Infections in Patients With Cystic Fibrosis Following Lung Transplantation*

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Background: There is controversy over whether colonization with drug-resistant organisms is a contraindication to lung transplantation.

Methods: We undertook a retrospective review of the results of lung transplantation for patients with cystic fibrosis (CF) at Duke University Medical Center.

Results: As of May 1996, 21 patients with CF underwent bilateral lung transplantation. The first patient died within 24 h of transplantation from sepsis due to Stenotrophomonas maltophilia. Of the remaining 20 patients, 17 (85%) are alive and in stable condition. The three deaths were related primarily to bronchiolitis obliterans at 4 and 18 months in two patients and to cytomegalovirus pneumonia at 5 months in the other patient. The 17 surviving patients have been followed up for a mean of 13 months (range, 0.5 to 54 months). Most of them were colonized and infected with multidrug-resistant organisms before transplantation. Following transplantation, 11 patients had complications from infections. One patient had bacteremia due to a panresistant Burkholderia cepacia and was treated successfully. Two patients had bacteremia and wound infection due to Burkholderia gladioli, previously thought to be pathogenic only in plants. Both patients were treated successfully. Of the six patients with Aspergillus fumigatus isolated from cultures before transplantation, only one had invasive disease following transplantation and responded to treatment.

Conclusion: The organisms present before transplantation were not the primary cause of mortality in our patient population. Our findings suggest that lung transplantation should be considered in CF patients infected with multidrug-resistant organisms.

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Key words: cystic fibrosis; infections; lung transplantation

Abbreviations: CF=cystic fibrosis; CMV=cytomegalovirus; CMVIG=CMV immunoglobulin; D=donor; MRSA=methicillin-resistant Staphylococcus aureus; MSSA=methicillin-sensitive S aureus; R=recipient

In whites, the most common inherited disorder causing end-stage pulmonary disease is cystic fibrosis (CF).1 Seven million persons in the United States are thought to be carrying the gene, and 30,000 have diagnosed disease. Despite the poor prognosis associated with this disease, over the last 10 years, the median length of patient survival has dramatically increased to reach >29 years of age because of aggressive management of recurring bronchopulmonary infections. Now, further improvements in survival2 and in quality of life3 are offered through lung transplantation. The procedure is being increasingly performed for end-stage CF, with improving results as experience is gained.2,4 Studies show that ion transport abnormalities do not recur in the transplanted lungs.1

A serious complication that can compromise transplantation is infection. It has been suggested that this is largely attributable to the presence of bacterial or fungal pathogens prior to transplantation. Pseudomonas aeruginosa is the most commonly isolated pathogen.1 Other organisms commonly isolated from CF patients are Staphylococcus aureus, Haemophilus influenzae, Burkholderia cepacia, and Stenotrophomonas maltophilia. Some centers consider the presence of multidrug-resistant pathogens, including P...
aeruginosa, B cepacia, and S maltophilia, an absolute contraindication for transplantation.5

Herein, we review our experience with patients with CF who have undergone lung transplantation at Duke University Medical Center. We report on survival statistics, complications, including episodes of bacterial, viral, and fungal infections in the post-transplant period, and the occurrence of rejection and bronchiolitis obliterans.

Materials and Methods

We reviewed the records of all patients who underwent lung transplantation for CF at Duke University Medical Center. From April 1992 until May 1996, the procedure was performed on 97 patients, of whom 21 had CF. The criteria for transplantation of patients with CF included the following: life expectancy of <24 months as assessed by significant hypercarbia, increasing oxygen requirement, an FEV1 of <30% of the predicted value, and frequent hospitalizations. Exclusion criteria were the presence of significant liver or kidney disease, malignancy, evidence of psychological instability, and inadequate social support for postoperative care. A finding of multidrug-resistant bacterial organisms or aspergillosis in the sputum was not considered an absolute contraindication to lung transplantation.

All candidates were evaluated by a team consisting of physicians, psychologists, social workers, and nurses experienced in the management of CF and transplantation. All patients participated in a program of pulmonary rehabilitation prior to transplantation and for at least 2 months after transplantation. The mean duration of follow-up after transplantation for patients with CF was 13 months (range, 0.5 to 34 months). Of the 22 patients, 12 (54.5%) were male and 10 (45.5%) were female. The ages ranged from 11 to 36 years (mean, 27 years; median, 29 years).

