Epidemiology of Legionella Pneumonia and Factors Associated with Legionella-Related Mortality at a Tertiary Care Center

Lisa S. Tkatch,* Shimon Kusne, William D. Irish, Sharon Krystoflak, and Edward Wing

From the Division of Infectious Diseases, and the Departments of Medicine, Surgery, and Infection Control, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

Legionella pneumophila is an important pathogen that may cause nosocomial and community-acquired pneumonia in patients with normal or altered immunity. The epidemiology of 40 cases of legionella pneumonia in patients hospitalized between 1986 and 1994 was studied. Fourteen patients (35%) were solid organ transplant recipients. The calculated annual prevalence of L. pneumophila infection was highest among lung transplant recipients (2.07 cases per 1,000 transplant-years). There was a trend toward reduced mortality rates and less severe disease among transplant patients vs. nontransplant patients: mortality rate, 36% vs. 54%; incidence of intubation, 50% vs. 69%; rate of concurrent infections, 29% vs. 38%; and overall rate of complications, 86% vs. 96%; respectively. In a multivariate analysis, factors independently associated with an increased mortality rate were nosocomial acquisition, need for intubation, formation of lung abscess or cavitation, and presence of pleural effusion. Thus, despite differing host immune responses, the most important prognostic factors affecting the outcome of legionellosis are nosocomial acquisition and the development of pulmonary complications.

Since its discovery in 1976, Legionella pneumophila has been recognized as an important cause of community- and hospital-acquired pneumonia in both healthy and immunosuppressed hosts including organ transplant recipients [1, 2]. Legionnaires’ disease has occurred in patients receiving heart, liver, kidney, lung, and bone marrow transplants [3–7]. In the nontransplant population, legionella remains a significant cause of pneumonia, with an associated mortality rate of 14%–43% [8, 9]. Organ transplantation may increase the risk and severity of disease and the mortality rate associated with legionellosis, but comparative data are lacking [2, 10, 11]. The largest series of legionella pneumonia reported in the literature comprises 65 cases, of which only six were in organ transplant recipients [2]. At our institution, a large organ transplantation center, sporadic cases of legionellosis have occurred in both transplant recipients and other immunocompromised as well as immunocompetent hosts. In a historical prospective study, we investigated the epidemiology and outcome of legionella infection in both transplant and nontransplant patients over an 8-year period.

Patients and Methods

Case definition. All cases of legionella-related infection occurring from 1 January 1986 through 30 December 1994 at Presbyterian University Hospital, a 600-bed teaching hospital in Pittsburgh, were identified from review of infection control and microbiology laboratory records. A case was defined as culture of a specimen from any body fluid or tissue that was positive for Legionella species (39 cases) or direct fluorescent antibody (DFA) staining positive for Legionella species if the culture had an overgrowth of normal flora (one case).

Chart review. All medical records were reviewed for data collection. For two patients whose medical records were not available for review, information was obtained from the hospital’s electronic information database MARS (Medical Archival Retrieval System). Included in this database are the admission history and physical examination results, discharge summary, dictated progress notes, medications dispensed from the pharmacy, and all laboratory data.

Demographic data including race, birth date, sex, dates of admission and discharge, dates of all previous organ transplant operations, and outcome of present hospitalization were tabulated. The admission history and physical examination results were reviewed for the presence or absence of the following symptoms: fever, cough, hemoptysis, chills or rigors, headache, dyspnea, chest pain, diarrhea, nausea, vomiting, anorexia, and confusion. In cases of nosocomial acquisition, the progress notes of the week preceding the diagnosis of legionellosis were examined.

Daily progress notes were reviewed for the presence of complications and/or concurrent infections, daily maximum temperature elevations, surgical procedures performed, and the need for intubation. Daily medications and antibiotics administered with respective dose, route, and inclusive dates were recorded. All reports of radiographs and CT studies of the chest were reviewed for the location and type of pneumatic infiltrate and the presence of pleural effusion and/or pulmonic cavitation.
Microbiology data recorded included the date, body fluid site, and results of cultures of all specimens; results of DFA staining; and results of testing with a DNA probe for *Legionella* species. The cause of death was recorded from the discharge summary, death certificate, or autopsy report.

