Respiratory Viruses and Severe Lower Respiratory Tract Complications in Hospitalized Patients*

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Background: Acute respiratory viral infections are generally self-limited in healthy subjects but can lead to severe complications in immunocompromised hosts. We report the clinical impact of acute lower respiratory tract viral infections in hospitalized patients.

Materials and methods: Of 1,001 fiberoptic bronchoscopies performed during a period of 5 years, 33 BAL samples were positive for respiratory viruses by cell culture. The main diagnosis, length of hospitalization, response to initial treatment, and the mortality rate at 30 days were analyzed. Spirometry performed before and after infection was compared in lung transplant recipients.

Results: The following respiratory viruses were identified in 33 cases: influenza A or B (n = 13), parainfluenza virus 1–3 (n = 7), rhinovirus (n = 5), respiratory syncytial virus (n = 4), and adenovirus (n = 4). All cases were immunocompromised patients who acquired new respiratory symptoms and/or radiologic abnormalities suggesting a pulmonary infection. Twenty-five patients (74%) did not respond to initial broad-spectrum antibiotics, and 11 patients (33%) required intensive care for respiratory failure. The overall mortality rate at 1 month was 24%. In patients with a sole viral pathogen identified in their BAL, the mortality rate was 39%. In lung transplant recipients (n = 10), the mean FEV1 decreased from 2.2 to 1.9 L/s before and during the infection episode, respectively (p < 0.01); 3 months later, 60% of the patients had still not completely recovered to baseline values.

Conclusion: Respiratory viruses recovered in BAL samples of immunocompromised patients are associated with severe lower respiratory complications. In lung transplant recipients, we observed a persisting impairment of pulmonary function.

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Key words: adenovirus; BAL; immunocompromised host; influenza; parainfluenza virus; respiratory syncytial virus; rhinovirus; viral infection

Abbreviations: BMT = bone marrow transplant; CMV = cytomegalovirus; HSV = herpes simplex virus; PIV = parainfluenza virus; RSV = respiratory syncytial virus
hosts. However, few studies have assessed the clinical impact of respiratory viruses in unselected hospitalized subjects in whom respiratory viruses are recovered in bronchoalveolar specimens. Most reports in the literature have either analyzed selected types of respiratory viruses or focused on selected subgroups of patients, which limits our understanding of the spectrum of complications associated with respiratory viral infections. A detailed analysis of hospitalized subjects is of interest to better describe the common features, complications, and outcome of severe viral lower respiratory tract infections. Such data may also help us to better understand the potential role of new antiviral drugs in hospitalized patients. We report the clinical features and outcome of adult patients hospitalized at our institution with an acute pulmonary event and in whom a respiratory virus was identified in their BAL sample.

**Materials and Methods**

**Study Location and Patients**

The study was conducted at the University of Geneva Hospitals, a large university teaching hospital. During a 5-year period (January 1996 to December 2000), all viral cultures performed on BAL specimens were reviewed. Cases were defined as any hospitalized patient (>16 years old) with a virus identified in the BAL specimen. Medical records of patients with positive sample findings were retrospectively reviewed for demographic data, respiratory symptoms, primary and secondary diagnosis, concomitant bacterial or fungal infections, and treatment. We recorded any underlying disease indicative of immunosuppression, transplantation, and immunosuppressive therapy, including steroid doses (>10 mg). Data were available for all patients including follow-up at 1 month.

**Outcome**

The main outcome measures analyzed were the mortality at 1 month after the BAL procedure and the response to antibiotic treatment. A secondary outcome was established for the subset of lung transplant recipients to evaluate the spirometry results before, during, and after the viral infection episode.

**Processing of BAL specimens**

At our institution, viral cultures are routinely performed on BAL specimens obtained for identification or exclusion of an infectious process. Local guidelines suggest performing BAL in the following patients: all immunocompromised subjects presenting with a lung infiltrate of unknown origin or a pneumonia that does not resolve despite empiric therapy; lung transplant recipients who undergo lung biopsies as a part of their posttransplant follow-up; cases investigated for presumably noninfectious, interstitial lung diseases; and cases presenting with a severe nosocomial or community-acquired pneumonia that remains unresolved despite wide-spectrum antibiotic treatment. BAL is not performed routinely in cases of severe community-acquired pneumonia in nonimmunosuppressive subjects or in other populations such as the elderly.

All samples were processed for identification of aerobic and anaerobic bacteria, fungi, and mycobacteria using standard laboratory procedures. We also recorded results of any respiratory sample or blood culture performed during the hospitalization preceding the BAL procedure. In lung transplant recipients, spirometry results performed before, during, and after the infection episode were analyzed.

