PEDIATRIC AND ADULT LUNG TRANSPLANTATION FOR CYSTIC FIBROSIS

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Objective: **This paper was undertaken to review the experience at our institution with bilateral sequential lung transplantation for cystic fibrosis.** ***Methods:*** **Since 1989, 103 bilateral sequential lung transplants for cystic fibrosis have been performed (46 pediatric, 48 adult, 9 redo); the mean age was 21 ± 10 years. Cardiopulmonary bypass was used in all but one pediatric (age <18) transplant, and in 15% of adults.** ***Results:*** **Hospital mortality was 4.9%, with 80% of early deaths related to infection. Bronchial anastomotic complications occurred with equal frequency in the pediatric and the adult populations (7.3%). One- and 3-year actuarial survival are 84% and 61%, respectively (no significant difference between pediatric and adult age groups; average follow-up 2.1 ± 1.6 years). Mean forced expiratory volume in 1 second increased from 25% ± 9% before transplantation to 79% ± 35% 1 year after transplantation. Acute rejection occurred 1.7 times per patient-year, with most episodes taking place within the first 6 months after transplantation. The need for treatment of lower respiratory tract infections occurred 1.2 times per patient in the first year after transplantation. Actuarial freedom from bronchiolitis obliterans was 63% at 2 years and 43% at 3 years. Redo transplantation was performed only in the pediatric population and was associated with an early mortality of 33%. Eight living donor transplants (four primary transplants, four redo transplants) were performed with an early survival of 87.5%.** ***Conclusion:*** **Patients with end-stage cystic fibrosis can undergo bilateral lung transplantation with morbidity and mortality comparable to that seen in pulmonary transplantation for other disease entities. (J Thorac Cardiovasc Surg 1998; 115:404-14)**

Cystic fibrosis (CF) is a genetic disorder affecting 1 in every 3000 live births in the United States, and 3.3% of all Americans are asymptomatic carriers of the CF gene.[1] It is the most common lethal genetic disease in Caucasians, with 95% of all deaths caused by respiratory failure related to bronchiectasis. Intense research into the pathophysiology of this disease combined with aggressive medical therapies have extended the median survival from l0 years of age in the 1960s to 30 years of age in the 1990s; however, 25% of patients still die before the age of 20.[2] Despite the fact that a better understanding of the genetic basis for the disease exists, no cure has been found and 300 to 400 patients with CF still die from respiratory failure in the United States alone each year.

Although it would seem counterintuitive to perform transplantation (with its obligatory need for immunosuppression) in a chronically infected patient, this is the only therapy available at present for those CF patients with end-stage lung disease. Heart-lung transplantation was first performed on a patient with CF in 1983 and isolated bilateral lung transplantation in 1987.[3] Heart-lung transplantation was the preferred method of transplantation for these patients in the 1980s. At present, except in those few centers still favoring combined heart-lung transplantation, isolated bilateral sequential lung

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Table I. *Factors associated with a high risk of mortality in <2 years*

Factors	*Risk*
FEV_1	<30% predicted for women and children
FEV_1	<20% predicted for adult males
PaO_2	<55 mm Hg
$PaCO_2$	>50 mm Hg

transplantation is now the procedure of choice. According to the January, 1997, report of the St. Louis International Lung Transplant Registry, 932 transplants have been performed for this disease worldwide.[4] We reviewed the lung transplantation experience for CF at the Washington University School of Medicine with the aim of evaluating survival, rejection incidence, complications of the procedure, infection risk after transplantation, and rate of development of obliterative bronchiolitis (OB). This experience covers a period from 1989 to the present and includes all ages, both adult and pediatric.

Methods

Patient selection. Since November 1989, 116 bilateral sequential lung transplants have been performed at our combined adult (Barnes-Jewish Hospital) and pediatric (St. Louis Children's Hospital) hospitals for patients with CF. The pediatric population at our institution is defined as those less than 18 years old at the time of transplantation. This study focuses on the 103 (55 pediatric, 48 adult) bilateral sequential lung transplantations performed in 94 patients as of September of 1996. The remaining have insufficient follow-up to be included. This group represents 23% of the total transplantations performed at this institution over the same time period. Nine patients, all in the pediatric population, have undergone retransplantation. Additionally, the pediatric group contains eight patients who have undergone living donor transplants, four as a primary transplantation procedure and four as retransplantation procedures. Mean age at transplantation for the entire population was 21 ± 10 years (13 ± 3 years in the pediatric population and 29 ± 8 years in the adult group) and mean weight was 43 ± 15 kg (32 ± 10 kg in the pediatric and 52 ± 12 kg in the adult group).

As with most centers, we have used the parameters outlined by Kerem and associates[5] that predict a 50% 2-year mortality as guidelines for initial referral for transplantation (Table I). Despite these general guidelines, it is clear that people with CF, especially children, are prone to have a somewhat unpredictable decline in pulmonary function, making their clinical course and appropriate window for transplantation somewhat difficult to forecast. This is supported by data showing a mortality rate as high as 40% to 60% among patients with CF on transplant waiting lists in the United States and the United Kingdom.[6] Other factors that may serve as relative indicators in deciding to proceed toward transplantation include need for continuous supplemental oxygen, increased frequency of hospitalizations to receive parenteral antibiotics, progressive weight loss, and unacceptably poor quality of life. Contraindications to transplantation are listed in Table II.

