

Lung transplantation: the Cleveland Clinic experience

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- **BACKGROUND** Lung transplantation has been steadily developing as a therapeutic option for end-stage lung disease.
- **METHODS** Retrospective analysis of all 26 patients who underwent lung transplantation at the Cleveland Clinic Foundation between February 1990 and February 1992.
- **RESULTS** Nineteen single-lung transplantations and seven bilateral lung transplantations were performed. The 1-year actuarial survival for all recipients was 65%. A trend was noted towards better survival in recipients with emphysema (100%) and poorer survival in those with pulmonary hypertension (37.5%). Fungal sepsis and reimplantation lung injury were the most common causes of death, and most deaths (8 of 9) occurred within the first 4 weeks. Of 119 pulmonary complications, 82% occurred in the first 3 months, with infection (39%) and acute rejection (29%) being the most common. Bacterial and fungal infections occurred mainly in the first month, and cytomegalovirus infections occurred mainly in the second and third months. The majority of survivors have shown improvement in functional status.
- **CONCLUSIONS** The early perioperative and 1-month post-transplantation period appears critical to long-term survival. Even though the complications are numerous, they are usually manageable and, in general, do not result in long-term morbidity.

■ **INDEX TERMS:** LUNG TRANSPLANTATION; SURVIVAL RATE; FOLLOW-UP STUDIES
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THE LAST TWO DECADES have seen the establishment of kidney, heart, and liver transplantation as viable therapeutic options for patients with end-stage organ diseases. Despite considerable interest and research, lung transplantation has lagged behind other areas of organ transplantation until recently because of several problems unique to the lungs, such as ischemia of the anastomotic site due to failure to restore bronchial arterial supply, and increased susceptibility to infection from exposure to the atmosphere in a setting of immunosuppression.¹

The first human lung transplantation was performed by Hardy in 1963; the patient died of renal failure after 18 days.² Over the next 20 years about 40 lung transplantations were performed worldwide, with dismal results.^{3,4} These early attempts were complicated by a significant incidence of infection, rejection, and, in particular, airway dehiscence.¹ In 1981, Reitz⁵ reported the first successful heart-lung transplantation in a patient with primary pulmonary hypertension, and this served as a stimulus for further efforts. With better patient selection, advances in

TABLE 1
SELECTION CRITERIA FOR LUNG RECIPIENTS

Inclusion criteria
Severe obstructive ($FEV_1 < 35\%$ or $FEV_1/FVC < 0.4$) ^{**†} or interstitial ($FVC < 35\%$ or $DLCO < 40\%$) [‡] lung disease or severe pulmonary hypertension (systolic PAP > 90 mm Hg or mean PAP > 50 mm Hg) [§]
Physiologic age < 60
Life expectancy < 12 to 18 months with class III or IV disease by the New York Heart Association criteria
Absence of systemic illness or infection
Cancer-free survival > 5 years
Adequate left ventricular function without significant coronary artery disease
Potential for rehabilitation
Adequate nutritional status
Absence of drug or alcohol dependence
Good motivation with adequate family support
Absolute contraindications
Physiological age > 60 years
Current or recurrent (< 5 years) malignancy
Systemic disease with nonpulmonary organ involvement
Current smoking
Active extrapulmonary infection
Significant coronary artery disease or left ventricular dysfunction
Psychosocial problems, drug or alcohol abuse
Relative contraindications
Ventilator dependency
Steroid use (prednisone > 15 g/day)
Previous cardiothoracic surgery
History of noncompliance
Presence of tracheostomy

* FEV_1 , forced expiratory volume in 1 second

†FVC, forced vital capacity

‡DLCO, diffusing lung capacity for carbon monoxide

§PAP, pulmonary arterial pressure

organ preservation, improved postoperative care, development of bronchial omentopexy in an attempt to restore donor bronchus circulation,⁶ a better understanding of the effects of steroid therapy on the healing of bronchial anastomosis,⁷ and the availability of cyclosporine,^{8,9} successful lung transplantation became a reality in the 1980s.