Donor Selection

Donors were selected if they had a clear chest radiograph, normal oxygenation, and no bronchoscopic evidence of pulmonary contusion or pulmonary secretions to suggest aspiration. They were excluded if serologic studies showed infection with HIV, hepatitis B, or hepatitis C. The ages of the donors varied from 9 to 62 years (mean, 28.4 years; median, 30.5 years).

Immunosuppression

The immunosuppressive regimen consisted of the following: preoperatively, the patients received, orally, cyclosporine (cyclosporin A; Sandoz; Basel, Switzerland) at 2.0 to 2.5 mg/kg and azathioprine at 2 mg/kg. A bolus of 500 mg of methylprednisolone sodium succinate (Solu-Medrol) was given intraoperatively prior to the reperfusion of the transplanted lung. In the postoperative period, the patients received cyclosporine at 2 to 4 mg/h by continuous IV infusion to achieve a level of 250 to 300 ng/mL; azathioprine at 2 mg/kg IV or orally titrated to maintain the WBC count at >=4,000; and methylprednisolone at 125 mg every 12 h for 48 h followed by prednisone (20 mg/d, decreased to 10 mg/day by 6 months). Rejection was diagnosed by transbronchial lung biopsy specimens according to published criteria. Mild to moderate rejection was treated with 500 mg of methylprednisolone daily for 3 days. This regimen was followed by an oral prednisone taper, begun at 60 mg and decreased by 5 mg/d until the original dose was reached. For severe or steroid-resistant rejection, three doses of IV or IM rabbit antithymocyte globulin were given.

Antimicrobial Prophylaxis

As with all patients who undergo lung transplantation at Duke, treatment with cefazolin and vancomycin was started preoperatively and continued for 7 to 10 days or until invasive lines were removed. Antimicrobial prophylaxis also depended on the results of the cultures obtained from the donor and the recipient prior to transplantation, and the results of the recipient’s cultures after transplantation. In the absence of a positive perioperative culture, the antibacterial regimen was tailored to the organisms found at the last cultures. If the patient was infected with P aeruginosa, B cepacia, or S maltophilia, at least two antibiotics active against the organisms were used. Treatment with these antibiotics was usually continued for 2 weeks or until the clinical outcome was certain. Also, the patients infected with multidrug-resistant Gram-negative rods received inhaled colistin for the first 2 weeks posttransplantation. Patients were also given trimethoprim/sulfamethoxazole double-strength tablets three times per week for prophylaxis against Pneumocystis carinii pneumonia.

Antiviral Prophylaxis

Four different antiviral regimens were used depending on the serology of the donor (D) and the recipient (R). If both the D and the R were seronegative for cytomegalovirus (CMV), but the R was seropositive for herpes simplex virus, acyclovir at 200 mg was given three times a day for 12 weeks. Only CMV-negative or leukocyte-filtered blood products were used. In CMV D+/R− patients, ganciclovir was used IV at 5 mg/kg twice a day for 14 days, followed by 5 mg/kg/d for 10 weeks. CMV immunoglobulin (CMVIG; Cytogram) was also used IV at 150 mg/kg on postoperative days 1 and 7, then at 100 mg/kg on postoperative day 14, 25, 42, and 56. In CMV D−/R+ patients, IV ganciclovir was used at 5 mg/kg twice a day for 2 weeks, followed by acyclovir at 800 mg orally three times a day for 10 weeks. For CMV D+/R+, ganciclovir was used at 5 mg/kg twice a day for 2 weeks, then at 5 mg/kg per day for 2 weeks, followed by acyclovir at 800 mg orally three times a day for 10 weeks. The doses of acyclovir and ganciclovir were adjusted on the basis of the creatinine clearance.