Table II. *Contraindications to lung transplant*

Absolute	*Relative*
HIV	Highly resistant bacterial colonization *(B. cepacia, S. maltiphalia)*
Malignancy	Renal failure
Hepatitis B (active)	Hepatic failure
Mycobacterium tuberculosis (active)	Left ventricular dysfunction
Irreversible central nervous system injury	Diabetes mellitus with vasculopathy
	Osteoporosis
	Medical noncompliance issues
	Familial dysfunction

Once the decision has been made to consider transplantation, a thorough pulmonary and general transplant evaluation is initiated. Among other studies, this includes pulmonary function testing, a 6-minute walk test, room air blood gas, establishing the patient's microbiologic profile by sputum culture or bronchoalveolar lavage (BAL) (includes use of standard selective media to enhance recovery of *Burkholderia cepacia* and other unusual gram-negative organisms), examination of the family's psychosocial and financial resources, education of the patient and family regarding transplantation, cardiologic evaluation (echocardiogram, radionuclide ventriculography, and cardiac catheterization in adults), and initiation of an aggressive pretransplantation rehabilitation program. Evaluation of sinus disease by coronal computed tomographic scan of the head is performed, but surgical therapy is undertaken only for significant symptoms or severe polyp disease. Close communication with referring physicians is vital in instituting and maintaining a regimen of appropriate antibiotics, aggressive feeding (including nighttime gastrostomy feeding supplements), exercise, and chest physiotherapy—all with the aim of maximizing pulmonary function and overall physical condition before transplantation. Once the patient has been listed long enough that we expect the transplant to take place within 3 months, we then ask him or her to relocate to St. Louis. This allows for regular medical checkups to more closely monitor the patient's condition and maximize the frequently tenuous physiologic and psychologic state as the time of transplantation approaches. Additionally, it permits the family an opportunity to establish a support network within our local transplant community.

The transplant procedure. The method of standard donor lung harvest has been previously described.[7] The lungs are perfused with alprostadil (prostaglandin E_1), flushed with modified Euro-Collins solution, excised en bloc, and transported on ice to the recipient's surgical suite. Recipients receive perioperative antibiotics appropriate for their specific microbiologic profile. The transplantation itself is performed through a bilateral thoracosternotomy incision, which provides ready access to both hilar regions and also allows improved exposure for

taking down chest wall adhesions, which may be extensive and severe in patients with CF who have frequently had previous interventions.[8] Prior surgery has not been used as a contraindication to transplantation, and 29 of 103 (28%) of our patients have had either previous surgery, thoracostomy tube, or pleurodesis for recurrent pneumothorax.

Although the bilateral sequential technique of transplantation has obviated the need for cardiopulmonary bypass (CPB) in 85% of our adult population, it has been used in all but one transplant in the pediatric population. CPB is used routinely in children because the smaller airways make single lung ventilation with either a double-lumen endobronchial tube or bronchial blockers very difficult, particularly in the setting of CF where tenacious secretions are difficult to clear. These patients may have very poor tolerance of any manipulation because of the frequently heavy bacterial burden contained within the severely bronchiectatic lungs. Use of CPB allows for simultaneous pneumonectomy in the recipient and thus provides a window of opportunity before implantation of the new lungs during which the anesthetist can perform a thorough lavage of the colonized trachea and blind mainstem bronchial stumps with tobramycin solution. Implementation of CPB can potentially minimize donor lung ischemic time by allowing for rapid dissection of hilar structures without compromising stability of the recipient. Patients are weaned from CPB once both lungs are implanted, and aprotinin has been used routinely in an attempt to reduce the amount of postoperative bleeding in this relatively high-risk patient population.[9] Since 1993, in the absence of systemic hypotension, all patients are treated with a continuous infusion of alprostadil beginning at the time of reperfusion and continuing for 48 hours after the operation.

Postoperative management. Weaning from mechanical ventilation has been achieved as rapidly as possible after transplantation. Lung perfusion scans and bronchoscopy are performed within the first 24 hours after the transplantation to assess adequacy of revascularization, mucosal viability, and bronchial anastomotic appearance. Aggressive nutritional support and physiotherapy initiated in the preoperative interval are reinstituted early postoperatively and ambulation is encouraged as soon as possible. Routine hematologic, biochemical, and drug level analyses are performed and adjustments in medications are made accordingly. Surveillance bronchoscopy for rejection (assessed by transbronchial biopsy) and lower respiratory infections (assessed by BAL) is performed routinely at 1 to 2 weeks, 1 month, 2 months, 3 months, 6 months, and 12 months postoperatively and also when clinically indicated by chest x-ray examination, fever, or increasing oxygen requirements. Additionally, graft function and overall patient rehabilitation and functional status are assessed by pulmonary function testing and 6-minute walk. On discharge from the hospital, each patient is provided with a home spirometer (Puritan-Bennet model PB110, Wilmington, Mass.) and asked to perform spirometry twice daily. A drop in forced expiratory volume in 1 second (FEV_1) of greater than 10% from baseline is considered an indication for contacting our transplant service for possible intervention.

Immunosuppressive and antimicrobial regimens. Immunosuppression consists of cylosporine (INN: ciclosporin), azathioprine, and prednisone. Azathioprine is given immediately before going to the operating room in a dose of 2.5 to 3.0 mg/kg intravenously and is continued at this same level as a single daily dose postoperatively. Cyclosporine (CSA) is begun as a continuous intravenous infusion immediately after the operation and, along with azathioprine and steroids, is converted to oral dosing once the patient is extubated and tolerating enteral feeding. Our target CSA trough level is 300 to 350 ng/ml in the early postoperative period until approximately 1 year after transplantation and 250 to 300 ng/ml thereafter if no evidence of ongoing rejection exists. Extreme variability exists between individuals in dose range because gastrointestinal absorption and the rate of hepatic clearance vary greatly within this patient population. Systemic corticosteroids are similarly begun in the immediate postoperative period with methylprednisolone at 0.5 mg/kg per day intravenously. After conversion to oral prednisone, the dose is left at 0.5 mg/kg per day for the first 3 to 6 months after transplantation and is then gradually tapered to 0.1 to 0.2 mg/kg per day by 12 months. Acute rejection episodes, as documented by transbronchial biopsy, are treated with intravenous methylprednisolone in a dose of 10 mg/kg per day for 3 days in the pediatric population and 0.5 to 1 gm intravenously for 3 days in the adult population. Second- and third-line forms of therapy for refractory rejection include antithymocyte gamma-globulin (ATGAM, The Upjohn Company, Kalamazoo, Mich.), methotrexate, and OKT3.