In 1983, Cooper¹⁰ performed the first successful single-lung transplantation (SLT) in a patient with idiopathic pulmonary fibrosis (IPF), and in 1986 Patterson¹¹ performed the first successful double-lung transplantation in a patient with chronic obstructive pulmonary disease (COPD). Lung transplantation is now a viable therapeutic option for patients with end-stage lung diseases, and the indications for SLT¹²⁻¹⁷ and bilateral lung transplan-

TABLE 2
FORMAL PRETRANSPLANTATION ASSESSMENT

Pulmonary
Pulmonary function survey
Six-minute walk test with oximetry
Cardiopulmonary exercise study in patients with pulmonary hypertension, if tolerated
Ventilation-perfusion scan
Computed tomographic scan of the chest
Pulmonary angiography, when indicated
Cardiac
Two-dimensional echocardiography
First-pass radionuclide angiography
Cardiac catheterization
Coronary angiography in patients over age 40
Dynamic magnetic resonance imaging to evaluate right heart function in patients with pulmonary hypertension
Hematologic
Complete blood count, blood grouping, human lymphocyte antigen typing, antileukocyte antibody screening
Coagulation studies
Renal
Serum electrolyte levels, blood urea nitrogen concentration, serum creatinine concentration
Hepatic
Liver function studies
Infectious disease
Skin energy panel, including purified protein derivative
Serologic tests for fungi, cytomegalovirus, toxoplasmosis, hepatitis, syphilis, human immunodeficiency virus, herpes simplex virus, Epstein-Barr virus, varicella zoster
Nutritional
Dental
Otolaryngologic
In patients with cystic fibrosis with chronic sinusitis, to assess need for prophylactic surgical intervention
Psychosocial

tation (BLT)¹⁸⁻²⁰ have expanded considerably with an ever-increasing number of transplantations being performed each year. The first lung transplantation at the Cleveland Clinic was performed on February 14, 1990, and 26 lung transplantations have been performed through February 28, 1992. This article summarizes our experience with SLT and BLT with an emphasis on survival, complications, and functional status.

METHODS

Patient selection

Patients referred for lung transplantation were screened based on the selection guidelines listed in Table 1. The previous belief that steroid use before

transplantation increases the risk of anastomotic bronchial dehiscence has not been shown in recent studies^{14,21}; hence, our policy has been to taper the dose of oral prednisone to 15 mg or less prior to transplantation.

Previous cardiothoracic surgery or pleurodesis makes lung transplantation technically difficult and increases the risk of bleeding from adhesions; therefore, such patients were evaluated on an individual basis with careful review of radiographic studies.

Once a referral was initiated, preliminary data were screened, and if the patients appeared to meet the noted selection criteria, they underwent formal in-hospital pre-transplantation assessment (Table 2). A multidisciplinary transplantation team reviewed all data and decided to accept, reject, or postpone placing the patient on the transplant list. We did not mandate that patients relocate to Cleveland, provided they had adequate follow-up at their place of residence and agreed to come to our center for follow-up on a regular basis.

Type of procedure

Depending on the recipient's underlying pulmonary condition, either a BLT or a SLT was performed using standard techniques.^{11,19,20,22} SLT was performed in patients with pulmonary fibrosis (PF), COPD, lymphangiomyomatosis (LLM), primary pulmonary hypertension, and Eisenmenger's syndrome (with correction of the underlying cardiac defect). BLT was performed in patients with cystic fibrosis (CF) and one patient with IPF.

Immunosuppression

Immediately following transplantation, immunosuppression was achieved using cyclosporine (3 to 5 mg/kg intravenously over 24 hours), azathioprine (1 to 2 mg intravenously per day), and methylprednisolone (125 mg intravenously every 8 hours for 48 hours, followed by 20 mg twice a day until resumption of oral medications). Initially, the dose of cyclosporine was adjusted to maintain a trough level of 250 ng/mL. At 4 weeks after transplantation, oral immunosuppression therapy usually consisted of prednisone 0.5 mg/kg per day, azathioprine 1 mg/kg per day, and cyclosporine twice daily. During the initial 6 to 12 months, the dose of prednisone was gradually tapered as tolerated to 10 to 20 mg daily, and the cyclosporine dosage was adjusted to maintain a trough level of 150 to 200 ng/mL. Azathioprine was continued at

the same dosage unless the white blood cell count fell below 3,500/mm³.

Diagnosis of rejection

The clinical diagnosis of acute lung rejection (ALR) was based on clinical presentation (low-grade fever, dyspnea, malaise, mildly elevated white blood cell count, deterioration in oxygenation and pulmonary function), and classic radiographic changes (perihilar flaring with small effusion on the transplant side, decreased perfusion to the transplanted lung on perfusion lung scan in patients with SLT) in the absence of any evidence of infection and response to treatment.²³ In the setting of an unexplained infiltrate, the diagnosis was based on histologic evidence of ALR on transbronchial biopsy.^{24,25} The diagnosis of chronic lung rejection (CLR) or obliterative bronchiolitis (OB) was based on findings of gradually progressive obstructive airway disease in a setting of worsening dyspnea, and on histologic evidence of lymphocytic peribronchial infiltration and bronchial distortion, narrowing, and plugging caused by granulation tissue or scarring or both.²⁶