Definitions

Colonization of the respiratory tract was defined as a positive bacterial or fungal culture from respiratory secretions (sputum, endotracheal secretions, or BAL) without evidence of clinical signs or symptoms and without histologic evidence of pneumonia. Clinically important fungal or bacterial infection was defined as the presence of positive cultures from blood, tissue or respiratory secretions, in the setting of clinical signs or symptoms, or histologic evidence of disease. CMV infection was defined as the presence of viral replication, detected by either culture or the CMV antigenemia assay, without signs, symptoms, or histopathologic evidence of disease. CMV disease was defined as the presence of the CMV infectious-mononucleosis-like syndrome, with fever, myalgias, leukopenia, and occasional thrombocytopenia, in the setting of viral shedding, or the presence of end-organ damage, with findings on histopathology examination of cytomegalic cells with characteristic inclusion bodies or positive immunostaining for CMV. Episodes of rejection were classified by histologic criteria as minimal, mild, moderate, and severe. Bronchiolitis obliterans was defined, according to histologic or clinical criteria, as a decrease in FEV1 of ≥20% from baseline not explained by infection, bronchial stenosis, or rejection.

Bronchoscopies and Biopsies

Following transplantation, patients underwent surveillance bronchoscopies with BAL at 1, 3, 6, 9, 12, and 18 months, and
then yearly and when clinically indicated. Samples from the BAL were sent for cytology, Gram’s, potassium hydroxide, and acid-fast bacilli stains, and immunostains for respiratory viruses, herpes simplex virus, and CMV. Also, bacterial, mycobacterial, fungal, and viral cultures were performed.

RESULTS

Survival

Of the 21 patients with CF who underwent bilateral lung transplantation, 17 are alive and in stable condition (survival rate, 80%) at a mean follow-up of 13 months (range, 0.5 to 34.0 months). The first CF patient to undergo transplantation died within 24 h after surgery, from sepsis caused by S maltophilia. Two patients died at 4 and 18 months posttransplantation following the development of bronchiolitis obliterans: the first patient’s course was complicated by invasive Aspergillus fumigatus pneumonia, bacteremia with coagulase-negative staphylococcus, and pneumonia and bacteremia caused by vancomycin-resistant enterococcus. The second patient’s severe, rapidly progressive bronchiolitis obliterans was documented by lung biopsy specimen. Her course was also complicated by Pseudomonas fluorescens pericarditis, Nocardia asteroides, and Mycobacterium avium-intracellulare pulmonary infections, and P aeruginosa pneumonia, the latter leading to her death. The fourth death was due to CMV pneumonia, which occurred 4 months after transplantation; the patient had been seronegative for CMV prior to transplantation but received lungs from a CMV-seropositive donor. He was treated prophylactically with a prolonged course (2 months) of ganciclovir and CMVIG. He also had coagulase-negative staphylococcus bacteremia and P aeruginosa pneumonia.

Rejection

Of the 20 patients who survived beyond 24 h, 6 did not have any episodes of acute or chronic rejection and consequently did not receive any immunosuppressive augmentation. The other 14 patients had one or more episodes of minimal or mild rejection (mean, 2.3 episodes). One of them also had one episode of moderate rejection. These episodes were treated with bolus doses of steroids as already described. In addition, 4 of the 14 patients had evidence of bronchiolitis obliterans, with 2 of them dying of the accompanying complications.

Viral Infections

Organizing pneumonia caused by adeno virus infection occurred in one patient and was self-limited. One patient had respiratory syncytial virus isolated from BAL in the setting of worsening respiratory status, and was treated successfully with inhaled ribavirin. CMV infection developed in 9 of 21 patients. Four of them had evidence of viral cytopathic changes on lung biopsy specimens with positive immunostaining for CMV. The other five patients had evidence of viral shedding, detected by the CMV antigenemia assay (four patients) or positive BAL cultures (three patients). Two of these patients had fever with leukopenia. Patients with CMV infection or disease were treated with 2 to 3 weeks of ganciclovir and did well, except for one patient, who died of the associated complications despite treatment with ganciclovir and CMVIG.

Fungal Infections: Filamentous Fungi

One patient with a clinical picture of bronchiolitis obliterans had a positive BAL culture for Cunninghamhamella elegans without evidence of tissue invasion. She was treated with IV amphotericin B but died 2 months later with P aeruginosa pneumonia. Pretransplantation, two patients were colonized with Aspergillus flavus and five with A fumigatus (Table 1). In the posttransplant period, A fumigatus was isolated from four patients (Table 2) (one of the four had negative fungal cultures pretransplantation). Only one of these four patients was thought to have invasive aspergillosis and was treated with IV amphotericin B. The second patient was already receiving IV amphotericin B for the C elegans isolated from BAL. The other two patients received antifungal prophylaxis: one with itraconazole at 400 mg daily, and one with inhaled amphotericin B at 50 mg every day for 5 days followed by once-a-week treatment for 2 months.

