Parainfluenza Virus Infection Among Adults Hospitalized for Lower Respiratory Tract Infection


To better define the contribution of human parainfluenza viruses (HPIVs) to lower respiratory tract infection in adults, we tested acute- and convalescent-phase serum specimens from hospitalized adults participating in a population-based prospective study of lower respiratory tract infection during 1991–1992. We tested all available specimens from the epidemic seasons for each virus and ~300 randomly selected specimens from the corresponding off-seasons for antibodies to HPIV-1, HPIV-2, or HPIV-3. During the respective epidemic season, HPIV-1 infection was detected in 18 (2.5%) of 721 and HPIV-3 infection in 22 (3.1%) of 705 patients with lower respiratory tract infection. Only 2 (0.2%) of 1,057 patients tested positive for HPIV-2 infection. No HPIV-1 infections and only 2 (0.7% of 281 patients tested) HPIV-3 infections were detected during the off-seasons. HPIV-1 and HPIV-3 were among the four most frequently identified infections associated with lower respiratory tract infection during their respective outbreak seasons.

Human parainfluenza viruses (HPIVs) are exceeded only by respiratory syncytial virus (RSV) as important causes of lower respiratory tract infection in young children [1]. Most children are infected at least once with HPIVs by the age of 5 years, but infections occur throughout life. Reinfections are more likely to result in acute upper respiratory tract infection [2]. HPIVs have been associated with zero to 12% of acute lower respiratory tract infections in adults [3–14]. HPIVs have also been identified in outbreaks of lower respiratory tract infection in nursing home populations [15] and in adult patients with compromised immune systems [16]. HPIV-3 infection in adult bone marrow transplant recipients has been associated with high mortality rates [16]. Although some of these studies have shown that the HPIVs, among other respiratory viruses, contribute to community-acquired lower respiratory tract infection in adults, most have not provided detailed characteristics of clinical HPIV infection nor taken into account the characteristics seasonality of HPIV epidemics.

A recent study in the United States has addressed the role of some respiratory viruses as potential causes of community-acquired infection among adults hospitalized for lower respiratory tract infection [17, 18]. In the current study, we expanded diagnostic testing to the HPIVs and determined the frequency with which HPIV infections are associated with community-acquired lower respiratory tract infection requiring hospitalization in the context of laboratory-based surveillance data, as well as the clinical and epidemiological features associated with these infections.

Methods

Study site. The study design and methods for enrolling patients have been described in detail previously [17]. The study was conducted in Franklin and Summit counties in Ohio, both mostly urban and suburban agglomerations. Franklin County includes the city of Columbus and has a population of noninstitutionalized adults (≥18 years of age) of ~706,000 [17, 19]. Summit County includes the city of Akron and has a population of noninstitutionalized adults of ~380,000. The demographic characteristics (age, sex, race, employment rate, median income) of the study counties closely reflect those of the United States as a whole, except that persons of nonwhite, nonblack race and Hispanic persons are underrepresented in the study counties [17, 19].

Patients and study design. All patients ≥18 years of age who were noninstitutionalized residents of Franklin or Summit counties in Ohio and were hospitalized at any of the 15 adult-care hospitals in these two counties with the clinical diagnosis of acute lower respiratory tract infection between 1 January
1991 and 31 December 1992 were evaluated for the Community-Based Pneumonia Incidence Study (CBPIS). Eligible patients who had not been discharged from a hospital within the 30 days preceding the admission and who gave informed consent were included in the study. Information on underlying medical conditions, clinical and radiographic findings, and hospital course was abstracted from hospital medical records of all patients. Consenting patients were interviewed by study technicians by use of a standard form; specimens of urine, sputum, and serum were collected soon after admission. The patients were contacted again after 4–6 weeks to complete a follow-up questionnaire and to have a convalescent-phase serum sample collected. A total of 7,927 patients were enrolled in the CBPIS: 5,380 (67.9%) in Franklin County and 2,545 (32.1%) in Summit County.