Diagnosis of infection

The diagnosis of definitive bacterial pneumonia was based on the radiographic appearance of a new or progressive pulmonary infiltrate and any of the following: (1) sputum Gram's stain showing > 25 leukocytes and < 10 squamous epithelial cells per high-power field with a predominance of a single organism; (2) Gram's stain of the centrifuged specimen of bronchioalveolar lavage showing predominance of a single organism; (3) bronchioalveolar lavage culture of $\geq 10^5$ colony-forming units per mL of a single organism²⁷; or (4) protected specimen brush culture showing > 10^3 colony-forming units per mL of a single organism.^{28,29} The diagnosis of cytomegalovirus (CMV) pneumonia was based on the presence of inclusion bodies on cytologic analysis of bronchioalveolar lavage or histology specimen in an appropriate clinical setting.³⁰ The diagnosis of *Pneumocystis carinii* pneumonia was based on a demonstration of the organism in the sputum, bronchioalveolar lavage fluid, or a lung biopsy specimen.³⁰

Infection prophylaxis

Postoperatively, all recipients received cefuroxime (1.5 g every 12 hours) for 3 days unless

TABLE 3
PROFILE OF LUNG TRANSPLANT RECIPIENTS

Type of transplant (n)	Age (mean ± SD)	Sex (M:F)	Disease category (n)	Specific disease (n)
Single-lung transplant (19)	46 ± 9	7:12	Emphysema (7)	Chronic obstructive pulmonary disease (5) Alpha-1 antitrypsin deficiency (2)
			Interstitial disease (4)	Idiopathic pulmonary fibrosis (1) Berylliosis (1) Systemic lupus erythematosus (1)
			Pulmonary hypertension (8)	Lymphangiomyomatosis (1) Primary pulmonary hypertension (5) Eisenmenger's syndrome (3)
Bilateral lung transplant (7)	26 ± 10	4:3	Bronchiectasis (6)	Cystic fibrosis (6)
			Interstitial disease (1)	Interstitial pulmonary fibrosis (1)

the antibiotic choice had to be changed depending on preoperative donor and recipient sputum Gram's stain and cultures, in which case antibiotics were usually continued for 7 to 14 days. A 14-day course of intravenous ganciclovir (5 mg/kg every 12 hours) was started postoperatively if either the donor or the recipient had a serologic test that was positive for CMV. After completion of intravenous ganciclovir, oral acyclovir was started at a dose of 800 mg four times a day for 2 months followed by 200 mg four times a day for prophylaxis against Herpes simplex or CMV infection. Oral trimethoprim-sulphamethoxazole (150/800 mg twice daily) was started after 1 month as prophylaxis against *P carinii* pneumonia.

Diagnosis of reimplantation lung injury

Reimplantation lung injury is nonimmunologic and includes morphologic, roentgenographic, and functional changes that occur in a transplanted lung in the early postoperative period as a result of either surgical trauma, ischemia, denervation, lymphatic interruption, or other injurious processes (exclusive of rejection).³¹ This reimplantation response was diagnosed radiographically as a patchy alveolar or interstitial disease beginning immediately after transplantation and reaching its peak by day 3, and not due to either fluid overload, left ventricular failure, rejection, infection, or atelectasis.³¹ This type of lung injury was considered a complication if it persisted without any signs of improvement beyond 7 days or resulted in primary graft failure in the form of a noncardiogenic pulmonary edema with histologic evidence of diffuse alveolar damage.³¹

Follow-up evaluation

Following discharge, patients were evaluated weekly during the first month, every 2 weeks during the second month, once a month from 3 to 6 months, every 2 months between 6 to 12 months, and every 3 months thereafter, or more frequently if necessary. We performed chest roentgenography, spirometry, and oximetry at rest and with exercise, and checked arterial blood gases, complete blood count, electrolytes, creatinine, serum magnesium level, lipid profile, and cyclosporine level at each visit. In patients with pulmonary hypertension, magnetic resonance imaging of the chest and cardiopulmonary exercise studies were performed every 3 months until no further improvement was noticeable. Additional tests such as ventilation-perfusion lung scanning, computerized tomography of the chest, and diffusion capacity were performed if clinically indicated. Flexible fiberoptic bronchoscopy was not performed for routine surveillance, but only if the patient had an unexplained infiltrate or abnormal pulmonary function, or if airway complication was clinically suspected. The 6-minute walk test, which was recently included in our protocol to assess the functional status, was not available for all recipients in this study.