Intraoperative and postoperative antimicrobials are chosen on the basis of preoperative sputum culture isolates and generally include intravenous tobramycin and a β-lactam or fluoroquinolone. Intravenous antibiotics are typically administered for 7 to 10 days postoperatively and drug levels are followed closely because at least a mild degree of renal insufficiency frequently occurs early after surgery. Inhaled tobramycin and colistin are added after the course of intravenous antibiotics in most patients. Patients with early and late postoperative lower respiratory infections are treated with appropriate oral, inhaled, and intravenous antibiotics as an outpatient as often as possible. In the pediatric population, if either the recipient or donor are cytomegalovirus (CMV) IgG positive at the time of transplantation, prophylactic intravenous ganciclovir is given for 6 weeks, whereas in the adult patients 2 to 3 weeks of intravenous ganciclovir is administered only in cases where the donor is CMV IgG positive and the recipient is CMV IgG negative. Indications for treatment of CMV infections occurring after the postoperative prophylactic course of ganciclovir have been based on the clinical picture in combination with a positive shell vial assay on BAL culture and positive immunohistochemical staining on transbronchial biopsy specimen. Viremia, as documented by a positive blood buffy coat culture, in the absence of symptoms is not considered an indication for treatment. Prophylaxis against *Pneumocystis carinii* consists of trimethoprim-sulfamethoxazole given once daily until discharge at which time the regimen is changed to three times per week. Although some degree of fungal colonization of the airway is quite frequent preopera-

tively, it is generally not treated aggressively unless colony counts are heavy. Presence of fungus on postoperative sputum cultures is treated by a variety of approaches on the basis of the organism and colony count on culture. In general, the patient may be treated with oral itraconazole and aerosolized amphotericin B for 2 to 3 weeks, or they may first receive a 5- to 10-day course of intravenous amphotericin followed by 1 to 2 weeks of aerosolized amphotericin B. Need for further therapy depends on the results of follow-up cultures, which are performed routinely.

Statistics. Results are expressed as median with range except where otherwise indicated. Actuarial freedom from OB and death was calculated according to Kaplan-Meier method and levels of significance with respect to survival differences between groups were calculated using Mantel-Haenszel method. Other comparisons were made using Student's t test and χ^2 analysis when indicated.

Results

Characteristics of the study population at large are summarized in Table III. In addition to waiting time and blood type, donors and recipients are matched primarily on the basis of height. Median waiting periods from the time of listing to the time of transplantation were 267 days (range 3 to 989 days) for the entire group and 192 days (range 3 to 989) and 337 (range 40 to 969) days in the pediatric and adult populations, respectively ($p = 0.03$). Previous surgery (e.g., lobectomy) or pleurodesis with thoracostomy tube drainage had been performed in 18 of the 55 pediatric transplant recipients (32.7%) and in 11 of 48 adults (22.9%). Mechanical ventilatory support at the time of transplantation as used for 17.5% of the recipients.

Donor lung ischemic times were shorter for the pediatric lung recipients. Median times for the first lung implanted were 271 minutes (range 188 to 382 minutes) and 300 minutes (range 146 to 412 minutes) ($p = 0.07$), whereas those for the second lung implanted were 318 minutes (range 244 to 425 minutes) and 421 minutes (range 207 to 633 minutes) ($p = 0.0001$) in the pediatric and adult groups, respectively. Adequate size match between donor and recipient was obtained such that only one adult required lobectomy of a donor lung to perform the transplantation. Similarly, in the pediatric population only one patient other than the eight who underwent living donor transplantations required lobar transplantation because of size mismatch with the donor.

Average length of follow-up for the entire population is 2.1 ± 1.6 years. One- and 3-year actuarial survivals are 84% and 61%, respectively. Breaking this down into groups, the 1- and 3-year survival for adults are 79% and 56%, whereas survival at the same intervals in the pediatric age group are 90% and 73%, respectively. The latter of these two, that is, 3-year survival, approaches statistical significance ($p = 0.056$) when comparing the pediatric to the adult population. Early mortality, defined as death within 30 days of surgery or at any time during the same hospitalization as the operation, occurred in 5 of 103 transplantations (4.9%). There were two early deaths in the adult population. One of these was due to respiratory failure related to early graft dysfunction and superimposed viral pneumonia. The second occurred in the only adult patient with *Burkholderia cepacia* who underwent transplantation. This patient's death 10 days after his transplantation was due to *B. cepacia* pneumonia and bacteremia in conjunction with bilateral bronchial dehiscence. In the pediatric population, no deaths occurred after primary transplantation procedures, and all three early deaths occurred in the group of nine patients who underwent redo transplantations. Two of these three patients had their redo transplantation performed during the same hospitalization as their primary transplantation (one 3 weeks and the other 3 months after the primary transplantation). Although generally multifactorial in nature, the primary cause of death in the three pediatric patients were pulmonary emboli with bacteremia, invasive aspergillosis, and chronic respiratory failure caused by graft failure, respectively.

