Infection in the Transplanted and Native Lung After Single Lung Transplantation*


Objective: To analyze a single-center experience with infectious complications of single lung transplantation (SLT) with special emphasis on risk factors for infection in the transplanted and native lung.

Design: Consecutive case series.

Setting: University teaching hospital.

Patients: Fifteen consecutive SLT recipients (mean age, 43 years; 9 men and 6 women). Mean follow-up was 337 days.

Results: Fifteen patients had 24 infectious episodes (1.6 per patient) of which 83 percent were life-threatening, 79 percent involved the lung, airway, or pleural space, and 79 percent occurred in the first 4 months after transplantation. Despite this high infectious morbidity, there were no infectious deaths. The most important infections were bacterial pneumonia (n = 10), cytomegalovirus (CMV) pneumonia (n = 5), and bronchial anastomotic infections (n = 3). Significant risk factors for bacterial pneumonia were a diagnosis of primary or secondary pulmonary hypertension (p < 0.05) and the presence of airway complications of stenosis or dehiscence (p < 0.05). No risk factors for overall lung infections were identified. The native lung was involved in 6 of 16 lung infections and was the exclusive site of infection in 4 cases. Underlying disease in the native lung may have predisposed to infection at that site by a mechanism of inadequate blood flow or impaired ventilation. Three bronchial anastomotic infections (Pseudomonas, Candida, Aspergillus) occurred, all with dehiscence of the anastomosis. These were highly morbid but resolved with antibiotics, stent placement, and surgical retention in two of the three cases. The five episodes of CMV pneumonia caused mild (four patients) or moderate (one patient) dysfunction and responded to antiviral agents without relapse.

Conclusion: The frequency, complexity, and morbidity of infections after SLT were great, but most infections were manageable and good outcomes were achieved. A pretransplant diagnosis of pulmonary hypertension or posttransplant occurrence of bronchial stenosis or dehiscence were associated with a higher rate of bacterial pneumonia. The underlying disease in the native lung may predispose to infection at that site.

Infection has been a major complication of combined heart-lung transplantation.1-3 Recently, isolated single lung transplantation (SLT) has replaced heart-lung transplantation as the accepted treatment for many types of end-stage lung disease4-7 and is performed in more than 30 centers in the United States. To date and to our knowledge, only one detailed report on infections associated with isolated lung transplantation has appeared.8 We report our experience of infectious complications in our first 15 SLT recipients with emphasis on risk factors for pulmonary infections and the occurrence of native lung infection.

METHODS

Patients

Infectious episodes were reviewed in 15 patients (9 men, 6 women) who received SLTs from March 9, 1990 to April 30, 1992 at Vanderbilt University Medical Center. Indications included emphysema (five), pulmonary fibrosis (four), primary pulmonary hypertension (two), secondary pulmonary hypertension (two), veno-occlusive disease with pulmonary hypertension (one), and silicosis (one). Mean age was 43 years (range, 11 to 61 years). The mean follow-up was 337 days.

Operative Technique

Seventeen SLTs (6 right, 11 left) were performed on 15 patients. Bronchial anastomosis was either end-to-end (n = 11) or by intussusception (n = 6). Thirteen anastomoses were wrapped with omentum (n = 10) or pericardium (n = 3) and 4 were not wrapped. Cardiopulmonary bypass was used in five patients because of preexisting pulmonary hypertension. The mean ischemic time was 180 min.

Patient Management

Recipients were screened with a tuberculin skin test, antibody tests for herpes viruses, and Toxoplasma gondii. Bronchial cultures and cytomegalovirus (CMV) antibody titers were obtained on the donor. Antimicrobial prophylaxis included ceftazadime and either nafcillin or vancomycin for 4 days. The duration of treatment was extended to 10 to 14 days if there was evidence of donor lung infection or colonization. Antiviral prophylaxis for CMV-seropositive patients was acyclovir, 800 mg 3 times a day orally for 6 months. The CMV-seronegative patients with seropositive donors received intravenous (IV) ganciclovir instead of acyclovir for the first 2 weeks and also received intravenous immunoglobulin, 400 mg/kg IV every 2 weeks for 4 doses. Antifungal prophylaxis was either fluconazole, 200 mg/d (10 patients) or amphotericin B, 10 to 15 mg/d (4 patients). The fluconazole therapy was continued during primary hospitalization; the amphotericin B therapy was continued to a total dose of 300 mg. Sulfamethoxazole-trimethoprim was administered at 2 DS tablets weekly on Mondays for Pneumocystis prophylaxis. Immu-
nosuppression included cyclosporine dosed for a blood level of 200 to 300 ng/ml as determined by high-pressure liquid chromatography, azathioprine at 2 mg/kg/d adjusted to keep the WBC count greater than 5,000, prednisone at 0.2 mg/kg/d starting on day 7 to 14, and rabbit antilymphocyte serum, 15 ml IV for the first 14 days. Surveillance bronchoscopy for rejection and anastomotic evaluation was done every 2 weeks during the first 2 months and then at 3, 6, 9, and 12 months. The CMV and bacterial cultures were routinely obtained at these times.