Statistical analysis

Group data are presented as the mean plus or minus the standard deviation, where necessary. Differences between mean values of results before and after transplantation were analyzed by the paired *t* test. Survival estimates were made using the Kaplan-Meier method, and differences in survival between different groups were compared using the

TABLE 4
CHARACTERISTICS OF NON-SURVIVORS

Type of treatment	Age	Sex	Diagnosis	Survival (days)	Cause of death
Single-lung transplantation	38	F	Eisenmenger's syndrome secondary to PDA*	4	Reimplantation lung injury
	45	F	Primary pulmonary hypertension	14	<i>Candida</i> sepsis
	50	F	Pulmonary fibrosis (systemic lupus erythematosus)	11	<i>Candida</i> sepsis
	42	M	Primary pulmonary hypertension	<1	Coronary artery air embolism
	40	F	Eisenmenger's syndrome) secondary to ASD†	7	Reimplantation lung injury
	55	M	Idiopathic pulmonary fibrosis	100	Invasive aspergillosis, cytomegalovirus
	36	F	Primary pulmonary hypertension	20	Reimplantation lung injury
Bilateral lung transplantation	36	M	Cystic fibrosis	<1	Massive intrathoracic hemorrhage
	22	F	Cystic fibrosis	27	Subarachnoid hemorrhage

*Patent ductus arteriosus

†Atrial septal defect

log-rank *t* test. A probability value less than .05 was considered significant.

RESULTS

Between February 14, 1990 and February 28, 1992, 174 patients were screened for possible lung transplantation at our institution. Eighty-five (49%) underwent formal evaluation and 50 (59%) were subsequently listed for transplantation. Of those patients listed, 26 (52%) underwent transplantation, with an average waiting period of 96 ± 70 days (range 4 to 234 days). Nine of the listed patients (18%) died while awaiting transplantation (5 with primary pulmonary hypertension, 3 with CF, 1 with COPD) and the cause of death in all 9 was related to progression of their underlying disease. The characteristics of the 26 lung transplant patients are listed in Table 3. There were 19 SLT and 7 BLT recipients. BLT was performed in all patients with CF and in 1 patient with IPF due to the presence of purulent secretions in both lungs. The remaining patients underwent SLT, including 3 patients with Eisenmenger's syndrome who underwent simultaneous repair of their underlying cardiac defect. The ages of the SLT recipients ranged from 25 to 60 years (mean 46 ± 9 years) with a male-female ratio of 7:12. The ages of the BLT recipients ranged from 11 to 43 (mean of 26 ± 10 years) with a male-female ratio of 4:3.

Survival data

Table 4 summarizes the characteristics of the nine lung transplant recipients who died. Two patients (8%) died perioperatively, six patients (23%) died postoperatively; one patient (4%) who underwent SLT for IPF died of invasive aspergillosis and disseminated CMV infection following the initial hospital discharge (Figure 1). Two patients who received their transplanted lung from the same donor died of donor-related sepsis caused by *Candida tropicalis*. Eight of the nine deaths occurred during the first 4 weeks following transplantation.

The operative survival rates in the SLT and the BLT recipients were 95% and 86%, respectively (overall survival 92%). The in-hospital survival rates in the SLT and BLT recipients were 68% and 71%, respectively. Figures 2 and 3 show the 2-year Kaplan-Meier survival curves for 26 transplant recipients compared by the type of surgery and primary disease groups, respectively. The overall survival probability in all lung transplant recipients was 69% at 3 months and 65% at 1 and 2 years. The 3-month survival probability in the SLT recipients was 68%, and at 1 and 2 years it was 63%; the longest-surviving patient recently completed his second year. In the BLT recipients, both the 3- and 6-month survival probabilities were 71%, and the longest-surviving patient recently completed 7 months. The log rank test revealed no significant difference in survival between SLT and BLT groups