BAL specimens were routinely inoculated on four different cell lines (human fibroblast, A549, MDCK, and LLC-MK2 cells) in tubes and incubated at two different temperatures (37°C and 33°C). Cell cultures were read daily during 10 days to identify any cytopathic effect. For both positive and negative cytopathic effects observed after this period, immunofluorescence with commercially available monoclonal antibodies (Chemicon; Temecula, CA) was carried out for the screening of RSV, PIV, and influenza A or B virus antigens.

**Data Analysis**

The results are summarized as absolute values, either as mean (± SD) or as median (range). One-way analysis of variance was performed for the comparison of the FEV₁ before, during, and after the viral episode. The Kaplan-Meier product-limit method was used to compare the actuarial mortality rate at 30 days after infection in patients with an isolated viral pathogen or with a combined viral and bacterial infection; p < 0.05 was considered statistically significant.

**Results**

Thirty-three patients met our case definition with all medical records available for analysis. The median age was 50 years (range, 16 to 76 years), and 24 were men. All cases had a severe underlying immunosuppressive condition. Eleven patients (32%) were lung transplant recipients (1 female and 10 male patients), 5 patients (15%) were BMT recipients, 5 patients (15%) had HIV infection, 3 patients (8%) had hematologic malignancies, 3 patients (8%) had autoimmune diseases, and 1 patient had a solid tumor, and COPD was present in the remaining patient.

Twenty-four patients (73%) were treated with immunosuppressive therapy at the time of virus isolation (high-dose prednisone, 70%; cyclosporine, 55%; mycophenolate mofetil, 36%; chemotherapy for cancer, 12%; and azathioprine and methotrexate, 6% in each case). Median time for the onset of viral infection following transplantation was 2 years (range, 1 day to 5 years) for lung transplant recipients, and 4.5 months (range, 9 days to 7.5 months) for BMT recipients. Severe neutropenia, defined as <500 neutrophils per milliliter, was present in four patients (12%) at the time of virus isolation. Patients with HIV infection had a median CD4 cell count of 87/µL (mean, 149/µL; range, 6 to 337/µL).

**Virology**

During the 5-year study period, 1,001 BAL specimens were sent to our laboratory for virus detection. A
Concomitant Respiratory Infections

remaining 18 cases, one or more other respiratory pathogens recovered at the time of collection. In five cases (15%), respiratory viruses were isolated from the BAL specimen concomitant to other viruses such as CMV or HSV. In addition to respiratory viruses, the following bacteria or fungi were identified from the BAL specimens of 13 cases: Streptococcus pneumoniae (n = 4), Pseudomonas aeruginosa (n = 3), Aspergillus spp (n = 3), Moraxella catarrhalis (n = 1), Haemophilus influenzae (n = 1), and Pneumocystis carinii (n = 1).

Clinical Features and Outcome

All patients were hospitalized for a median duration of 16 days (range, 2 to 60 days), and all presented an acute lower respiratory event. Eighty-eight percent of cases had dyspnea, 84% had cough, 78% had fever, and 28% had sputum. In 26 cases (79%), a new pulmonary infiltrate was documented on the chest radiograph obtained at the time of virus isolation. Of these, 17 patients had a localized infiltrate, 5 patients had diffuse alveolar or interstitial abnormalities, and 4 patients had changes related to an ARDS.

In lung transplant recipients, a significant decrease in pulmonary function as assessed by spirometry was observed. Figure 1 shows the mean FEV1, 3 months before, during, and 3 months after the acute episode of respiratory viral infection. Mean FEV1 values changed from 2.19 ± 0.94 (before) to 1.9 ± 1.06 L/s during the acute phase at the time of viral isolation (p = 0.003). Three months after the infection episode, the mean FEV1 was 2.15 ± 1.03 L/s, with 6 of 10 patients who had not completely recovered to baseline values.

Broad-spectrum antibiotic therapy was prescribed in all patients; in 74% of cases, no clinical improvement was observed. Eleven patients (33%) were admitted to the ICU for severe deterioration of the respiratory status requiring ventilatory support.

Overall crude mortality at 30 days was 24% (n = 8). Two of three patients with influenza B infection died, as did 2 of 4 patients with adenovirus infection, 1 of 4 patients with RSV, 2 of 10 patients with influenza A, and 1 of 5 patients with rhinovirus. Patients in whom a respiratory virus was the only pathogen identified were compared with those in whom another significant respiratory pathogen was also identified (Fig 2). The mortality rate at 30 days was 39% (7 of 18 patients) in those with a viral infection only, compared with 7% (1 of 15 patients) in those with a concomitant bacterial, fungal, or dual virus infection (p = 0.05). Patients with hematopoietic cancer had the highest mortality rate (56%). Four patients with severe neutropenia died, as did four patients with ARDS.