**Infection Definitions**

Bacterial pneumonia was defined as a new fever greater than 38°C coupled with a new infiltrate on chest radiograph, isolation of a predominant pathogen, and detection of numerous neutrophils on bronchoalveolar lavage (BAL) or sputum specimen. Rejection was ruled out by transbronchial biopsy specimen in most cases. Cytomegalovirus infection was diagnosed with a positive culture from any site or a fourfold or greater rise in IgG antibody titer. The diagnosis of CMV disease required new fever >38°C with isolation of CMV, no other source of fever, and either atypical lymphs <3 percent, leukopenia <4,000/μl, or thrombocytopenia <100,000/μl. The diagnosis of pulmonary CMV required inclusion bodies on lung biopsy specimen or BAL cytologic study. The diagnosis of invasive fungal infection required isolation from a sterile site or evidence of tissue invasion on biopsy specimen.

**Analysis**

Total lung infections and bacterial pneumonias were studied for their association with the following risk factors: age, gender, underlying diagnosis (primary or secondary pulmonary hypertension vs other diagnoses), side of transplant, total ischemic time, use of cardiopulmonary bypass, and presence of airway complications (stenosis or dehiscence). The number of infection episodes occurring 2 months after a treated rejection episode was compared with the number of infection episodes occurring 2 months before the episode. Proportions were compared using χ² with Yates’ correction. Means were compared with Student’s t test. Significance was assumed if the p value was less than 0.05.

**RESULTS**

Twelve (80 percent) of the 15 patients had a significant infectious episode. Overall there were 24 infections (Table 1) or 1.60 infections per patient. All infections occurred in the first year after transplantation. The timing of the infections is shown in Figure 1. This figure shows that 75 percent of the infections occurred in the first 4 months after transplantation. Twenty (83 percent) of the infections were considered to be severe and 19 infections involved the lung, airway, or pleural space. The most frequent infection was bacterial pneumonia (ten cases). One of the bacterial pneumonias was present in the donor lung before transplantation and was documented by lung biopsy specimen and culture of donor pleural fluid; the infection resolved with postoperative antibiotics. Other common infections were CMV pneumonia (five cases), anastomotic airway infections (three cases), and urinary tract infections (three cases). Miscellaneous infections occurring as single cases were peritonitis from a ruptured colonic diverticulum, bacterial empyema, and cutaneous herpes zoster. The flora in

<table>
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<th>Patient No.</th>
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*This pneumonia was detected in donor before implantation. Abbreviations: T = transplant lung; N = native lung; CMV = cytomegalovirus; BAL = bronchoalveolar lavage; GNR = Gram-negative rod.
bacterial lung infections was typical of hospitalized patients and included organisms such as *Staphylococcus aureus*, *Pseudomonas*, and enteric Gram-negative rods.

No association was found between age, gender, underlying diagnosis, side of transplant, ischemic time, use of cardiopulmonary bypass, or presence of airway complications with the rate of overall lung infections. However, on analysis of these factors for association with bacterial pneumonias, it was found that a pretransplant diagnosis of pulmonary hypertension and the presence of airway complications after transplantation were both associated with a higher rate of bacterial pneumonia (1.4 vs 0.2 pneumonias per patient for both observations, p<0.05, t test). The rate of lung infection occurring in a 2-month time span before and after treated rejection episodes was also analyzed. Eight lung infections occurred in a 2-month interval after 21 antirejection treatments (mean observation time, 1.84 months). Three lung infections occurred in a 2-month interval before these same 21 rejection treatments (mean observation time, 1.22 months). The difference in infection rates was not significant, even without adjustment for the difference in observation time.