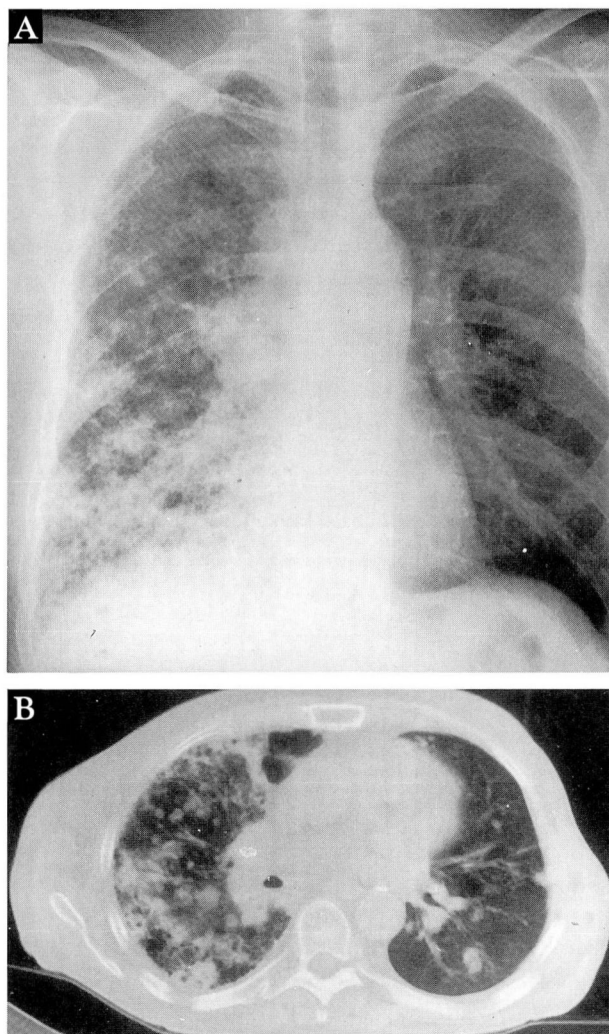


FIGURE 1. Chest roentgenogram (A) and computed tomographic scan of the chest (B) in a patient with left single-lung transplantation for idiopathic pulmonary fibrosis who contracted invasive aspergillosis infection in the fourth month after transplantation.

($P = .749$). The survival probability in the five recipients with interstitial lung disease (which included PF and LLM) was 80% at 3 months and 53% at 1 and 2 years. In recipients with pulmonary hypertension, both the 3-month and 1-year survival were 37.5%. In recipients with COPD or alpha-1 antitrypsin deficiency or both, the survival probability was 100% at 1 year, and in recipients with CF the survival probability at both 3 and 6 months was 67%. However, the survival differences among the four disease groups were not statistically significant ($P = .083$).

Pulmonary complications

The spectrum of pulmonary complications that occurred in three different time frames following transplantation is listed in Table 5. A total of 119 complications were noted in the 26 recipients, resulting in 4.6 complications per recipient.

Infectious pulmonary complications. Infections accounted for 47 of 119 (39.4%) pulmonary complications and were caused by bacteria, CMV, *P carinii*, fungi, and mycoplasma. Overall, there were 1.8 pulmonary infections per recipient.

Twenty-eight bacterial infections developed in 14 patients, accounting for 23.5% of all pulmonary complications and 59.5% of all pulmonary infections. Bacterial pneumonia was the most frequent type of infection noted, and the organisms implicated were *Pseudomonas aeruginosa* (4), *Staphylococcus aureus* (4), *Pseudomonas cepacia* (2), methicillin-resistant *S aureus* (2), polymicrobial organisms (1), *Branhamella catarrhalis* (1), *Acinetobacter* (1), *Klebsiella pneumoniae* (1), *Pseudomonas maltophilia* (1), *Xanthomonas* (1), *Hemophilus influenzae* (1) and beta-hemolytic streptococcus (1). Thus, the majority (60%) of the cases of pneumonia were due to gram-negative organisms (mainly *Pseudomonas*) followed by the staphylococci (30%). Fourteen (70%) of these cases occurred in the first month following transplantation, and all responded well to antibiotics.

Six patients acquired bacterial bronchitis with the following organisms: *Pseudomonas cepacia* (2), *Pseudomonas aeruginosa* (1), *S aureus* (1), mixed *Pseudomonas cepacia* and *H influenzae* (1), and mixed *Acinetobacter* and *S aureus* (1). Four of the six episodes of bronchitis occurred within the first month after transplantation and none occurred after 3 months. Again, gram-negative organisms, mainly *Pseudomonas* and staphylococci, were the major offending pathogens. All cases of *Pseudomonas* bronchitis developed in recipients with CF. Empyema developed in two patients on the same side as the transplant, one due to methicillin-resistant *S aureus* and the other due to *Pseudomonas aeruginosa*. Both episodes occurred in the first 2 weeks after transplantation, and both responded to antibiotics and chest-tube drainage. Bacterial infection accounted for 34% (12 of 35) of all pulmonary complications seen in patients with CF compared with 19% (16 of 84) of pulmonary complications seen in patients without CF.

Nine cases of CMV pneumonia represented 7.6%

of all pulmonary complications and 19% of all pulmonary infections. Table 6 shows the CMV status of the 26 transplant recipients and their donors along with the number of episodes of CMV pneumonia. All nine episodes of CMV occurred after the first month, with six (67%) occurring in the second and third months. None of the CMV-negative recipients contracted CMV pneumonia, and the incidence of pneumonia was highest (78%) when both recipient and donor were CMV-positive. Seven episodes of CMV pneumonia occurred in three recipients who had not received prophylactic ganciclovir in the immediate postoperative period. All episodes of CMV pneumonia responded to ganciclovir, but one recipient who had five episodes of CMV pneumonia also received CMV hyperimmunoglobulin during the last episode.

