumonia, 6; hyperinflation, 2; and atelectasis, 1). Abnormalities were seen in 6 (55%) of 11 patients aged between 5 and 35 years (hyper-

Table 2. Spectrum of clinical illness in hospitalized patients with “common cold” virus infections.

Clinical diagnoses ^a	Age group, years		
	<5 (n = 20)	5–35 (n = 15)	>35 (n = 26)
Asthma	7	14	5
Bronchiolitis	5	—	—
Congestive heart failure	—	—	7
Chronic obstructive pulmonary disease	—	—	7
Croup	1	—	—
Fever/conjunctivitis	1	—	—
Otitis media	2	—	—
Pneumonia	4	1	8
Possible sepsis	5	—	—
Upper respiratory infection	1	—	—

^a Can have >1 diagnosis.

inflation, 4; and infiltrates, 2), and abnormalities were detected in 18 (72%) of 25 patients aged >35 years (pneumonia, 7; CHF/cardiomegaly, 5; emphysematous changes, 4; and pulmonary nodule, 2).

Discussion

Rhinoviruses and coronaviruses are usually recognized as causes of upper respiratory illnesses that are mostly benign and self-limited. However, these “common cold” viruses have also been associated with illnesses that require hospitalization. In previous reports, the role of one or both of these viruses has been evaluated in a select population, on the basis of age or underlying disease [8–19]. Our study is the first to analyze the clinical characteristics of patients from all age groups who were admitted with acute respiratory disease and were infected with a rhinovirus or coronavirus. We found that the distribution of presentations varied with the age and underlying disease of the patient. Only 35% of patients aged <5 years had underlying chronic pulmonary disease (asthma). In contrast, 93% of patients aged between 5 and 35 years had asthma, and 73% of patients aged >35 years had asthma, COPD, or CHF.

Bronchiolitis and pneumonia are the most common clinical syndromes associated with rhinovirus infection in hospitalized children aged <5 years [8–16], a finding confirmed by our study. RSV is the most frequently identified respiratory virus for which young children are hospitalized for an acute respiratory condition, and in some studies rhinovirus has been the second most common [10–13]. The clinical presentation of rhinovirus infection may be similar to that of RSV [15]. In addition, coronavirus infections have been associated with lower respiratory tract illness, including pneumonia and bronchiolitis, in children aged <5 years [19]. There is less information available regarding the relative importance of coronavirus infections in this age group. We identified only 2 coronavirus infections in patients aged <5 years, although paired sera were available for only ~20% of the patients in this age group.

The association of respiratory virus infections with exacer-

bations of asthma has been recognized for several decades [25–27]. In the last several years, respiratory virus infections have been identified in up to 80% of wheezing episodes in school-aged children and in >50% of wheezing episodes in adults [17, 28, 29]. Virus-associated exacerbations can be severe enough to require hospitalization [17, 18], and a correlation between hospitalizations for asthma and the seasonal prevalence of upper respiratory virus infections has been noted, especially in children. In several studies, rhinovirus is the most common respiratory virus associated with asthma exacerbations, and coronavirus is the second most frequent [17, 28, 29]. In the current study, the principal reason for hospitalization of older children and young adults with a rhinovirus or coronavirus infection was an asthma exacerbation.

Respiratory virus infections have also been associated with worsening of other chronic diseases, including cardiopulmonary disorders such as COPD and CHF [31–34]. Although the proportion of exacerbations of these diseases associated with respiratory virus exacerbations has been lower than that seen for asthma, the burden of these infections is substantially greater in chronically ill patients than in healthy subjects of a similar age [33, 34]. In the current study, many of the patients aged >35 years had underlying lung disease or CHF. In addition, several patients were admitted with pneumonia. It is unclear whether rhinovirus can cause pneumonia itself [35, 36]. It has been recovered from the lower respiratory tract of infected individuals [37, 38], and an increase in the number of inflammatory cells in the bronchial mucosa has been noted after experimental infection of the upper respiratory tract [39]. The possibility that these viruses might be associated with an increased risk of bacterial pneumonia, similar to that described for influenza [40, 41], is suggested by the identification of at least 2 pneumonia illnesses in the oldest age group associated with a concomitant *S. pneumoniae* infection. However, this study was not designed to delineate such a virus-bacteria interaction.

There are several potential shortcomings of the current study. Paired sera were available for only a subset of the population; thus, there is substantial potential for the introduction of a bias in identifying the relative importance of coronavirus infections in this population. On the other hand, infections with additional

Table 3. Clinical features and medical care requirements for patients with infections caused by “common cold” viruses.

Data	Age group, years		
	<5	5–35	>35
Mean (median) duration of hospitalization, days	3.8 (3)	3.5 (2)	6.0 (6)
Admission temperature $\geq 38^{\circ}\text{C}$	55	27	15
Wheezing on admission	45	87	50
ICU/IMC care	30	60	23
Supplemental oxygen	25	73	77
Mechanical ventilation	0	7	8
Antibiotics administered	70	40	85

NOTE. Data are percents unless indicated otherwise. ICU, intensive care unit; IMC, intermediate care unit.

respiratory viruses, such as influenza virus or RSV, may have been missed in those persons who did not have serologic studies performed. Another potential shortcoming is that control populations were not included in the study; therefore, the frequency of rhinovirus or coronavirus infections in ambulatory populations, in populations hospitalized with nonrespiratory conditions, or in asymptomatic populations cannot be determined. However, in a study for which virologic studies were performed in the same laboratory during the same period, <2% of cultures were positive for any respiratory virus from an asymptomatic adult and <1% of serologic studies identified a respiratory virus infection during an asymptomatic period [33]. The use of RT-PCR assays for rhinovirus and coronavirus has increased the frequency with which these virus infections were identified, compared with cell culture or serologic methods in previous studies of asthmatic patients [17, 28, 29]. Such assays were not performed in the current study; therefore, the burden of these infections detected in this study is likely to be a minimal estimate of their infection frequency.

The morbidity associated with rhinovirus and coronavirus infections, especially in high-risk populations such as patients with chronic lung disease, suggests that these infections should be a target for prevention or treatment strategies. The development of a conventional vaccine for rhinovirus has been hampered by the existence of >100 different serotypes and by the lack of protection associated with experimental parenteral vaccines [42]. Less is known about the number of coronavirus serotypes, and no experimental human vaccines have been evaluated. IFN- α is an antiviral agent that has been effective in both experimental rhinovirus and coronavirus infection [43–45], and also has been used effectively as postexposure prophylaxis for natural colds [46, 47]. The utility of IFN- α in normal healthy populations has been limited by its local (nasal) toxicity. Only a single study has evaluated its efficacy for the prevention of respiratory virus infections and the resulting complications in patients with chronic lung disease [48]. No beneficial effects of IFN- α were seen in this population of patients with asthma and COPD; however, the study had insufficient power to demonstrate an effect caused by the prevention of rhinovirus and coronavirus infections. Newer antirhinovirus drugs, such as tremacamra and pleconaril, have recently been shown to have beneficial effects in the treatment of experimental rhinovirus infection [49, 50], which suggests that there may be a role for these drugs in high-risk populations. Because of the morbidity associated with rhinovirus and coronavirus infections in high-risk patients, these groups should be targeted in future evaluations of antiviral chemotherapy strategies.

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