To evaluate the role of HPIV in community-acquired lower respiratory tract infection, we studied three sets of patients from the CBPIS who developed lower respiratory tract infection during the epidemic seasons for HPIV-1, HPIV-2, and HPIV-3. The HPIV seasons were determined from national surveillance data from the U.S. laboratory-based National Respiratory and Enteric Virus Surveillance System; the epidemic period for HPIV-1 was 29 June to 13 December 1991 (figure 1A); for HPIV-2 it was 24 August to 6 December 1991 and 12 September to 31 December 1992; and for HPIV-3 it was 23 March to 12 July 1991 and 2 May to 28 August 1992 (figure 1B) [20].

All CBPIS patients with radiographic evidence of new lower respiratory tract infection within 48 hours of admission and with both acute- and convalescent-phase serum specimens available were eligible for the HPIV study. Patient information data were not available for patients residing in Summit County for the last 6 months of the study, June–December 1992; these patients were excluded from the HPIV study. Some CBPIS patients included in the HPIV study were initially noted in the medical record to have radiographic evidence of pneumonia, but the final interpretation by a radiologist was negative for a new infiltrate. Patients for the HPIV studies included all eligible CBPIS patients admitted during the respective HPIV season and ~300 patients admitted during the respective off-seasons. Serum specimens from patients selected for each of the HPIV study sets were tested for antibodies to the respective HPIV.

**Diagnostic testing for agents other than HPIVs.** The approaches used to diagnose other causes of lower respiratory tract infection varied by agent [17, 18]. Serum specimens from all CBPIS patients were tested for antibodies to *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*, and serum specimens from selected patients were tested for antibodies to RSV (all eligible patients during the RSV season and selected patients during the RSV off-season) [18], *Histoplasma capsulatum*, influenza virus serotypes A and B (all acute- and convalescent-phase serum pairs from patients admitted between October 1991 and April 1992), and adenovirus. Urine specimens were tested for *L. pneumophila* serogroup 1 antigens and, when available, sputum specimens were cultured for *Legionella* species. Testing for other agents was done at each treating physician’s discretion and included blood and sputum cultures and gram staining of sputum specimens; the results of these tests were abstracted from medical records.

To compare the clinical characteristics associated with HPIV infection with those associated with other agents, we classified non-HPIV agents into three groups. Group I agents included *C. pneumoniae*, *L. pneumophila*, and *M. pneumoniae*, which have historically been associated with interstitial or atypical pneumonia; all study patients were evaluated for serological evidence of infection by these agents. Group II agents included *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Streptococcus pyogenes*, *Moraxella catarrhalis*, *Neisseria meningitidis*, group A streptococci, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, which have historically been associated with classical pyogenic pneumonia; study patients were evaluated for infection by these agents at the discretion of each patient’s physician. Group III agents included RSV, influenza virus serotypes A and B, and adenovirus; selected patients were tested for serological evidence of infection by these agents as noted above [18].

Details of the testing procedures and criteria for defining infection with specific etiologic pathogens other than HPIV have been described elsewhere [17]. Briefly, patients were categorized as having a definite infection with a specific agent if any of the following were true: pathogens were isolated from sterile fluids; the patient had a fourfold or greater rise in titer of antibody to *L. pneumophila* serogroup 1 (indirect immunofluorescent antibody assay), *M. pneumoniae* (complement fixation test), *C. pneumoniae* (IgG and IgM microimmunofluorescence test), RSV (IgG indirect EIA), or influenza virus (hemagglutination inhibition assay); *Legionella* species or influenza virus was isolated from respiratory secretions; or there was a ratio of *L. pneumophila* serogroup 1 antigen in the patient’s urine to that in control subjects of ≥3. A probable infection with *S. aureus*, *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, Enterobacteriaeae, or *P. aeruginosa* was indicated if the respective agent was isolated from purulent sputum.