**Definitions.** Date of diagnosis of legionella infection was the date on which a positive DNA probe test or DFA staining was reported or the date of death if the diagnosis was not established before death. Nosocomial acquisition was defined as signs or symptoms of infection occurring >48 hours after hospital admission. Legionella-related mortality was defined as death that was directly attributed to *Legionella* species recovered by culture or positive Dieterle’s staining of autopsy specimens of lung tissue [12] or death for which autopsy demonstrated pneumonia along with a premortem culture positive for *L. pneumophila* or *Legionella micdadei*. In those cases in which an autopsy was not performed, patients whose deaths were respiratory-related within 3 weeks of the diagnosis of legionellosis were considered to have legionella-related mortality. Concurrent infections were those occurring between 2 weeks before and 4 weeks after the diagnosis of legionellosis was established. Complications of legionella infection were those that occurred simultaneously with or as a direct result of legionellosis or as an indirect result from management of legionella infection.

Empyema was defined as culture of pleural fluid positive for *L. pneumophila* or *L. micdadei*. Severity of illness was evaluated by using the following criteria: number of days of hospitalization following diagnosis, incidence of intubation, maximum temperature, number of concurrent infections, and number of complications (including barotrauma, renal insufficiency or failure, pleural effusion, empyema, or lung abscess or cavitation). Renal insufficiency was defined as either a serum creatinine level of ≥2.0 mg/dL in patients without known preexisting renal failure or a doubling of the baseline serum creatinine level within 7 days of the diagnosis of legionellosis for all other patients.

**Microbiology.** Before 1 July 1993, all respiratory tract and pulmonary specimens that were submitted to the microbiology laboratory for routine culture were inoculated onto buffered charcoal–yeast extract (BCYE) agar containing α-ketoglutarate. Culture specimens that were specifically requested for legionella workup were also inoculated onto BCYE agar containing antibiotics (anisomycin, polymyxin B, and cefamandole), but there was no pretreatment of the specimen. Cultures that contained >20–50 colonies of non-*Legionella* organisms after 48 hours of incubation were treated with an acid wash and then were replated. DNA screening with use of polyvalent *L. pneumophila* serogroups 1–6 and *L. micdadei* (SciMedex, Denville, NJ) or a DNA probe for *Legionella* species (Gen-Probe, San Diego) was performed according to the manufacturers’ protocols.

As of 1 July 1993, the inoculation of all routine sputum culture specimens on legionella-selective media was discontinued. Only specimens for which legionella culture was specifically requested were processed in this manner. Cultures were incubated in a humidified atmosphere at 35°C and were examined daily for 5 days by using a dissecting microscope to identify colonies resembling *Legionella* species. Suspicious colonies were gram-stained and subcultured to plates with sheep blood agar and BCYE agar. DNA probe and/or DFA testing was performed to confirm the presence of *L. pneumophila* or *L. micdadei* isolates.

**Statistical analysis.** Differences in means between groups were tested by using the standard two-sample *t* test, while differences in proportions were tested by either Pearson’s χ² test or Fisher’s exact test. The Wilcoxon rank-sum test, a non-parametric equivalent to the standard two-sample *t* test, was used for highly skewed data.

The approximate average yearly incidence of legionellosis and estimates of relative risk for the different transplanted organs were computed by using a multiplicative Poisson regression model [13]. The group of liver transplant recipients was used in this analysis as a reference group. The calculations were performed by using the statistical program GLIM (Generalized Linear Interactive Modeling) [14].

Patient survival was calculated from the date of admission until death. Survival curves were generated by using the Kaplan-Meier product limit method [15] and were compared by the logrank test [16]. Univariate Cox regression [17] was used to identify factors with potential prognostic significance. Variables were included in multivariate Cox regression if they had a *P* value of <.2 at the univariate level or were clinically relevant. The backward elimination method was used to assess simultaneously the effect of each factor and to identify those factors independently associated with legionella-related mortality. The relative risk of mortality and 95% confidence intervals were computed by using Cox regression. Patients who were alive at the end of follow-up or who died of causes not attributable to legionellosis were censored. A *P* value of <.05 was considered statistically significant.