Analysis of the side of lung infection showed that ten infections occurred in the transplanted lung but two of these also involved the native lung and four occurred exclusively in the native lung. These occurred both early (14 days) and late (192 days) after transplantation. Responsible pathogens included *S aureus*, *Pseudomonas aeruginosa*, Acinetobacter, and Aspergillus. All three bacterial native lung infections occurred in patients with a preoperative diagnosis of pulmonary hypertension suggesting that low blood flow to the native lung postoperatively may have played a role in the pathogenesis. We investigated results of perfusion scans done in the patients to see if there was indeed evidence of lower blood flow to the native lung in patients with pulmonary hypertension preoperatively. The 15 patients had between 4 and 21 perfusion scans each. The mean of the median percentage perfusion to the native lung in patients with pulmonary hypertension was 10.5±6.6 percent compared with 26.0±9.3 percent in patients without pulmonary hypertension (p<0.01, t test). The Aspergillus infection appeared to arise in a large bullous space in the upper lobe of the native right lung and emphysematous changes in the lung may have been a risk factor.

Cytomegalovirus infection occurred in 12 (85 percent) of 14 patients at risk. A CMV lung infection with inclusion bodies was diagnosed in 4 of 12 seropositive patients and in 1 of the 2 seronegative patients with a CMV-seropositive organ donor. Radiographic manifestations of CMV lung infection occurred only in the transplanted lung but no biopsy specimen was taken of the native lung to rule out involvement at that site. None of the patients with CMV pneumonia was severely ill when diagnosed and all responded to IV ganciclovir given for 2 to 3 weeks. No patient had a relapse of CMV lung infection. In addition, six other patients received ganciclovir either as postoperative prophylaxis (two patients) or because of positive cultures for CMV associated with either enhanced immunosuppression for rejection treatment (two patients) or signs suggestive but not diagnostic of CMV disease (two patients). Overall, 11 of the 14 patients at risk for CMV infection received at least one course of ganciclovir.

Airway anastomotic infections with dehiscence were seen in three patients. These occurred from 27 to 48 days after transplantation and were due to Candida, *P aeruginosa*, and Aspergillus. Both fungal infections
were treated with surgical resection, stent placement, and antifungal therapy; the Pseudomonas infection was treated with stent placement and antibiotics. There was no association of bronchial anastomotic infection with any of the following operative variables: total ischemic time, suture type, type of anastomosis, use of bronchial wrap, use of cardiopulmonary bypass, or side of transplant. The patients with anastomotic infections all had short total ischemic times (120, 122, and 178 min). Both patients with fungal infections of the airway had received fluconazole prophylaxis.

One patient (patient 1) died during retransplantation for bronchiolitis obliterans 682 days after his first transplantation. By end of follow-up, all patients had clinically resolved their infections and were not receiving therapy.

**DISCUSSION**

We found that SLT recipients were at high risk for infections. These usually involved the lung and bacterial pneumonia was the most common infection. *Staphylococcus aureus, P aeruginosa*, and other Gram-negative rods were the major pathogens even when the pneumonia developed after the patient was living at home. Thus, empiric antibiotic treatment of infections in these patients should cover a broad spectrum of pathogens while awaiting culture results. Cytomegalovirus infection occurred in nearly all patients at risk and more than a third of the patients at risk had pneumonitis by histologic criteria. Radiographically, this pneumonia was restricted to the transplanted lung. Similar findings in both heart-lung and isolated lung transplants have been reported. The outcomes of all of our cases of CMV lung involvement have been favorable and there have been no relapses. This may in part relate to the low frequency in this series of primary infection which in previous studies was a risk factor not only for severe disease but also for mortality, or it may be due to prophylactic measures and early diagnosis and treatment.