Table 1—Virus Types Recovered in BAL Specimens of Hospitalized Patients

<table>
<thead>
<tr>
<th>Virus Types</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV</td>
<td>52 (42)</td>
</tr>
<tr>
<td>HSV</td>
<td>38 (31)</td>
</tr>
<tr>
<td>Respiratory viruses</td>
<td>33 (27)</td>
</tr>
<tr>
<td>Influenza A</td>
<td>10 (30)</td>
</tr>
<tr>
<td>PIV-3</td>
<td>5 (15)</td>
</tr>
<tr>
<td>Rhinovirus</td>
<td>5 (15)</td>
</tr>
<tr>
<td>RSV A or B</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Influenza B</td>
<td>3 (9)</td>
</tr>
<tr>
<td>PIV-1</td>
<td>2 (6)</td>
</tr>
</tbody>
</table>

Virus was identified in 138 cases (89%); 15 cases (11%) were children (not analyzed in the present study), and 123 cases (89%) were adults. Of the 123 viruses identified in adults, 52 viruses (42%) were cytomegalovirus (CMV), 38 viruses (31%) were herpes simplex virus (HSV), and 33 viruses (27%) were respiratory viruses. Among these 33 cases, influenza A was identified in 10 cases, PIV-3 in 5 cases, rhinovirus in 5 cases, adenovirus in 4 cases, RSV in 4 cases, influenza B in 3 cases, and PIV-1 in 2 cases. These 33 cases were further analyzed and form the basis of our report. A seasonal pattern in the incidence of respiratory viral infections was observed, and 70% of episodes were diagnosed between October and March of each year. This was particularly clear for influenza A and B, since 9 of 10 isolations occurred when these viruses were circulating in the community. Although rhinovirus and PIV-1 and PIV-3 infections were predominantly detected during the winter months, a substantial number of cases occurred throughout the year.

A hospital-acquired respiratory viral infection was defined as an infection identified in a patient with no respiratory symptoms at the time of hospital admission and who subsequently acquired respiratory symptoms and/or radiographic abnormalities with a positive BAL culture specimen at least 7 days after hospital admission. Seven patients (24%) fulfilled these criteria. The most frequent causes of nosocomial infection were influenza A or B (n = 4), followed by adenovirus (n = 2) and rhinovirus (n = 1).

Concomitant Respiratory Infections

Analyses were conducted to determine if other significant or potentially significant respiratory pathogens were recovered in BAL specimens in addition to respiratory viruses. In 15 of 33 cases (45%), respiratory viruses were the sole respiratory pathogen recovered at the time of collection. In the remaining 18 cases, one or more other respiratory pathogens were concomitantly isolated.
Specific antiviral therapy directed against respiratory viruses (including oral amantadine, IV ribavirin, or oral oseltamivir) was prescribed in seven cases (21%), and all of these patients survived. All lung recipients underwent transbronchial biopsy at the time of virus isolation, and none had evidence of an acute rejection according to the criteria of the International Society of Heart and Lung Transplantation.

**Figure 1.** Longitudinal change in FEV1 in lung transplant recipients (n = 10). Data are not available for one patient.

**Figure 2.** Survival according to the presence or absence of co-infection. *Patients in whom a bacteria and/or a fungi and/or virus was recovered in the BAL sample in addition to the respiratory viruses.
Cell Count and Histopathology Specimens

The mean cell count in BAL specimens was 96/mL of fluid, with 55% of macrophages, 34% of neutrophils, and 11% of lymphocytes. No significant differences were observed between the differential cell counts of patients in whom only a respiratory virus was detected compared with those with other significant pathogens in their BAL specimen (data not shown).

Histopathologic results were available from 13 patients (40%). Ten patients underwent bronchial biopsy, 1 patient underwent open-lung biopsy, and two results were obtained from autopsy samples. A nonspecific inflammatory process was identified in eight cases. Two cases were associated with necrosis of pulmonary tissue, one patients had bronchiolitis, and interstitial fibrosis was observed in another patient. No significant histopathologic abnormalities were observed in the remaining four cases.