**Results.**

*Legionella* species were isolated in cultures of specimens from 39 of 40 patients during the study period. Culture of one patient’s specimen had overgrowth of *Pseudomonas aerugi-nosa*. This patient developed a new infiltrate on a chest radiograph 2 days after intubation for respiratory failure. Gram staining of bronchoalveolar lavage fluid showed many WBCs, and DFA staining was positive for *L. pneumophila* serogroup 1.

The number of cases by year according to transplant status is shown in figure 1. In 1992, mechanical failure of the chlorination system of the potable water supply resulted in nine nosocomial cases of legionellosis (authors’ unpublished data). Control measures included superchlorination of the potable water system and consumption of bottled water by patients. Only tub or basin baths were permitted. A second chlorinator was installed...
The relative risks for lung and heart transplant recipients were 8.60 (95% CI, 1.01–73.57) and 7.18 (95% CI, 2.19–23.52), respectively, compared with liver transplant recipients.

**Demographics.** The legionella-infected population included 40 patients, of whom 14 were organ transplant recipients (table 2). Fifty-seven percent of the cases in transplant recipients and 54% of the cases in nontransplant recipients were nosocomially acquired. The mean age, the male-to-female ratio, and race distribution were similar between the two groups. The median length of hospitalization before the diagnosis of legionellosis was 7.5 days (range, 2–105 days) for the transplant group compared with 4 days (range, 0–34 days) for the nontransplant group ($P = .210$).

In the transplant group, infection was identified in 6 heart, 5 liver, and 2 kidney transplant recipients and in one lung transplant recipient. The most frequent underlying medical or immunosuppressive condition in the nontransplant group was use of corticosteroids (9 cases [23%]), followed by cirrhosis (5 [13%]), hematologic or oncological malignancy (4 [10%]), diabetes mellitus (2 [5%]), and AIDS (2 [5%]). Four patients (10%) did not have any recognized underlying disease.

**Microbiological characteristics.** Seventy-five isolates of *Legionella* species were recovered from the 40 patients. These isolates were from seven different types of culture specimens: sputum (43), bronchoalveolar lavage fluid (18), pleural fluid (6), lung tissue (5), blood (1), fascia (1), and chest wound (1). More specimens were acquired via bronchoscopy from the transplant recipients than from the nontransplant recipients (nine vs. six, respectively) because of a more aggressive approach in management of transplant patients with lung infiltrates. Nonpulmonary (fascia, blood, and chest wound) isolates were recovered only from transplant patients. We have not encountered any legionella infections of skin, soft tissue, or blood in nontransplant patients.

Of the 40 patients with legionellosis, 29 had *L. pneumophila* or *L. micdadei* isolated from a sputum culture. For six patients, no sputum samples were submitted for culture. Legionella pneumonia was diagnosed by analysis of bronchoalveolar lav-

### Table 1. Incidence of legionellosis in organ transplant recipients during 1986–1994 at Presbyterian University Hospital in Pittsburgh.

<table>
<thead>
<tr>
<th>Type of transplant</th>
<th>Total no. of first time organ transplants ($n = 6,223$)</th>
<th>Interval (y)</th>
<th>No. of cases of legionellosis ($n = 14$)</th>
<th>Average yearly incidence* of legionella infection per 1,000 transplants</th>
<th>Relative risk² (95% CI)</th>
<th>$P$ value³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>3,655</td>
<td>9</td>
<td>5</td>
<td>0.28</td>
<td>1.0</td>
<td>.001</td>
</tr>
<tr>
<td>Heart</td>
<td>545</td>
<td>9</td>
<td>6</td>
<td>1.85</td>
<td>7.18 (2.19–23.52)</td>
<td>.001</td>
</tr>
<tr>
<td>Lung</td>
<td>224</td>
<td>4</td>
<td>1</td>
<td>2.07</td>
<td>8.60 (1.01–73.57)</td>
<td>.049</td>
</tr>
<tr>
<td>Kidney</td>
<td>1,799</td>
<td>9</td>
<td>2</td>
<td>0.24</td>
<td>0.86 (0.16–4.20)</td>
<td>.806</td>
</tr>
</tbody>
</table>

* No. of cases of legionellosis/total no. of transplants at the midpoint of the interval × interval) × 1,000.