Multiple factors explain the high frequency of infection in lung recipients. Immunosuppressive drugs, residence in ICUs, and the use of mechanical ventilation are recognized risks for pneumonia. Lung transplantation results in disrupted lymphatic and neural connections to the implanted organ. Alterations in ciliary action of respiratory epithelium and phagocytosis in alveolar macrophages have also been reported. Our results suggest that airway anastomotic complications may increase the rate of bacterial pneumonia, probably related to either impaired clearance of secretions or the need for frequent procedures to place or examine stents. In this regard, we observed three instances in which patients developed acute fever, cough, and dyspnea within 24 h after routine bronchoscopy. Two of these patients (patients 6 and 11) had anastomotic complications and developed bacterial pneumonia. While frequent bronchoscopy is necessary to monitor the airway and permit early detection of rejection and CMV infection, it may also predispose to pneumonia.

Pathogenic organisms and neutrophils can frequently be found in the donor lung at the time of transplantation and are associated with increased infections and mortality after transplantation. In a dog model, a small inoculum of $10^6$ cfu of pneumococci is incapable of causing pneumonia in an immunosuppressed animal, but will produce pneumonia in a canine lung recipient when it is inoculated into the donor lung shortly before transplantation. An inoculum of bacteria this small would not normally be detectable by Gram stain and might not be cultured out.

Previous reports have not commented on the frequency of native lung infection in single lung recipients. We found native lung infection in six cases, four of which spared the transplanted lung. We believe that inadequate blood flow is a reasonable explanation for the native lung infection in the patients with bacterial infection. Further observations from this and other centers will be necessary to confirm this finding. The Aspergillus infection in the native lung of a patient with emphysema may have occurred because of ventilatory abnormalities. A very similar case has been presented by Coloqohoun et al.

There were three anastomotic infections. These occurred within the first 2 months and were notable for the paucity of symptoms when diagnosed in two patients; the third patient had concurrent pneumonia and was symptomatic. Very loud, harsh, tubular breath sounds could be auscultated and in one case were also audible to the patient's wife before diagnosis. These physical findings may be a useful clue to the diagnosis of bronchial dehiscence and prompt early bronchoscopic evaluation.

Optimal use of antimicrobial prophylaxis in lung transplantation has not been determined. Human donors, as residents of ICUs, are at high risk for airway and lung infection. The donors often receive antibiotics which complicates the interpretation of stains and cultures. Thus, it is important to treat the recipients perioperatively for flora found in ICUs. Our patient with donor-derived pneumonia had an Enterobacter infection and would not have been adequately treated with conventional antistaphylococcal wound prophylaxis with possible catastrophic outcome.

Antiviral prophylaxis is used mainly for herpes simplex virus (HSV) and CMV. The risk of lung disease due to HSV appears to be higher after lung transplantation than other forms of transplantation. De Hoyos et al. noted a reduction of HSV pneumonitis after the introduction of acyclovir prophylaxis. Cytomegalovirus
prophylaxis remains controversial. Bailey et al²⁰ reported no benefit and one case of resistance with routine use of ganciclovir along with polyvalent immune globulin in seven seronegative recipients of seropositive organs. The value of high-dose acyclovir for CMV in this population is also not clear; Bolman et al³ used no antiviral prophylaxis in 40 patients. Twelve of their 51 infections were viral (6 disseminated zoster, 4 HSV pneumonia, and 2 CMV pneumonia; 2 of these pneumonias were fatal. Preliminary data on the use of CMV immune globulin in seven seronegative recipients of seropositive kidneys.²¹ Controlled trials of antiviral prophylaxis will be important in lung transplantation but will require multicenter studies.

Antifungal prophylaxis is likewise controversial. Fluconazole is attractive because of its oral formulation and low toxicity but it will not likely prevent infections due to Aspergillus and similar fungi. Our case of anastomotic infection with yeast occurred during therapy with fluconazole, but since the diagnosis was only made histologically, we could not determine if the yeast was resistant to fluconazole. Low-dose amphotericin and itraconazole are potential alternative prophylactic agents with activity against a wider range of fungi, including Aspergillus.⁵²² Both have been used in transplant patients, but extensive further experience will be necessary before firm recommendations regarding their use can be made.

Finally, our results show that despite the high rates of serious lung infection similar to those seen in heart-lung transplant recipients, good overall outcomes can be achieved in single lung recipients. Further study and delineation of risk factors for infection will be important in helping to reduce the infectious morbidity in this population.

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REFERENCES
1 Dummer JS, Montero CG, Griffith BP, Hardesty RL, Paradis IL, Ho M. Infections in heart-lung transplant recipients. Transplantation 1986; 41:725-29

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