Eight fungal infections accounted for 6.7% of all pulmonary complications and 17% of all pulmonary infections. Three of the five episodes of fungal pneumonia occurred within the first month after transplantation, and *C. tropicalis* was subsequently isolated from the pretransplantation donor lung bronchoscopy specimen. In two cases the infection led to fungemia and eventual death. One SLT recipient with IPF contracted invasive aspergillosis in the fourth month after transplantation. This infection appeared to have originated in his native lung, and we hypothesize that colonizing *Aspergillus*

progressed to invasion due to immunosuppression. He died of invasive aspergillosis and, perhaps, disseminated CMV infection. A recipient with emphysema contracted cryptococcal pneumonia in the sixth month after SLT and responded to fluconazole therapy. Three episodes of *C. albicans*

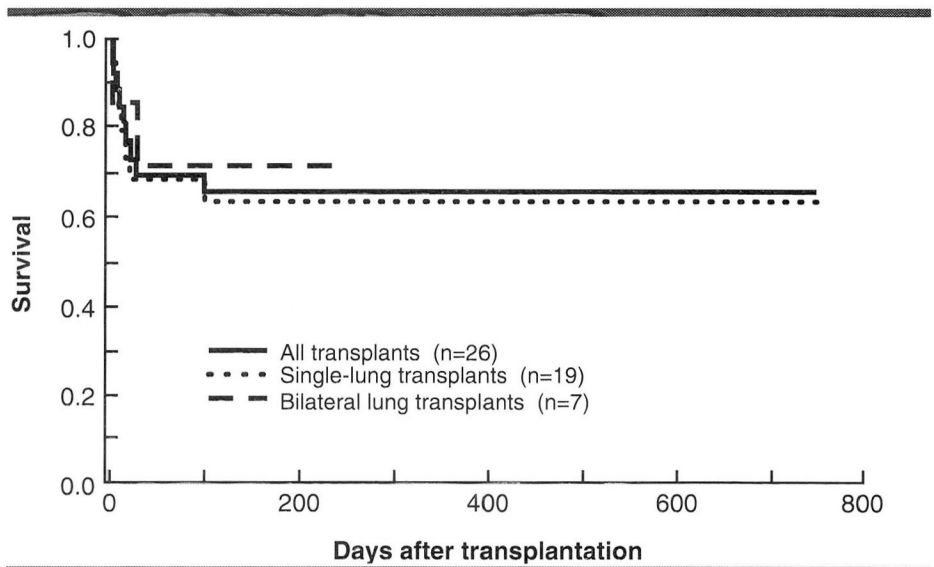


FIGURE 2. Kaplan-Meier survival curves for 26 lung transplant recipients as a combined group and according to the type of surgery during the period February 1990 to February 1992.

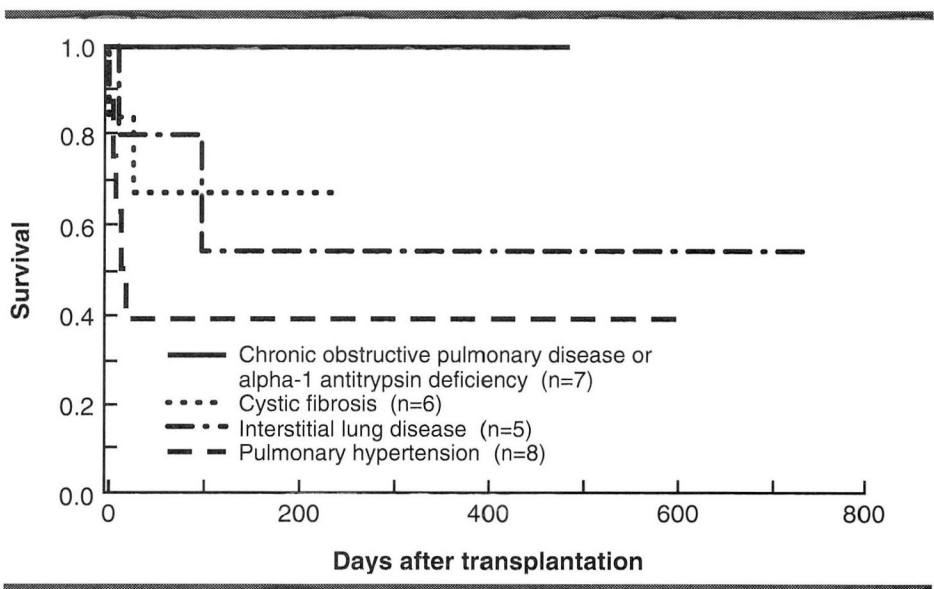


FIGURE 3. Kaplan-Meier survival curves for the 26 lung transplant recipients according to the disease groups.