Other filamentous fungi isolated from respiratory

<table>
<thead>
<tr>
<th>Organism</th>
<th>No. of Patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>P aeruginosa</td>
<td>18</td>
</tr>
<tr>
<td>Multidrug-resistant P aeruginosa</td>
<td>15</td>
</tr>
<tr>
<td>S maltophilia</td>
<td>4</td>
</tr>
<tr>
<td>B cepacia</td>
<td>2</td>
</tr>
<tr>
<td>B gladioli</td>
<td>2</td>
</tr>
<tr>
<td>A xylosoxidans</td>
<td>2</td>
</tr>
<tr>
<td>H influenzae</td>
<td>2</td>
</tr>
<tr>
<td>MRSA</td>
<td>5</td>
</tr>
<tr>
<td>MSSA</td>
<td>3</td>
</tr>
<tr>
<td>Molds not speciated</td>
<td>12</td>
</tr>
<tr>
<td>A fumigatus</td>
<td>5</td>
</tr>
<tr>
<td>A flavus</td>
<td>2</td>
</tr>
</tbody>
</table>

*Some patients had more than one organism isolated at different occasions.

MSSA = methicillin-sensitive S aureus.
cultures included penicillium species (four patients) and dematiaceous fungi (four patients) (Table 2), including Geotrichum species, Scopulariopsis species, and Paecilomyces. All these organisms were believed to be colonizers and were not treated. There were no late sequelae in any of the eight patients.

Yeast

Of the 21 patients, 16 had yeast isolated on one or more occasions from respiratory secretions (Table 2). The yeast was reported as “yeast not Cryptococcus neoformans” and was not speciated. Because of the absence of clinical signs and symptoms, these were thought to represent colonization, and were not treated except in two patients who developed invasive Candida infections. One of these two had Torulopsis glabrata fungemia, which was treated with amphotericin B. He later had a relapse with biopsy specimen-proven pneumonia and empyema, caused by the same organism, which was treated successfully with IV amphotericin B and fluconazole. The other patient had a positive blood culture with Candida albicans 1 day after transplantation. She was treated successfully with IV fluconazole. Three patients had urinary tract infections, two with C albicans, which was treated with IV fluconazole, and one with T glabrata, which was treated with bladder irrigation with amphotericin B. Disseminated Malassezia furfur infection presenting with high-grade fever and a pustular rash on the trunk occurred in two patients who were receiving lipid formulations with total parenteral nutrition and had central lines. In both patients, the symptoms improved after stopping the total parenteral nutrition and initiating IV fluconazole therapy.

Bacterial Infections

In the 21 patients with CF who underwent bilateral lung transplantation, the bacterial organisms isolated in culture pretransplantation included S maltophilia (4 patients), B cepacia (2 patients), B gladioli (2 patients), methicillin-resistant Staphylococcus aureus (MRSA; 5 patients), methicillin-sensitive S aureus (3 patients), P aeruginosa (18 patients, of whom 15 had multidrug-resistant isolates), H influenzae (2 patients), and Alcaligenes xylosoxidans (2 patients) (Table 1). All the patients infected with these organisms had recurrent episodes of respiratory tract infections prior to transplantation and were treated with several courses of antibiotics.

Following transplantation, one patient died on the first day of surgery, from S maltophilia sepsis. The other three patients who died had P aeruginosa pneumonia among other complications from infectious diseases. Of the 17 patients who are alive, 9 did not have any bacterial infections that required treatment in the posttransplant period. The other eight patients had one or more episodes of invasive bacterial infections (Table 3). These included episodes of respiratory tract infections, with bronchitis or pneumonia attributable to the following organisms: MRSA (6 patients) on days 4 to 43 posttransplant, P aeruginosa (6 patients) on days 78 to 224, enterococcus (2 patients, one of them with vancomycin-resistant enterococcus) on days 24 and 41, A xylosoxidans (1 patient) on day 17, Streptococcus pneumoniae (1 patient) on day 182, and Nocardia asteroides (1 patient) on day 478. Pericarditis with P fluorescens occurred in one patient on day 276. Wound infections caused by B gladioli occurred in two patients on days 29 and 69. Both were infected with B gladioli pretransplantation and became bac-