**HPIV diagnostic testing.** Type-specific IgG antibodies to HPIV-1, HPIV-2, and HPIV-3 were detected by an indirect EIA modified from previously published laboratory protocols [21]; testing for HPIV-4 was not done. Briefly, a 1:100 dilution of the serum specimen was reacted against HPIV-infected and -uninfected NCI-H292 cell culture lysate coated onto duplicate wells of a 96-well microtiter plate. Bound antibodies were detected with a commercial goat anti-human IgG-peroxidase conjugate (catalog no. A8667; Sigma, St. Louis) and a tetra-
methylbenzidine substrate solution. The difference in mean absorbance between the duplicate wells containing HPIV-infected and -uninfected lysate was used to determine the presence and relative amount of HPIV-specific IgG antibodies. Paired acute- and convalescent-phase serum specimens were tested in parallel, and pairs with ratios of absorbance in convalescent specimens to that in acute specimens of \( \geq 1.5 \) were retested at serial twofold dilutions. Patients with a fourfold or greater rise in titer of HPIV-specific IgG antibody between the acute- and convalescent-phase specimens were considered to have been recently infected with the corresponding HPIV. Specimen pairs with a fourfold or greater increase in antibody to one HPIV type were later tested for antibody to the other two HPIV types.

**Statistical analysis.** HPIV-infected and -uninfected patients were compared by use of the two-tailed Fisher’s exact
test for categorical variables and the Wilcoxon rank-sum test for continuous variables.

Results

We were able to locate and test serum pairs from 1,008 patients for HPIV-1, 1,057 patients for HPIV-2, and 986 patients for HPIV-3. These represented 98.4% of eligible patients admitted during the HPIV-1 epidemic season, 97.6% during the HPIV-2 seasons, and 87.7% during the HPIV-3 seasons. During the respective HPIV off-seasons, we tested specimens from between 12.0% and 12.2% of eligible CBPIS patients. The demographic characteristics of patients tested for HPIVs were similar to those not tested: 83.8% vs. 86.1% were white, 15.5% vs. 13.5% were black, and 51.3% vs. 47.1% were male.

Proportions of patients with HPIV infection. During the HPIV-1 epidemic season, 18 (2.5%) of 721 patients had serological evidence of HPIV-1 infection, compared with none of 287 patients tested during the off-season (figure 1A). The ages of the 18 HPIV-1-infected patients ranged from 26.0 to 92.0 years, with a median of 61.5 years, similar to the 984 patients who tested HPIV-1-negative (range, 18.0–97.0 years; median, 64.0 years). Because only 2 (0.2%) of 1,057 patients were infected with HPIV-2 (1 during the HPIV-2 epidemic season), HPIV-2-infected patients were not analyzed further. Twenty-two (3.1%) of 705 patients admitted during two HPIV-3 seasons and 2 (0.7%) of 281 patients admitted during the off-seasons were infected with HPIV-3 (figure 1B). The median age (77.5 years; range, 19.0–84.0 years) of the 24 HPIV-3-infected patients was higher than the median age (63.0 years; range, 18.0–99.0 years) of 961 patients who tested HPIV-3-negative (P = .04). Although we saw heterologous increases in antibody in some specimens, the greatest rise usually occurred in titer of antibody to the epidemic HPIV type (e.g., positive specimens from the HPIV-1 epidemic period had the greatest rise in response to HPIV-1 antigens), suggesting that increases in antibody to heterologous infections were not likely to confound our results.

During their respective epidemic seasons, HPIV-1 (summer–autumn 1991) and HPIV-3 (spring–summer 1991 and 1992) were among the most commonly identified etiologic agents of lower respiratory tract infection. For the 721 patients admitted during the epidemic period for HPIV-1, the four most commonly identified pathogens were influenza virus serotype A (9.8%), S. pneumoniae (3.5%), L. pneumophila (3.2%), and HPIV-1 (2.5%). For the 705 patients admitted during the epidemic period for HPIV-3, L. pneumophila (5.1%), M. pneumoniae (5.0%), S. pneumoniae (4.8%), and HPIV-3 (3.1%) were the most commonly identified pathogens. For both epidemic periods, however, the majority of patients (76%–81%) had no pathogen identified.

Multiple infections. Eight (44%) of 18 HPIV-1-infected patients and 2 (8%) of 24 HPIV-3-infected patients had evidence of infection with other pathogens. Among the HPIV-1-infected patients, other pathogens identified included C. pneumoniae (3 patients), M. pneumoniae (2), L. pneumophila (2), influenza virus serotype B (1), and E. coli (1). Among those infected with HPIV-3, one patient had evidence of infection with S. pneumoniae and one had evidence of infection with E. coli.