The group of nine patients that underwent redo transplantation did so for primary graft dysfunction on three occasions and OB in the other six. Retransplantation took place at a median of 395 days (range 20 to 778 days) after the initial transplantation. Four of these nine patients had living donors for their secondary transplantation. Posttransplantation lymphoproliferative disease (PTLD) occurred only once in the adult population (2.1%) and in eight of 46 (17.4 %) of the pediatric patients. Three patients with PTLD died as a complication of this disease. PTLD was generally managed by tapering immunosuppression, and five patients treated as such subse-

Table III. *Recipient/donor characteristics*

Recipient age (yr)	20.6 ± 9.8 (range 6-50)
Donor age (yr)	19.9 ± 11.3 (range 3-46)
Recipient height (cm)	145 ± 18.3 (range 41-185)
Donor height (cm)	150.2 ± 22 (range 39-188)
Recipient sex	F49/M54
Donor sex	F43/M52
CMV mismatch	59/103

Table IV. *Postoperative course (values expressed as median)*

Mechanical ventilation (days)	3 (range 1-47)
Intensive care unit stay (days)	5 (range 1-53)
Hospitalization (days)	20 (range 9-225)

quently had OB develop. Three of these five have undergone redo transplantation and the other two are relisted for transplantation.

The overall timetable of the typical hospital course after bilateral sequential lung transplantation for CF is summarized in Table IV. As can be surmised from the data, patients are generally transferred out of the intensive care unit approximately 48 hours after being weaned from mechanical ventilation. Patients subsequently required another 2 to 3 weeks of hospitalization for overall rehabilitation (physical therapy, aggressive nutritional support) and education, including learning the often complicated medication regimens. Five patients out of the entire group required postoperative tracheostomy to assist in weaning from mechanical ventilation.

Bronchial anastomotic complications occurred in 15 of 206 or 7.3% of all anastomoses at risk, occurring with equal frequency in the pediatric and adult populations. Stents were required in the treatment of eight of these 15 airway complications. Complete or near complete bronchial anastomotic dehiscence occurred three times. One patient with complete dehiscence was treated with transplant pneumonectomy and another patient had bilateral, near complete dehiscence, which, along with *B. cepacia* pneumonia and bacteremia, was a contributing factor in his death. Partial dehiscence occurred in one anastomosis, and this was treated expectantly and resolved uneventfully. Stenosis of the airway anastomosis occurred 11 times. Silicone rubber stents were placed in eight and dilation alone was all that was required in three.

Treatment for acute cellular rejection as documented by transbronchial biopsy and graded by standard criteria occurred primarily in the first year after transplantation.[10] An average of 1.7 ± 1.4 episodes of acute cellular rejection occurred per patient in the first 6 months after transplantation, whereas 0.7 ± 1.3 episodes occurred per patient for the remainder of the follow-up period beyond 6 months. OB syndrome as determined by significant decline in FEV_1 generally in conjunction with a transbronchial biopsy was diagnosed an average of 17.3 ± 14.1 months postoperatively (range 2 to 54 months). As demonstrated in Fig. 1, actuarial freedom from this entity was 63% and 43% at 2 and 3 years after transplantation, respectively. The incidence of OB after transplantation in patients with CF is comparable to that seen in our other lung transplant populations.

The microbial spectrum was relatively typical for a group of patients with CF in that significant growth of *Pseudomonas* species from preoperative sputum culture was virtually a ubiquitous finding. A total of three patients with *B. cepacia* underwent transplantation. Other organisms obtained on preoperative sputum culture included methicillin-resistant *Staphylococcus aureus* in two patients and *Mycobacterium avium* and *Mycobacterium cheloneii* in one patient each. Lower respiratory infection requiring treatment with antibiotics most commonly occurred early after transplantation, with an average of 1.2 such infections per patient in the first year after transplantation. Diagnosis of lower respiratory infection was made by a combination of clinical picture, chest radiograph, and more than 100,000 colony-forming units/ml on quantitative BAL. The organism isolated was usually consistent with the pretransplantation flora. Preoperative airway culture positive for fungus in low colony counts was relatively common. In contrast, significant postoperative fungal infection occurred in only 13 of 103 transplantations, and species of fungi cultured included *Aspergillus fumigatis*, *Candida parasalopsis*, and *Rhizopus*. All significant fungal infections were successfully treated with a combination of intravenous, oral, and aerosolized medications with the exception of one patient who was found to have disseminated aspergillosis on autopsy. CMV pneumonitis occurring after the initial prophylactic postoperative course of ganciclovir was relatively common, taking place in 63 of 103 transplantations. Although the incidence of donor/recipient CMV mismatch was similar between adult and pediatric age groups, CMV pneumonitis tended to be more common in the former (48% vs 30%, p = not significant). Three patients had postoperative empyema, all of which responded to thoracostomy tube drainage and appropriate antibiotics.