<table>
<thead>
<tr>
<th>Fungal Organism</th>
<th>Site of Isolation</th>
<th>Treatment</th>
<th>No. of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>A fumigatus (4)</td>
<td>Resp, Blood, Urine, Tissue</td>
<td>Amphotericin B¹</td>
<td>2 with BO</td>
</tr>
<tr>
<td>Cunninghamella (1)</td>
<td>Blood, Urine</td>
<td>IV amphotericin B</td>
<td>1</td>
</tr>
<tr>
<td>Penicillium species (4)</td>
<td>Blood, Urine</td>
<td>IV amphotericin B</td>
<td>0</td>
</tr>
<tr>
<td>Dematiaceous fungi (4)</td>
<td>Blood, Urine</td>
<td>IV amphotericin B</td>
<td>0</td>
</tr>
<tr>
<td>Yeast (16)</td>
<td>Blood, Urine</td>
<td>IV fluconazole</td>
<td>2</td>
</tr>
<tr>
<td>C albicans (3)</td>
<td>Blood, Urine</td>
<td>IV fluconazole</td>
<td>0</td>
</tr>
<tr>
<td>T glabrata (2)</td>
<td>Blood, Urine</td>
<td>Amphotericin B¹</td>
<td>0</td>
</tr>
<tr>
<td>M furfur (2)</td>
<td>Blood, Urine</td>
<td>IV fluconazole</td>
<td>1</td>
</tr>
</tbody>
</table>

*Some patients had more than one fungal organism isolated. Resp = respiratory samples such as sputum, endotracheal suction, or BAL. BO = bronchiolitis obliterans.

¹The patient who had tissue invasion and a second patient who grew Cunninghamella elegans from BAL were treated with IV amphotericin B (amphotericin B). The other two patients received prophylaxis, one with itraconazole and one with inhaled amphotericin B.

²IV amphotericin B was used in the patient with tissue invasion. For the positive urine culture, bladder irrigation with amphotericin B was used.
teremic in the immediate postoperative course. They were treated aggressively with two antimicrobial agents to which the organisms were susceptible, but once treatment with the antibiotics was discontinued, they presented with sternal wound infections, which were treated successfully. Eleven episodes of bacteremia occurred in seven patients: three episodes with coagulase-negative staphylococci on days 16, 132, and 169; three with *P. aeruginosa*, two on the first day and one on day 136; one with MRSA on day 90; two with *B. gladioli* on days 1 and 20; one with *B. cepacia* on day 1; and one with *S. maltophilia* on day 1. One patient who was infected pretransplantation with a pan-resistant *B. cepacia* (which was also resistant to multiple combinations of antibiotics as tested at Columbia University) became bactereemic with the same organism in the immediate postoperative period. The susceptibility testing at that time revealed an intermediate sensitivity to amikacin. The patient was therefore treated with this agent, as well as with an investigational quinolone (clinafloxacin) to which the isolate was susceptible by *in vitro* testing. The patient did well on the combination therapy, and repeated blood and BAL cultures remained negative.

**DISCUSSION**

Despite the recent advances in identifying the genetic cause of CF,⁶⁷ the use of aggressive antimicrobial therapy, and the early results of gene therapy,⁸⁻¹⁰ we are far from having a cure for this disease. Although lung transplantation is now a viable option for treating the end-stage pulmonary disease inflicted by this disorder,¹¹⁻¹³ its use has lagged behind, in part because of the major problems attending patients with CF, problems such as nutritional deficiencies owing to malabsorption, hepatic dysfunction, renal insufficiency, owing to the use of aminoglycosides for treating recurrent Gram-negative respiratory infections, glucose intolerance, and colonization of the airways and sinuses with multidrug-resistant Gram-negative bacteria. Another reason is the concern that the epithelial CF defect could recur in the transplanted lungs.