TABLE 5
SUMMARY OF PULMONARY COMPLICATIONS FOLLOWING LUNG TRANSPLANTATION

Events (n) (%)	Total number (%) n = 119	Period after transplantation			Deaths from complications (n)
		<1 month	1 to 3 months	>3 months	
Acute rejection	35 (29.4)	16	10	9	—
Chronic rejection	1 (0.8)	—	—	1	—
Hemorrhage					
7 (5.9)	Intrathoracic	4	—	—	1
	Alveolar	2	1	—	—
Bacterial infection					
28 (23.5)	Pneumonia	14	3	3	—
	Bronchitis	4	2	—	—
	Empyema	2	—	—	—
Airway complication					
10 (8.4)	Dehiscence	3	1	—	—
	Stenosis or suture granuloma or both	3	3	—	—
Cytomegalovirus pneumonia	9 (7.6)	—	6	3	—
Fungal infections					
8 (6.7)	Pneumonia	3	—	2	3
	Bronchitis	3	—	—	—
<i>Pneumocystis carinii</i> pneumonia	1 (0.8)	—	1	—	—
Mycoplasma pneumonia	1 (0.8)	—	—	1	—
Mediastinal shift	1 (0.8)	1	—	—	—
Reimplantation injury	6 (5)	6	—	—	3
Pneumothorax					
6 (5)	Spontaneous	1	1	1	—
	Iatrogenic	2	—	1	—
Right vocal cord paralysis	1 (0.8)	1	—	—	—
Diaphragmatic hernia	1 (0.8)	—	1	—	—
Atelectasis	4 (3.4)	4	—	—	—

bronchitis occurred within the first month after transplantation and were treated with amphotericin. In two patients the infection was locally invasive at the site of bronchial anastomosis and probably contributed to partial anastomotic dehiscence. All six fungal infections occurring in the first month were from *Candida*.

One patient, who was not receiving trimethoprim-sulfamethoxazole prophylaxis because of allergy, contracted *P. carinii* pneumonia in the third month following treatment with muromonab-CD3 (OKT3) for recalcitrant ALR, but responded well to intravenous pentamidine. Another SLT recipient contracted mycoplasmal pneumonia in the sixth month and responded to erythromycin.

Noninfectious pulmonary complications

Noninfectious pulmonary events accounted for 72 of 119 pulmonary complications (60.5%) and resulted in 2.7 complications per recipient.

Rejection. Thirty-five episodes of ALR occurred in 16 recipients, making it the most common pulmonary complication (29.4%). Sixteen episodes (45.7%) occurred in the first month, 10 (28.6%) in the following 2 months, and 9 (25.7%) after 3 months. The latest episode in our series developed during the 23rd month after transplantation. Thirty episodes responded to methylprednisolone (500 mg to 1 g intravenously). Of the five episodes that did not respond to the steroid regimen, two responded to antilymphocytic globulin and three to murine monoclonal antibody OKT3. One patient with CF contracted OB in the third month after transplantation, following five separate episodes of ALR. The OB was documented by open-lung biopsy and did not respond to pulsed steroids or OKT3.

Airway complications. Ten airway complications developed in seven patients, representing 8.4% of all pulmonary complications. All four episodes of bronchial dehiscence occurred within the first 2

months after transplantation. In one SLT recipient with primary pulmonary hypertension, a small dehiscence developed in the posteromedial wall of the right main-stem bronchus on the 11th day after transplantation, requiring resection and reanastomosis with omental wrapping. On the 52nd day, a very small dehiscence on the posterior wall was again noted, which healed spontaneously but created significant bronchial stenosis. Two separate attempts to place a stent and perform neodymium-YAG laser photoresection of this stenotic area were unsuccessful, resulting in loss of function of both the right middle and lower lobes. Similarly, a second SLT recipient with LLM experienced bronchial dehiscence on the posterior wall on the 13th day after transplantation and required reanastomosis with pleuropericardial fat pad patching. This patient had mild stenosis at the anastomotic site but required no treatment for it. In both cases the pathology of the resected bronchus showed invasive *Candida*, necessitating intravenous and aerosolized amphotericin. The fourth case of a small bronchial dehiscence in a SLT recipient with emphysema was noted on the 14th day, but this healed spontaneously without residual stenosis.