Pulmonary function rapidly improved after lung transplantation. Compared with preoperative values, significant improvement in FEV_1 and FVC was observed at all time intervals up to 2 years after transplantation (Fig. 2). This is accompanied by a steady and significant improvement in the 6-minute walk test results (Table V). The average follow-up

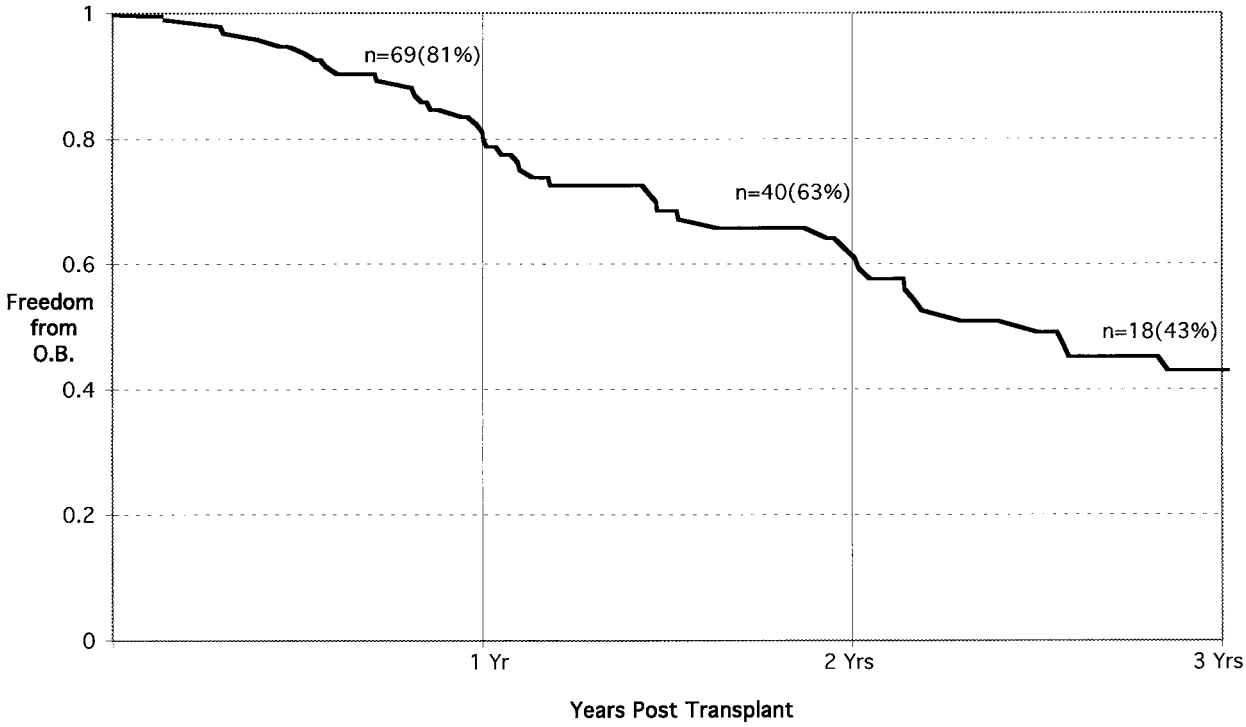

Fig. 1. Actuarial freedom from obliterative bronchiolitis *(OB)*.

values of both these parameters includes patients in whom OB has developed and, thus, tends to underestimate the true functional status of those not affected with this entity. These parameters of functional improvement after transplantation in patients with CF parallel results obtained from other groups of patients undergoing pulmonary transplantation for end-stage lung disease.[11]

Discussion

Less than 10 years ago, reports surfaced in the literature that painted a discouraging picture regarding heart-lung or bilateral lung transplantation for patients with CF, with early mortality ranging from 15% to 35% and an actuarial survival ranging from 42% to 64% at 1 year.[12-14] These early reports and others[15] suggested that infectious complications were a major obstacle to survival after transplantation in this group of patients. As it became clear that the original disease would not recur[16] and that the risk of sepsis in the transplanted lungs was not an insurmountable problem, bilateral lung transplantation became the accepted and the most widely applied surgical therapy for patients with end-stage lung disease from CF.

Nonetheless, the CF patient population presents formidable tasks with respect to numerous aspects of transplantation because, despite end organ failure being limited to one system, chronic malnutrition affecting wound healing and respiratory muscle function, pancreatic insufficiency influencing gastrointestinal absorption of immunosuppressive medications, and chronic infection in the paranasal sinuses all predispose to complications after transplantation. As worldwide experience has accumulated with lung transplantation for CF, results have significantly improved as documented in the impressive report of 44 lung transplantations by Egan and associates,[17] in which no operative mortality occurred and the actuarial survival at 1 and 2 years was 85% and 67%, respectively.

Reports have demonstrated that FEV_1 and FVC at time of listing are prognostic indicators in patients with CF awaiting transplantation.[1, 18] The severity of illness before transplantation in our group of patients is also reflected both in the number of patients who had undergone previous surgery or thoracostomy tube/pleurodesis (28%) and in the number who were on mechanical ventilation (17.5%) preoperatively. The report from the Marseille-Montreal Lung Transplant Program demonstrated an early mortality of 30% in patients with CF who were

Table V. *Six-minute walk results (feet)*

Preoperative	1425 ± 436	(n = 87)
3 Months postoperative	1960 ± 404	(n = 87)
6 Months postoperative	2111 ± 345	(n = 74)
12 Months postoperative	2220 ± 335	(n = 65)

mechanically ventilated preoperatively.[19] Aeba and coworkers[20] proposed that length of need for mechanical ventilation after transplantation is prolonged by use of CPB. This concept is not supported by the finding that our adult population, in which bypass was used selectively and in a minority of patients, had a median duration of mechanical ventilatory support identical to that in our pediatric population in which bypass was used routinely.