The survival of patients with CF who undergo lung transplantation has varied with time and with the centers performing the transplantation. The first successful heart-lung transplants for CF were performed in the United Kingdom in 1984.¹⁴,¹⁵ From 1984 until 1991, a total of 79 patients with CF underwent heart-lung transplantation at Harefield Hospital. The patients' survival at 1 and 2 years was 69% and 52%, respectively.⁴ Slightly better results were reported from Papworth Hospital, where analysis of the outcome of the first 32 transplants revealed a 1- and 2-year survival of 73% and 58%, respectively.¹¹ The initial North American results, however, were discouraging, with a 1-year actuarial survival for the first 33 heart-lung transplantations of 42%.¹⁶ The most common cause of death in these cases was sepsis. Results from the University of Toronto on double lung transplantation performed on 17 patients with CF showed a 1-year survival of 58%,⁵ with the most frequent cause of morbidity and mortality being *B. cepacia* pneumonia. In recent years, survival has improved. In 1992, Shennib et al.¹⁷ reported on the experience from two centers in the United States, in which the 1-year survival was 64%. Egan et al.² reported their experience at the University of North Carolina, where the 1- and 2-year

**Table 3—Bacterial Infections in the Posttransplant Period**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Organism</th>
<th>No. of Patients*</th>
<th>Death</th>
<th>Timing (Days)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory tract infections</td>
<td>MRSA</td>
<td>6</td>
<td>0</td>
<td>4,7,17,24,40,43</td>
</tr>
<tr>
<td></td>
<td><em>P. aeruginosa</em></td>
<td>6</td>
<td>3</td>
<td>78,108,120,148,159,224</td>
</tr>
<tr>
<td></td>
<td>Enterococcus</td>
<td>2</td>
<td>1</td>
<td>(VRE)¹</td>
</tr>
<tr>
<td></td>
<td><em>A. xylosoxidans</em></td>
<td>1</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td><em>S. pneumoniae</em></td>
<td>1</td>
<td>0</td>
<td>182</td>
</tr>
<tr>
<td></td>
<td><em>N. asteroides</em></td>
<td>1</td>
<td>1</td>
<td>478</td>
</tr>
<tr>
<td>Pericarditis</td>
<td><em>P. fluorescens</em></td>
<td>1</td>
<td>1</td>
<td>276</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>CNS¹</td>
<td>3</td>
<td>2</td>
<td>16,132,169</td>
</tr>
<tr>
<td></td>
<td><em>P. aeruginosa</em></td>
<td>3</td>
<td>1</td>
<td>1,1356</td>
</tr>
<tr>
<td></td>
<td>MRSA</td>
<td>1</td>
<td>1</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td><em>B. gladioli</em></td>
<td>2</td>
<td>0</td>
<td>1,20</td>
</tr>
<tr>
<td></td>
<td><em>B. cepacia</em></td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td><em>S. maltophilia</em></td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Wound infection</td>
<td><em>B. gladioli</em></td>
<td>2</td>
<td>0</td>
<td>29,69</td>
</tr>
</tbody>
</table>

*Some patients had more than one episode of infection. The total number of deaths was four.

¹CNS=coagulase-negative staphylococci; VRE=vancomycin-resistant enterococcus.

†Timing indicates the time from transplantation to the first episode of infection with the organism. Some patients had more than one episode.
survival were 85% and 67%, respectively. As experience is gained with the surgical procedure and the management of the postoperative complications, we are seeing marked improvements not only in survival but also in the quality of life of the transplant recipients.

The most common complications seen at our center were infections, but most of them were managed successfully with antimicrobial therapy. Respiratory infections with MRSA and enterococcus occurred in the first 43 days posttransplant, whereas infections with P aeruginosa occurred later in the course, on days 78 to 224 (Table 3). It has been suggested that the presence of airway pathogens prior to transplantation in patients with CF may place these patients at a higher risk for infections following transplantation. After transplantation, the CF abnormalities persist in the native proximal airways and sinuses, which remain colonized with multidrug-resistant organisms. Previously, most deaths (52%) in the North American transplant experience for CF were due to infections, which led to the conclusion that infections constituted major obstacles to the clinical usefulness of lung transplantation for CF. The Papworth group, however, found that posttransplant infections in patients with CF were not more prevalent than in patients without CF.11 Also, recent reports from the University of North Carolina indicate that patients with CF, despite the presence of airway pathogens, are at no greater risk of infections after lung transplantation than are other patients.18

A major concern has been infections with multidrug-resistant Gram-negative organisms. Several of our patients were colonized with multidrug-resistant Gram-negative bacilli, including P aeruginosa, B cepacia, B gladioli, and S maltophilia (Table 1). Nevertheless, infections with these organisms in the posttransplant course (Table 3) were treated successfully except in the four patients who died; one immediately posttransplant, two with bacterial infections in the setting of bronchiolitis obliterans, and one with pseudomonas pneumonia in the setting of CMV disease.