² Relative risk of development of legionellosis compared with that for liver transplant recipients.

³ Wald’s test.

⁴ During 1991–1994, 91% of lung transplantations were performed at our institution.
Table 2. Demographic characteristics of the legionella-infected population at Presbyterian University Hospital in Pittsburgh.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Transplant recipients (n = 14)</th>
<th>Nontransplant recipients (n = 26)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD (y)</td>
<td>52 ± 10</td>
<td>58 ± 19</td>
<td>.272</td>
</tr>
<tr>
<td>Male-to-female ratio</td>
<td>1:1</td>
<td>6:7</td>
<td>.816</td>
</tr>
<tr>
<td>No. (%) with race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>11 (79)</td>
<td>22 (85)</td>
<td>.191*</td>
</tr>
<tr>
<td>African American</td>
<td>1 (7)</td>
<td>4 (15)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (14)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Median no. of days hospitalized before diagnosis of legionellosis (range)</td>
<td>7.5 (2–105)</td>
<td>4 (0–34)</td>
<td>.210*</td>
</tr>
<tr>
<td>No. (%) of nosocomial cases</td>
<td>8 (57)</td>
<td>14 (54)</td>
<td>.842</td>
</tr>
</tbody>
</table>

* Fisher’s exact test.
† Wilcoxon rank-sum test.

Clinical symptoms. The most commonly recorded symptoms included the following: fever, 30 patients (86%); cough, 17 (81%); dyspnea, 20 (80%); and chills or rigors, 11 (73%). These symptoms were present at a similar frequency among both transplant and nontransplant patients.

Severity of illness. Parameters assessed to evaluate severity of illness are shown in table 4. Although there was no statistically significant difference between the two groups, the mortality rate, incidence of intubation, and incidence of concurrent infections and complications were higher among nontransplant patients than among transplant recipients, thus suggesting more severe disease.

Concurrent infections. Ten nontransplant patients and four transplant patients developed concurrent infections. Bacteremia was seen in six nontransplant patients but in none of the transplant patients, whereas invasive fungal infections occurred in two transplant patients and in none of the nontransplant patients. Other concurrent infections included bacterial pneumonia, cryptococcal meningitis, Clostridium difficile colitis, and cholangitis.

Complications. Twelve (86%) of 14 transplant patients and 25 (96%) of 26 nontransplant patients developed either renal failure or thoracic complications. Acute renal failure occurred in 54% of nontransplant patients (seven of whom required dialysis) and in 57% of transplant patients (two of whom required dialysis). Empyema occurred only in five transplant patients (P = .004), whereas barotrauma occurred only in seven nontransplant patients (P = .071). The overall number of patients with lung abscess or cavitation, pleural effusion, and empyema in the transplant group was 7 (50%), 6 (43%), and 5 (36%), respectively. In the nontransplant group, 19 patients (73%) developed pleural effusions, six (23%) developed lung abscess or cavitation, and none developed empyema.

Mortality. In the transplant group, there were six deaths (43%), five of which were legionella-related. In the nontransplant group, 16 patients (62%) died, 14 of whom had legionella-related deaths. To determine which factors were related to an increased mortality rate associated with Legionella species, a multivariate stepwise analysis with use of Cox regression was performed. The following factors were included in the stepwise analysis: length of time from onset of symptoms to diagnosis, length of hospitalization, occurrence of concurrent infections, and presence of Legionella species in sputum or bronchoalveolar lavage fluid.

Table 3. Species of Legionella isolated during the study period (1986–1994) at Presbyterian University Hospital in Pittsburgh.