Infection is the most common cause of early morbidity and mortality in all lung transplantation recipients, and on the basis of this study, it is also the case in patients with CF. Bacteremia or viral, fungal, or bacterial lower respiratory infection were important contributing factors in all cases of early mortality. Nonetheless, our finding of a relatively low incidence of postoperative lower respiratory infections requiring antimicrobial therapy supports the work of others. The preoperative underlying suppurative process involving the lungs and the persistent tracheal and sinus reservoirs that exist postoperatively do not place the success of the transplantation at undue risk. A recent study from our institution demonstrated that CF and non-CF recipients have a similar median occurrence of their first pulmonary infections after transplantation.[22] Similarly, growth of fungus from preoperative sputum specimen did not seem to predispose to significant postoperative fungal infections, a finding also supported by recent reports.[22] Colonization with panresistant *Pseudomonas* serves as a relative but not absolute contraindication to transplantation. Although it has been suggested that matching CMV status of the donor[23, 24] and recipient reduces the incidence of primary CMV infections after transplantation, we have not adopted a policy of matching donor and recipient for CMV status. As previously delineated, although the incidence of donor/recipient mismatch or cases of both donor and recipient being positive were similar between groups, CMV prophylaxis is used more frequently in the pediatric population and the need for treatment of CMV disease was more common in the adult population.

Disruption or stenosis of the bronchial suture line occurred in 7.3% of bronchial anastomoses at risk in our series and can generally be managed nonsurgically. Wrapping of the bronchial anastomosis with omentum or pericardium to enhance revascularization and healing has been performed in the past by several centers.[25] A previous study from our institution revealed that the use of mattress-type suture technique (as opposed to simple interrupted or figure of eight) for the bronchial anastomosis was associated with increased risk of complications.[26] Omental or pericardial wrapping of the bronchial anastomosis did not confer a decreased risk of such occurrences and, as a result, is no longer performed. Localized bronchial anastomotic stenoses have been managed with good results by a variety of interventions, including rigid bronchoscopic dilatation, hydrostatic balloon dilatation, or polymeric silicone stent placement.

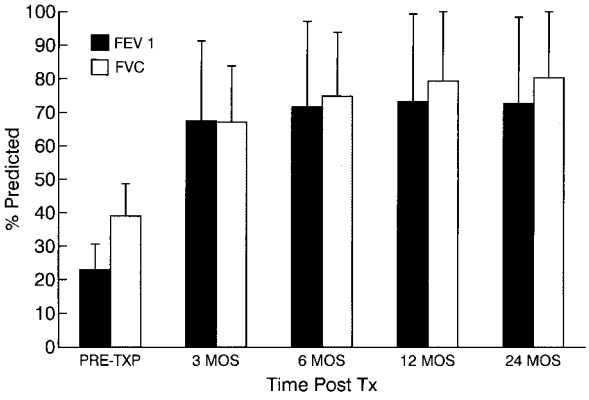

Fig. 2. Pulmonary function pretransplant *(PRE-TXP)* and posttransplant.

Three-year actuarial survival (Fig. 3) of 56% in our adult population is consistent with the predicted 3-year survival for adult bilateral lung transplant recipients in data published by the St. Louis International Lung Transplant Registry in January 1997. In contrast, the 3-year actuarial survival of 73% in our pediatric population is well above the 50% 3-year survival for all pediatric lung transplant recipients reported to the Registry as of January 1997. This may be due in part to our willingness to offer retransplantation as an option when the graft fails. Specifically, two of three patients with primary graft failure underwent successful retransplantation and are still alive. Likewise, two of three patients who had a clinical course in which decreased immunosuppression as therapy for PTLD led to remission of the PTLD but onset of OB have had successful retransplantation.