Clinical presentation. To look for unique clinical features of HPIV infections, we excluded patients with multiple infections, leaving 10 HPIV-1-infected patients and 22 HPIV-3-infected patients. Given the small number patients infected with HPIV-1 only, we did not compare their clinical characteristics with those of the other patient groups. Six of the HPIV-1-infected patients reported wheezing, one had wheezing noted on physical examination, three had rhonchi, and only one had radiographic evidence of lobar pneumonia. The average leukocyte count for the 10 patients with a fourfold or greater rise in titer of IgG antibody to HPIV-1 was 9,600/μL (normal range, 4,500–11,000/μL).

Several clinical characteristics of the 22 patients with infection solely with HPIV-3 were significantly different from those of patients with bacterial infections with group I (C. pneumoniae, L. pneumophila, or M. pneumoniae) or group II (historically associated with classical pyogenic pneumonia) bacteria (table 1). Wheezing was reported more often among HPIV-3-infected patients (86%) than among patients with group I (68%; P = .22) or group II (55%; P = .04) infections; however, wheezing was not found significantly more often by physical examination. Rhonchi were found more often among HPIV-3-infected patients (52%) than among patients with group I (32%; P = .09) or group II (25%; P = .02) infections, and the leukocyte counts were significantly lower for HPIV-3-infected patients (mean, 9,300/μL) than for patients infected with group I (mean, 11,350/μL; P = .03) or group II (mean, 12,800/μL; P < .01) bacteria.

Radiographic evidence of lobar pneumonia was found less often among HPIV-3-infected patients (27%) than among those infected with group I (48%; P = .07) or group II (66%; P < .01) bacteria, and radiographic evidence of no infiltrate was found more often among HPIV-3-infected patients (41%) than among those with group I (17%; P = .02) or group II (8%; P < .01) bacterial infections. Not surprisingly the radiographic findings in patients with other viral infections, group III, were very similar to those for HPIV-3-infected patients. The duration of the hospital stay was significantly shorter among HPIV-3-infected patients than among patients infected with group II bacteria, but the proportion of HPIV-3-infected patients who required intubation, oxygen therapy, or admission to the intensive care unit was similar to that seen in the other groups of patients (table 1). None of the HPIV-infected patients died, but the need for a convalescent-phase serum specimen precluded detecting infection for any patient who died during their acute illness.

Discharge diagnoses. None of the 44 HPIV-infected patients were diagnosed with HPIV infection (ICD-9-CM [Intern-
Laboratory surveillance data [20]. We may have been less successful in predicting HPIV-2 activity, because seasonal community outbreaks of HPIV-2 are not as regular and predictable [23]. Consequently, our study period may not have included a community HPIV-2 outbreak, and our data may underestimate the importance of this virus as a cause of community-acquired pneumonia.

Our findings support previous studies that suggest that HPIV-1 and HPIV-3 are associated with lower respiratory tract infection in adults [3–14]. After adjusting for oversampling of specimens from patients admitted during the epidemic seasons, we estimate that HPIV-1 infection occurred in 0.6% of patients, HPIV-2 in 0.3%, and HPIV-3 in 1.3% during the 2-year study period. For comparison in this CBPIS study, other seasonal respiratory viruses, RSV and influenza virus serotypes A and B, were estimated (after adjusting for oversampling during epidemic periods) to occur in 2.6% [18], 1.4%, and 1.4% [17] infections with unspecified organism (4 patients), chronic obstructive pulmonary disease (5), other bacterial pneumonia (4), and acute bronchitis (1); for the 22 patients who were found to be infected with HPIV-3 only, the discharge diagnoses included pneumonia with unspecified organism (11 patients), chronic obstructive pulmonary disease (10), other bacterial pneumonia (5), acute bronchitis (3), and pneumococcal pneumonia (1).