<table>
<thead>
<tr>
<th>Legionella species and/or serogroup</th>
<th>Transplant recipients (n = 14)</th>
<th>Nontransplant recipients (n = 26*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. pneumophila serogroup 1</td>
<td>10 (71)</td>
<td>18 (69)</td>
</tr>
<tr>
<td>L. pneumophila serogroup 3</td>
<td>0</td>
<td>3 (12)</td>
</tr>
<tr>
<td>L. pneumophila serogroup 4</td>
<td>2 (14)</td>
<td>0</td>
</tr>
<tr>
<td>L. pneumophila serogroup 5</td>
<td>1 (7)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>L. pneumophila serogroup 6</td>
<td>1 (7)</td>
<td>0</td>
</tr>
<tr>
<td>L. pneumophila serogroups 1 and 6</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>L. micdadei</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>L. pneumophila, not serogrouped</td>
<td>0</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

* In one case, culture yielded an overgrowth of Pseudomonas aeruginosa; thus, Legionella species could not be isolated, but direct fluorescent antibody staining and DNA probe testing were positive.
Table 4. Severity of legionella infection in 40 patients at the Presbyterian University Hospital in Pittsburgh.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Transplant recipients</th>
<th>Nontransplant recipients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median no. of days hospitalized after diagnosis of legionellosis (range)</td>
<td>18.5 (0–109)</td>
<td>11.5 (0–94)</td>
<td>.213*</td>
</tr>
<tr>
<td>No. (%) of patients requiring intubation</td>
<td>7 (50)</td>
<td>18 (69)</td>
<td>.231</td>
</tr>
<tr>
<td>Mean maximum temperature ± 1 SD (°C)</td>
<td>39.4 ± 0.9</td>
<td>39.2 ± 0.9</td>
<td>.652</td>
</tr>
<tr>
<td>No. (%) of patients with concurrent infections</td>
<td>4 (29)</td>
<td>10 (38)</td>
<td>.731</td>
</tr>
<tr>
<td>No. (%) of patients with complications</td>
<td>12 (86)</td>
<td>25 (96)</td>
<td>.276</td>
</tr>
<tr>
<td>No. (%) of patients who received appropriate antibiotic therapy</td>
<td>12 (86)</td>
<td>21 (81)</td>
<td>1.0</td>
</tr>
<tr>
<td>No. (%) of patients with legionella-related mortality</td>
<td>5 (36)</td>
<td>14 (54)</td>
<td>.273</td>
</tr>
<tr>
<td>No. (%) who underwent autopsy</td>
<td>5 (36)</td>
<td>9 (35)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* Wilcoxon rank-sum test.
† Fisher’s exact test.
§ Defined as any medical condition occurring simultaneously with or as a direct result of legionella infection or its treatment.

procedure: age, number of days to the diagnosis of legionellosis, culture specimen, organ transplantation, presence of concurrent infections, need for intubation, administration of appropriate antibiotics, lung abscess or cavitation formation, and presence of pleural effusions. In the stepwise procedure, some of the factors were incorporated as time-dependent covariates (i.e., presence of concurrent infections, need for intubation, administration of appropriate antibiotics, lung abscess or cavitation formation, and presence of pleural effusion). The factors independently associated with an increased mortality rate included hospital-acquired infection, need for intubation, formation of lung abscess or cavitation, and presence of pleural effusion (table 5).

Antibiotic treatment. Most nontransplant patients were treated with erythromycin with or without rifampin. One patient who was treated with erythromycin together with ciprofloxacin died. For three patients, the initial antibiotic regimen was changed because of clinical failure; of these patients, one who survived was initially treated for 5 days with ciprofloxacin and then with erythromycin. The other two patients died; one patient was treated with erythromycin and rifampin for 5 days and then with ciprofloxacin, and one patient was treated with erythromycin and trimethoprim-sulfamethoxazole for 3 days and then with erythromycin and rifampin. Although most transplant patients were treated with erythromycin with or without rifampin, it should be noted that three transplant recipients who survived were treated with ciprofloxacin, ofloxacin, and ciprofloxacin and rifampin, respectively. Appropriate antibiotic therapy was begun the day before the diagnosis of legionellosis in 10 patients, five of whom died. Appropriate antibiotic ther-