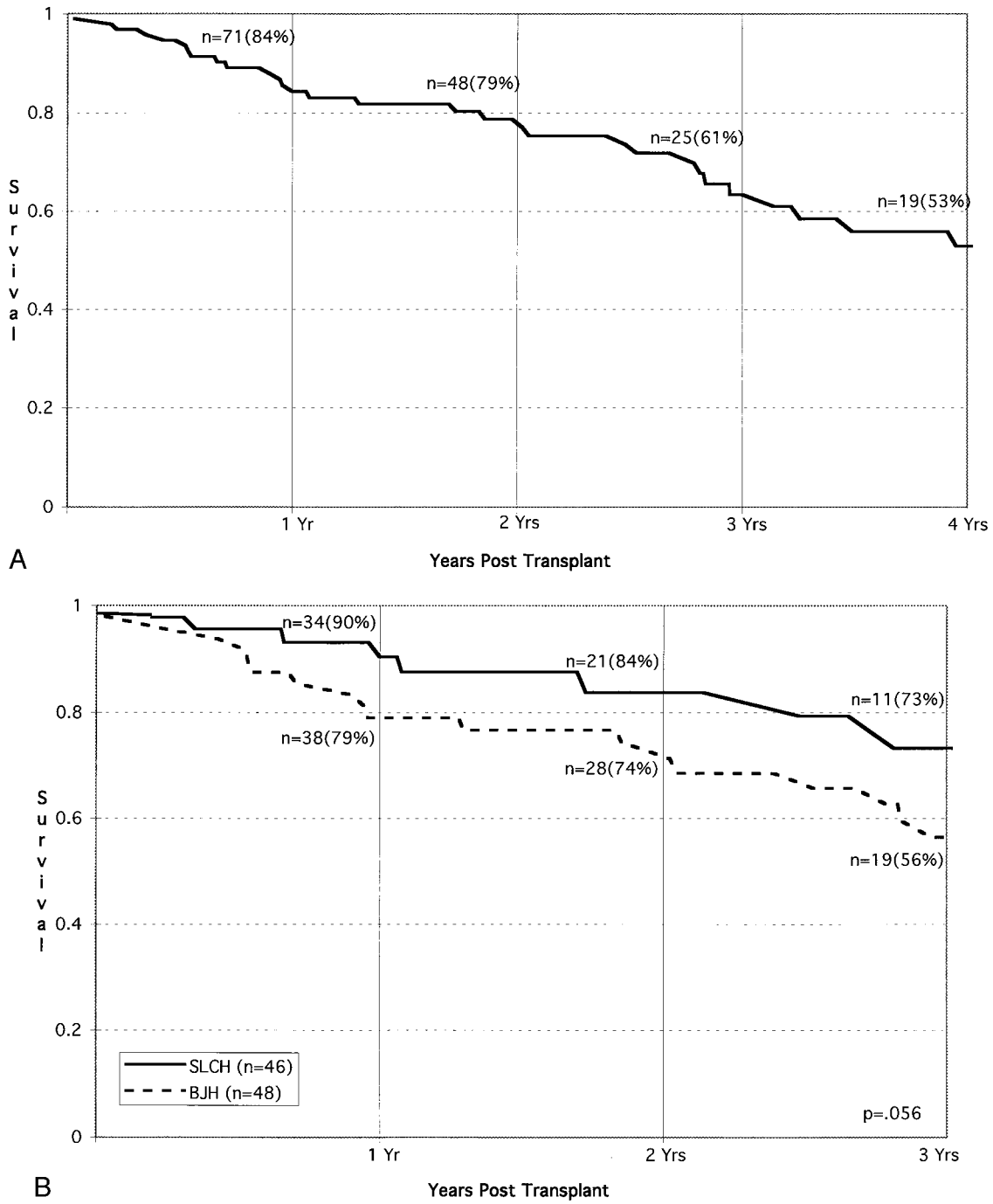

Fig. 3. A, Four-year actuarial survival for the entire group. **B,** Three-year actuarial survival by group. *SLCH,* Saint Louis Children's Hospital; *BJH,* Barnes-Jewish Hospital.

We are still confronted with the very troublesome issue of PTLD. The incidence of just more than 17% in our pediatric population is similar to that reported by Armitage and associates,[23] and all but two of our patients had PTLD develop within the first year after transplantation. The median time to onset of this complication in our patients was 4 months (range 2 to 56 months), and of the two patients in

whom PTLD developed late, one was diagnosed at autopsy 2 years after transplantation and the other was diagnosed 56 months after transplantation. Further investigation into the role of donor and recipient Epstein-Barr virus status and immunosuppression strategies are ongoing.

Finally, three of nine patients undergoing retransplantation died before hospital discharge for an early mortality in this subgroup of patients of 33%. This outcome is in keeping with previous reports showing that actuarial survival of adult and pediatric lung and heart-lung retransplant patients is markedly worse than recipients of initial transplants with a 1-year survival of less than 40%.[27] Living donor lung transplantation has thus far been considered a final option when it becomes unlikely, on the basis of the recipient's condition and place on the waiting list, that cadaveric organs will become available to save the life of the recipient. Eight patients in the entire group met these criteria, four of whom had undergone prior transplantation and seven of the eight (87.5%) are early and midterm survivors.

Bilateral lung transplantation can be performed with acceptable morbidity and mortality in patients with CF. Many questions remain unanswered, and important deterrents exist to long-term survival. Included in the list of challenges for the future are means of increasing the donor organ pool by better donor identification, innovative strategies such as living donor transplantation and use of non-heart-beating donors, research into prevention and treatment of OB, achieving a better understanding of the cause and optimal therapy for PTLD, and developing new and improved treatments for rejection. Although more definitive treatments and a true cure for CF through gene therapy may be on the horizon, optimizing and advancing our current understanding of lung transplantation currently provides the only survival opportunity for patients who are incapacitated by the ravages of this disease.

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Discussion

Dr. Frank C. Detterbeck *(Chapel Hill, N.C.).* I would like to congratulate the members of the teams at St. Louis Children's Hospital and Barnes Hospital for fine results in this combined series that we just heard about.

At the University of North Carolina we have done 81 transplantations in patients with CF with a 3-year survival of 61% and freedom from OB of 52%. So you can see that our overall results are very much the same, but some differences exist in the fine points, and I would like you to comment on three areas.

Your length of intubation was fairly long, almost a week. What do you think is the cause of that? I wonder if CPB has something to do with it. In our experience CPB was related to the length of intubation, and we have tried to avoid cardiopulmonary bypass for that reason. Even in patients who are less than 30 kg or 40 kg or patients who are on a ventilator preoperatively, we have found that we can usually avoid bypass and only need to resort to bypass approximately 15% of the time.

I would also like to ask about the nutritional status of the patients. In your report you implied that this correlated with a protracted hospital course. Do you have any data that support that? Low body weight is almost universal in patients with CF. We certainly have used feeding aggressively as well, but we find that when the feeding is due not to malabsorption but to increased CO_2 production, we really cannot have much of an impact by feeding patients aggressively preoperatively.

Last, I want you to comment on the issue of the respiratory flora before transplantation, specifically *B. cepacia* and panresistant organisms. You have done transplants in three patients with *B. cepacia*. During the same period of time we have transplanted almost three times as many patients with good results. In terms of panresistance, we recently looked at our data and found, to our surprise, that 40% of our patients had panresistant organisms at the time of transplantation, and yet, surprisingly, we found no difference in the survival or length of hospitalization or incidence of pneumonia in the panresistant patients versus the others. Have you looked at this and do you have any comments about it?

Dr. Hani Shennib *(Montreal, Quebec, Canada).* I would like to congratulate the St. Louis group for their outstanding results with transplantation for a very difficult group of patients, namely, CF patients.

I would like to ask if you could give us an idea why your results are superior to the results that are produced by the International Society of Heart and Lung Transplantation. Is it because you select your patients better? Do you eliminate patients with *B. cepacia*?