Discussion

This study demonstrated that during their respective epidemic seasons, HPIV-1 (summer and autumn of 1991) and HPIV-3 (spring and summer of 1991 and 1992) were among the most commonly identified infections in patients hospitalized for lower respiratory tract infection. HPIV-1 and HPIV-3 infections occurred with a distinct seasonal pattern, which corresponded to national epidemic periods based on national laboratory surveillance data [20]. We may have been less successful in predicting HPIV-2 activity, because seasonal community outbreaks of HPIV-2 are not as regular and predictable [23]. Consequently, our study period may not have included a community HPIV-2 outbreak, and our data may underestimate the importance of this virus as a cause of community-acquired pneumonia.

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of patients, respectively. Thus, HPIVs, RSV, and influenza virus serotype A and B infections were estimated to be present in 8.6% of the CBPIS patients with lower respiratory tract infection and accounted for more than one-third of patients with a definite or probable detection of an infectious pathogen. *M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila* infections were definitively or probably detected in 5.4%, 2.4%, and 2.4%, respectively, of patients during the first year of study [17]. *S. pneumoniae* and *H. influenzae* diagnostic tests were done at each physician’s discretion and showed definite or probable infection in 6.7% and 1.5%, respectively, of the CBPIS patients [17]. It needs to be kept in mind, however, that for >75% of CBPIS patients, there was no definite or probable detection of infection by a respiratory pathogen.

An important consideration in this study is whether the HPIV infections precipitated the hospitalization, were incidental to the hospitalization, or occurred during or after the hospitalization. The rise in titer of IgG antibody that occurred from acute to convalescent serum samples temporally links the HPIV infection to the hospitalization but does not indicate an etiologic link to lower respiratory tract infection in these patients. The absence of another identified pathogen in 92% of HPIV-3-infected patients and the suggestion of a somewhat different clinical presentation (i.e., higher rate of wheezing and rhonchi, lower rate of chest radiographic findings of a lobar infiltrate, and lower leukocyte counts) from that of patients with bacterial pneumonia support the conclusion that HPIV-3 infection caused the lower respiratory tract infection and subsequent hospitalization.

The association with disease is less clear for HPIV-1. In 44% of HPIV-1-infected patients, another pathogen was identified. It is possible that in some patients, the HPIV-1 infection predisposed the patient to infection and disease with the other pathogen, as previously suggested [24–26]. The high percentage of patients with a discharge diagnosis of chronic obstructive pulmonary disease suggests that these two viruses may be especially problematic to persons with underlying lung disease. Additional studies that include nonhospitalized controls are now needed to clarify the clinical importance of HPIV infection in adults with community-acquired lower respiratory tract infection.

As with most of the pathogens included in the CBPIS study, the lack of highly sensitive and specific diagnostic tests makes it difficult to definitively characterize the role of HPIV infections in adults respiratory disease. In this study, we used a fourfold rise in IgG antibodies from acute- to convalescent-phase serum specimens to detect infection. Though this rise in antibody is probably the most sensitive way to detect HPIV infections, even appropriately timed serum specimens will not show a diagnostic rise in antibodies for all infections, and thus, serological diagnostic tests underestimate the true number of HPIV infections [27, 28]. Furthermore, a diagnostic rise in antibodies usually will occur too late to be clinically helpful. Antigen detection and tissue culture isolation have proven to have good sensitivity and specificity for detecting acute HPIV infection in children but are less successful in adults. In adult infection, the titer of virus is lower and duration of virus excretion shorter [27–30]. Timely and sensitive assays, possibly based on the PCR, are needed to improve our ability to diagnose HPIV infections [31].

In summary, this study demonstrates that HPIV-1 and HPIV-3 are among the more commonly detected infections in adults hospitalized with community-acquired lower respiratory tract infections during their respective epidemic seasons and are uncommonly detected during their non-epidemic seasons. Our data suggest that HPIV-3 infections are likely to be clinically important; less information was provided on the clinical importance of HPIV-1 infections and little about the clinical importance of HPIV-2 infections. However, this and other studies make it clear that HPIV-1 and HPIV-3 infections are sufficiently common during their epidemic seasons that it is important to determine how diagnosis of HPIV-1 and HPIV-3 infections might improve the clinical management of adults with lower respiratory tract infection.

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