Table 5. Factors associated with legionella-related mortality at Presbyterian University Hospital in Pittsburgh according to Cox regression.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted RR (95% CI)</td>
<td>P value*</td>
</tr>
<tr>
<td>Age</td>
<td>1.02 (0.99–1.05)</td>
<td>.257</td>
</tr>
<tr>
<td>Days until diagnosis of legionellosis</td>
<td>0.99 (0.96–1.02)</td>
<td>.513</td>
</tr>
<tr>
<td>Nosocomial source</td>
<td>1.38 (0.54–3.51)</td>
<td>.492</td>
</tr>
<tr>
<td>Transplant recipient</td>
<td>0.51 (0.18–1.42)</td>
<td>.180</td>
</tr>
<tr>
<td>Presence of concurrent infections³</td>
<td>2.85 (1.04–7.82)</td>
<td>.042</td>
</tr>
<tr>
<td>Intubation required²</td>
<td>36.15 (4.78–273.18)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Received appropriate antibiotic therapy³</td>
<td>1.10 (0.39–3.11)</td>
<td>.854</td>
</tr>
<tr>
<td>Developed lung abscess or cavitation³</td>
<td>4.42 (1.43–13.61)</td>
<td>.014</td>
</tr>
<tr>
<td>Developed pleural effusion³</td>
<td>12.28 (2.77–54.44)</td>
<td>&lt;.00001</td>
</tr>
</tbody>
</table>

* Based on the likelihood ratio test.
† Incorporated as time-dependent covariates.
apy was begun on the day of the diagnosis of legionellosis in 15 patients, six of whom died. All seven patients who were not treated with appropriate antibiotics died.

Discussion

Legionellosis is a severe pulmonary infection occurring in immunosuppressed and normal hosts. Most reported cases of legionellosis in transplant recipients occurred in renal, heart, and bone marrow transplant patients, but only few cases in lung and liver transplant recipients have been reported [2–7, 10, 18–25]. In this study, approximately one-third of the patients were transplant recipients. The annual incidence of legionella infection was highest among lung transplant recipients, followed by heart, liver, and kidney transplant recipients. Previous studies showed that the incidence of legionella infection was 7.7% among heart transplant recipients [10], 23.6% among kidney transplant recipients [18], and 1.2% among liver transplant recipients [4]. These studies relied on positive serology; therefore, the rates overestimated the incidence of legionellosis. Our case definition was based on positivity of culture or DFA staining in addition to clinical symptoms; thus, our study resulted in a lower but more accurate incidence [3, 5].

The overall mortality rate among nontransplant patients with legionellosis has been reported as 14.6%–42.8%, with higher mortality rates (65%) in nosocomial cases [8, 9, 26, 27]. Our overall mortality rate associated with legionellosis was 54%. The mortality rate among patients who acquired legionella infection nosocomially, however, was 79% compared with 42% among patients with community-acquired cases. A comparison of the relative risk of nosocomial legionellosis between transplant and nontransplant patients would be of interest, but we were unable to perform this evaluation because our data were limited to patients with legionellosis only and all other hospitalized patients with pneumonia seen during the same period were not included in the study. Patients receiving corticosteroid therapy are at high risk for developing legionellosis and are more likely to die than are otherwise healthy hosts [2, 28]. The mortality rate among the nontransplant patients with underlying illnesses was higher than that among those without underlying illnesses, among whom the mortality rate was 50%. Specifically, the mortality rates among patients receiving corticosteroid therapy, patients with diabetes mellitus, patients with cirrhosis, and patients with hematologic or oncological malignancy were 56%, 100%, 80% and 75%, respectively; both of the patients with AIDS survived.

Mortality rates associated with legionellosis in the transplant population are not well documented [1, 4, 5, 7, 20]. In one study, the mortality rate among heart transplant patients with legiomnaires’ disease was 17% compared with 4.7% among nontransplant surgical cardiac patients [3]. Surprisingly, in our study, solid organ transplant recipients appeared to have relatively less severe illness than did other patients. The legionella-related mortality rate, the incidence of intubation, and the frequency of concurrent infections were lower among these patients, as was the overall incidence of complications (table 4). Although statistical significance was not achieved, there was a trend toward less severe disease in the transplant population. The explanation for these differences is not clear. Prophylaxis with trimethoprim-sulfamethoxazole cannot be implicated since only two of the transplant patients were receiving prophylaxis at the time of admission. It is possible that transplant patients may present to medical attention earlier, a result of a careful and continuous follow-up.