When you talk about mechanical ventilation, we now know that mechanical ventilation can have different modalities. It could be on intubated patients or it could be on patients who are not intubated on binasal positive airway pressure or continuous positive airway pressure. How many of those patients mechanically ventilated are actually intubated? I would also like to get your opinion as to how you handle the issue of Epstein-Barr virus serologic findings that are negative in those patients in view of the incidence of lymphoproliferative disorders.

Finally, how many of the living related donors in the transplants you have performed actually were intubated at the time of transplantation, at least to give us an idea of when you decide to perform living related transplants? I guess an issue here is also the question of how many patients are dying waiting for transplantation of a cadaveric donor and whether a process of natural selection for patients who are arriving to transplantation exists (i.e., are you actually transplanting better patients and the sicker patients are dying on the list?).

Dr. Dominique R. Metras *(Marseille, France).* Since 1988, we have had an experience of 39 transplantations, including 6 retransplantations done in the CF pediatric patients from age 5 to 16 years, with a mean age of 11, and support the authors' concepts in this subgroup. Bilateral single-lung transplantation done with the use of CPB is a safe and reproducible technique with excellent short-term results. As a matter of fact, we had no mortality in the first month for primary transplantation and no complication could be related to the use of CPB, in particular, bleeding or length of postoperative ventilation. I wish, however, to ask the author questions related to the CMV complications and prophylaxis. In our experience half of the midterm or late deaths were due to either intractable CMV lung infection or chronic lung dysfunction after cure of a severe CMV infection despite all protocols of immunosuppression and CMV prophylaxis. We also found a significant difference in long-term survival in positive CMV donors, particularly with negative recipients.

My questions to the author are as follows: First, what was the impact of CMV infection on the early results and late dysfunction of the lung or OB in your experience? What prophylaxis protocol would you recommend at present? And finally, do you try to match donor and recipient?

Dr. Mendeloff. I thank all of the discussants for their questions and I will try to answer them in order.

First of all, Dr. Detterbeck, I would like to thank you for reviewing the manuscript, and, as your results demonstrate, we continue to be very impressed at the transplantation work that you have previously published and again now these updated figures.

With respect to length of intubation as stated, I think

one of the things that explains the average length of intubation being almost a week is that there were several outliers that were intubated a long time and that skewed the average. If you look at the median length of intubation, it was actually 3 days. With respect to use of CPB, I know that work had been done by Dr. Aeba, and also data from your paper several years ago suggesting that CPB contributed to lengthy intubation. In fact, in our adult population in which CPB was used selectively and in a minority of patients, the actual length of intubation was longer than in the pediatric patients. So we do not have data to support that that in fact is true, at least for our population.

With respect to nutritional status and what is written in the manuscript, we have not done a critical analysis of nutritional status as a predictor of survival or outcome. All I would say is that we try to emphasize very aggressive nutritional support once these people move close to our transplant center and even before that so as to try to improve on their cachexia. A nutritionally depleted state certainly can contribute to respiratory muscle dysfunction and overall weakness after transplantation.

With respect to resistant flora, as you said, there are three patients in our entire population that we transplanted with *B. cepacia*, and one of these three died with *B. cepacia* infection both in the lungs and bloodstream. We have not used the presence of *B. cepacia* as an absolute contraindication but rather as a relative contraindication to transplantation. Microbiologists are starting to break down the *Burkholderia* into subspecies, and we are finding that in most of them we can find some type of synergistic antibiotic treatment for getting rid of that organism, and, as a result, it is only used as a relative contraindication, certainly not absolute. With respect to other flora cultured preoperatively, multiple patients have had panresistant *Pseudomonas*, and we have not used that as a contraindication to transplantation, nor have we found it to be a big problem after transplantation.

Dr. Shennib wanted to know how our survival is better for the pediatric transplant group compared to what is reported by the Registry, and I think that if you look at organ survival, actually our results are no better, but if you look at patient survival, we are saving several patients from being statistics on our mortality by (1) retransplanting them early on for primary graft failure and (2) taking several patients who would have died from either PTLD or OB that developed after decreasing immunosuppression for PTLD and retransplanted them, and they are survivors. So those are people who would have otherwise died who have survived. So I do not think we are picking better candidates. It is just a matter of using retransplantation for getting a better long-term survivorship.

With respect to mechanical ventilation, the data represented here are actual days on mechanical ventilation on an assist mode. So it would not include people on binasal positive airway pressure or CPAP.

With respect to Epstein-Barr virus and the lymphoproliferative disease, as is apparent from our study and several other studies, including data produced by the Pittsburgh group, posttransplantation lymphoproliferative disease is clearly an important problem and is associated with Epstein-Barr virus activation. We are currently scrutinizing the donor and recipient Epstein-Barr virus status for the entire population, and in addition we are investigating Epstein-Barr virus polymerase chain reactions and trying to figure out the use of those as far as predicting who might have this disease develop and how people are responding to treatment of this disease.

Four of the nine living donor transplants were intubated before undergoing their procedure. And finally, Dr. Metras, in response to your question regarding CMV complications, it has been pretty much a uniform finding in all of the lung transplant data, including Dr. Detterbeck's paper. They had almost a 60% involvement with CMV complications. We use ganciclovir prophylaxis when either donor or recipient is positive for IgG in the pediatric population, and in the adult population we are using ganciclovir prophylaxis when donors are CMV positive but recipients are CMV negative. It appears that a little bit more aggressive ganciclovir prophylaxis early postoperatively has resulted in a lower incidence of CMV in the pediatric population.