Discussion

This study showed that all patients identified with respiratory viruses in their BAL specimens were severely immunocompromised and presented respiratory symptoms and/or chest radiograph abnormalities that remained unresolved in most cases despite broad-spectrum antibiotic therapy. One third of patients presented with a respiratory failure leading to ICU admission, and one fourth died. Surprisingly, the overall mortality rate was higher in patients with only respiratory viruses recovered in their BAL specimens compared with those with concomitant respiratory pathogens. This latter observation strongly suggests that these viruses were not innocent bystanders. This group could represent patients in whom respiratory viruses were the only cause of all symptoms and, in this case, it is likely that we identified a subgroup of patients with severe complications of their viral infection. This group could also represent patients in whom other bacterial pathogens were successfully treated with the virus being the only remaining persistent infection. Taken together, our findings support a contribution of respiratory viruses to disease severity. The fact that all patients had severe immunosuppression is consistent with the knowledge that both an appropriate humoral and cellular responses are necessary for viral clearance. It is thus not surprising that immunocompromised hosts are a target of respiratory viruses and have a strong tendency to lower respiratory tract complications.3,5

In lung transplant recipients, a striking observation was the impact of the acute viral illness on the lung function. In this population, we observed a significant decrease of lung function related to the viral infection with a persistence of abnormalities for several months in a substantial number of cases.13,19 The additional observation that none of the lung recipients presented a cellular rejection during the acute infectious episode supports the role of the viral illness at the origin of the abnormalities found in these patients.

The crude mortality rate among patients with hematopoietic malignancies was higher than in other groups, which is consistent with previous observations reporting a mortality rate as high as 80% in BMT recipients.20 Of note, certain viruses such as RSV or PIV-3 are known to be associated with a higher rate of severe pneumonia or bronchiolitis compared to other viruses.3,21–24 No significant differences were observed between virus types, as numbers were small and this represents a limitation of our study. However, it should be recalled that the impact of a given virus type might greatly vary according to the circulating strain and the virus subtype. For example, small antigenic variations in influenza viruses can lead to significant differences in their virulence,25 a phenomenon that might explain the wide range of associated mortality observed in the literature.5

In our study, few patients received antiviral treatment including ribavirin, amantadine, or oseltamivir. Although the number of treated patients was too small to draw any conclusion, all 7 patients receiving antiviral therapy survived, compared to 18 of 26 nontreated patients. The role of antiviral drugs for the treatment of respiratory viruses in immunocompromised patients has not yet been tested in controlled studies. Some data support the use of ribavirin associated with immunoglobulins in treating severe RSV pneumonia in BMT recipients,26–30 but definite proof of efficacy is lacking. The new neuraminidase inhibitors have not been proven to be effective in treating influenza pneumonia but their efficacy in treating influenza illness supports their use in the case of severe complications. New antiviral compounds, such as pleconaril targeting the picornaviruses, are in development and may be a future option to treat rhinoviral complications.32,33 Taken together, our observations and published data support the use of appropriate antiviral drug as rapidly as possible when a respiratory viral infection is documented in an immunocompromised host.

We observed a seasonal pattern in respiratory viral infections that directly correlated with the epidemiologic trends observed in the community. This confirms that these viruses are easily transmitted to immunocompromised subjects exposed in the community.11,34 Nevertheless, one in five of our patients acquired their infection > 7 days after hospitaliza-
tion, thus strongly suggesting a nosocomial transmission. In particular, nosocomial transmission has been frequently described for RSV and influenza virus. This emphasizes the need to reinforce preventive strategies such as the implementation of droplet precautions, the restriction of visits, and the interdiction of health-care workers with acute respiratory symptoms to work with immunocompromised patients. It also supports the need for a hospital-wide influenza staff vaccination policy. Several reports have estimated that respiratory viruses account for 3 to 20% of viral infections in immunocompromised patients with acute lung diseases who undergo a BAL procedure. In our study, it was slightly higher (27%). The actual impact of respiratory viruses remains underestimated since most of the available studies have used cell culture for viral identification. Reverse-transcription polymerase chain reaction has the potential to increase both sensitivity and specificity of diagnostic procedures and to decrease the time to results availability. However, the use of reverse-transcription polymerase chain reaction for the detection of respiratory viruses raises several unresolved issues including sample processing and the need for assays capable to detect at least nine different viruses. In immunocompromised hosts, it is also very likely that concomitant respiratory infections may confound the diagnosis and diminish the likelihood to perform additional testing for respiratory viruses.

In conclusion, when respiratory viruses are recovered in BAL samples of hospitalized patients, severe lower respiratory tract complications are frequent and are observed in highly immunosuppressed patients. In hospitalized patients with lower respiratory tract infection that do not respond to wide-spectrum antibiotic treatment, the possibility of viral respiratory disease should actively be considered, particularly during epidemics in the community, to ensure that effective preventive and antiviral treatment can be initiated. Further studies are required to better determine the role of the new antiviral therapy in critically ill patients.

REFERENCES

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