L. micdadei pneumonia, which was originally described at our institution in 1979 [29], tends to occur in severely immunocompromised patients [18, 30]. Of the 40 cases of legionellosis, only one was caused by L. micdadei. This case was community-acquired and occurred in a nontransplant patient who received corticosteroid therapy for systemic lupus erythematosus.

Tacrolimus (formerly called FK-506), a new macrolide used to prevent organ rejection, has been widely studied as a primary immunosuppressive agent at our institution since August 1989. In comparison with cyclosporin A, it was associated with a lower incidence of bacterial and fungal infections but with a similar incidence of cytomegalovirus infection [31–34]. Only two of our transplant patients received tacrolimus therapy; the other 12 patients received immunosuppressive therapy with cyclosporin A.

Pleural effusion, empyema, and lung abscess or cavitation formation are recognized complications of legionella pneumonia, the latter of which is most commonly described in severely immunosuppressed patients [8, 35–37]. In our study, empyema occurred only in transplant recipients, and it may be a result of reduced ability to locally contain infection with Legionella species that is induced by immunosuppressive agents with activity against T cells. Renal insufficiency or failure is a recognized complication of legionellosis and portends a worse prognosis [38]. The etiologies of renal failure include sepsis, hypotension, rhabdomyolysis, administration of nephrotoxic agents, and acute tubulointerstitial nephritis due to L. pneumophila. The mortality rate among our patients who developed renal insufficiency or failure was 68%, similar to findings of other investigators [39]. Concomitant infections with legionella infection are reported to occur at a frequency of 5%–10% [2, 11, 40]. The higher incidence of bacteremia in the nontransplant group along with the higher incidence of invasive fungal infections in the transplant group suggests that the transplant patients may have received more empirical antibiotic therapy.

The sensitivity of DFA staining has been reported as 20%–70% [9, 41–43]. When compared with positive culture, the sensitivity of DFA staining was 88%, and that of DNA probe testing was 63% (which is comparable with sensitivities of 31%–67% previously reported by Finkelstein et al. [42]). We previously reported equivalent sensitivities for the two methods for patients who had cultures positive for Legionella species (DNA probe testing, 81.8%; DFA staining, 72.7%) [44]. Most of the previous studies used serology as a diagnostic criterion.
for legionella infection. In this series, the higher sensitivity of DFA staining may be a reflection of a more specific diagnostic test for legionella infection (culture instead of serology). Findings of gram staining, serology, and detection of urinary antigen were sporadic; therefore, we could not obtain meaningful conclusions regarding their utility for the diagnosis of legionellosis.

The standard antibiotic therapy for legionellosis is erythromycin. Anecdotal reports have demonstrated successful treatment of legionella infection with fluoroquinolones [21, 45, 46]. In our series, fluoroquinolones were used as primary therapy for three transplant patients, all of whom survived. Therefore, fluoroquinolones may be a valid therapeutic option for transplant patients. They offer an advantage over erythromycin, with its known interaction with cyclosporin A and tacrolimus. However, occasional failures of fluoroquinolone treatment have been described in patients with altered immunity, such as patients with AIDS and those with concomitant corticosteroid use [47, 48].

Previous reports have identified underlying immunosuppressive conditions and need for intubation as factors related to an increased mortality rate associated with legionella infection [2]. In this series, hospital acquisition of infection, need for intubation, formation of lung abscess or cavitation, and presence of pleural effusions were found to be independently associated with an increased mortality rate. Formation of lung abscess or cavitation and pleural effusion have not been reported to be associated with an increased mortality rate [8, 35, 37]. The higher mortality rate in nosocomial cases was possibly related to a delay in institution of antibiotic therapy for legionellosis. Thus, prompt recognition of legionellosis and institution of appropriate treatment are important determinants of outcome, irrespective of underlying host immune status.

Acknowledgments

The authors thank A. William Pasculle, Sc.D., and the microbiology laboratory technologists at Presbyterian University Hospital in Pittsburgh for performing the microbiological studies.

References