Infection with B cepacia has been a major concern because in some studies it was associated with increased morbidity19,20 and early mortality5,21 in the posttransplant course. Mortality was found to be especially high (80%) in patients who acquired the organism after transplantation.21 In fact, some centers consider colonization with B cepacia a contraindication to transplantation.5 Other centers have found that colonization with B cepacia does not predict a worse outcome.13 Studies have shown that patients get infected with the same strain that they harbored before transplantation, and do not acquire a more virulent strain.20 Our experience reflects a good outcome. We have had two patients who were infected with multidrug-resistant B cepacia before transplantation, both had recurrent infections in the immediate postoperative course, and both were treated successfully. Our patient with the panresistant B cepacia, who became bacteremic in the immediate postoperative period and was treated successfully with clinafloxacin and amikacin, exemplifies the need to consider investigational agents when treating these patients. Investigational quinolones are a promising class.

In this article, we also report the occurrence and successful treatment of two cases of bacteremia and subsequent sternal wound infections caused by B gladioli. To our knowledge, these two cases of B gladioli are the first to be described in lung transplant recipients. In fact, there has been only one previous report of human disease caused by this organism, and that report described two patients with chronic granulomatous disease who had pneumonia, as well as septicemia in one patient.22 Prior to that, this Gram-negative bacillus, which is in the pseudomallei group of pseudomonads, was primarily known as a plant pathogen, a cause of “flower rot” in gladiolas and other plants. B gladioli has been isolated from sputa of 11 patients with CF, but the organism did not appear to cause disease in any of them.23 Simpson et al24 analyzed previously identified strains of B cepacia from patients with CF, and found that they possessed biochemical and fatty acid characteristics atypical of B cepacia, but bearing close resemblance to B gladioli. It is therefore important to differentiate B gladioli from B cepacia because they have different antimicrobial susceptibility patterns; B gladioli tends to be susceptible to aminoglycosides and resistant to aztreonam and cephalosporins, whereas the opposite is true for B cepacia.22,23 The microbiology laboratory should be alerted to the possibility of this organism, so that special attention is paid to the correct identification and the antimicrobial susceptibility testing. Despite the virulence of this organism, documented by the early bacteremia and surgical wound infection, both of our patients were treated successfully with prolonged courses of antimicrobial therapy. Therefore, we believe that infection with this organism, at the time of pretransplant evaluation, should not be considered an absolute contraindication to transplantation.

In addition to bacterial pathogens, another major concern for patients with CF undergoing lung transplantation has been colonization with fungi, especially the aspergillus species.25 In our series, however, pretransplant colonization with aspergillus species did not predict the occurrence of dissemi-
nated aspergillosis in the posttransplant course. To the contrary, the incidence of invasive disease was lower (1 in 20 patients) than that previously reported in lung transplantation (15 to 18%). These results are not dissimilar to the experience at the University of North Carolina, where the incidence of invasive aspergillosis was lower in the CF patients who were colonized pretransplantation with aspergillus species than it was in the noncystic patients. The isolation of aspergillus species from sputum in the pretransplant course does not predict invasive disease following transplantation. Therefore, we believe that CF patients should not be excluded as transplantation candidates on the basis of the results of fungal cultures.

CONCLUSIONS

Despite the discovery of the CF gene, many patients with CF will continue to have recurrent pulmonary infections, which will shorten their life span. To date and to our knowledge, lung transplantation is the only therapeutic intervention that can offer these patients a second chance. New approaches with surgical techniques, advances in immunosuppressive therapy, and aggressive management of pulmonary infections have led to improving the survival and the quality of life of these patients. Nevertheless, complications including rejection, infection, and bronchiolitis obliterans continue to be major concerns in the posttransplant course, and more research is needed on the prevention and management of these complications. Colonization with multidrug-resistant organisms does not prohibit transplantation. Organisms such as B gladioli, previously thought to be nonpathogenic for humans, should be looked for and treated aggressively. Colonization with aspergillus does not predict invasive disease after transplantation, and should not be considered a contraindication for transplantation.

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