Four other patients acquired partial bronchial obstruction, two due to suture granulomas and two due to simple stenosis. Granulomas were treated with neodymium-YAG laser, while bougie dilation was used to treat one of the two patients with stenosis.

Atelectasis. Two SLT recipients experienced persistent right middle lobe atelectasis due to oversized donor lungs. Two additional patients, one with CF and the other with LLM, experienced lobar atelectasis from retained secretions and required therapeutic flexible fiberoptic bronchoscopy.

Reimplantation lung injury. Six episodes of significant reimplantation lung injury were noted, representing 5% of all pulmonary complications. Four episodes developed in patients with pulmonary hypertension, and three of these patients subsequently died from primary graft failure. The other two episodes developed in patients with emphysema and CF. In the three survivors, resolution

TABLE 6
RECIPIENT AND DONOR CMV STATUS
AND EPISODES OF CMV PNEUMONIA IN EACH CATEGORY

Recipient	CMV status		CMV pneumonia	
	Donor	Total number of patients	Episodes (number)	Number of patients
-	-	1	0	0
-	+	2	0	0
+	-	11	2	1
+	+	12	7	3

occurred over a period of 14 days without any long-term consequences.

Intrathoracic and alveolar hemorrhage. Four episodes of intrathoracic hemorrhage due to surgical complications presented as increased chest-tube drainage in the immediate perioperative period; three required surgical exploration. A 34-year-old patient with CF died of persistent bleeding from extensive pleural adhesions at the vascular anastomotic site in a setting of coagulopathy after cardiopulmonary bypass. In one recipient who did not undergo surgical exploration, the hemorrhage resolved following correction of the patient's coagulopathy with fresh-frozen plasma. There were three episodes of alveolar hemorrhage; two were related to transbronchial biopsy, and one occurred spontaneously secondary to thrombocytopenia in a setting of high pulmonary arterial pressure.

Pneumothorax. Of the six episodes of pneumothorax, three were related to transbronchial biopsy of the transplanted lung; two required chest-tube insertion. Three episodes of spontaneous pneumothorax resolved without treatment, one on the transplanted side and two involving the native lungs (1 LLM, 1 COPD).

Mediastinal shift. One patient with LLM experienced postoperative respiratory distress and hemodynamic instability caused by significant mediastinal shift; this patient required insertion of a double-lumen endotracheal tube and institution of differential lung ventilation to restore equal lung inflation and hemodynamic stability. After extubation, a chest roentgenogram showed significantly less mediastinal shift, and there have been no long-term consequences so far. Although two recipients with emphysema displayed radiographically impressive mediastinal shifts, they have not suffered clini-

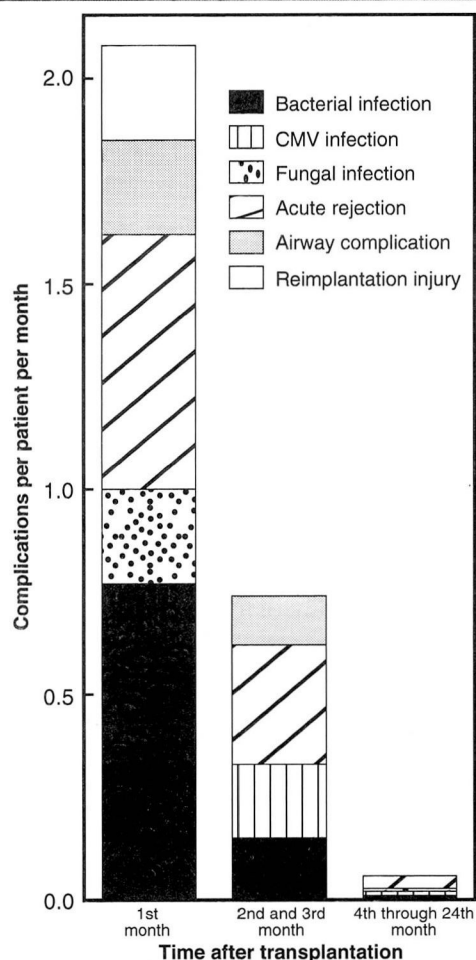


FIGURE 4. Comparison of complication rates for major pulmonary complications following transplantation adjusted for both time (monthly) and recipients at risk during each time frame. Reimplantation injury is an issue only in the first 2 weeks after transplantation, and all fungal infections occurring in the first month were from *Candida* while those occurring after the third month were not candidal in origin.

cal consequences and, hence, were not considered to have complications.

Miscellaneous surgical complications. One recipient was noted to have transient right vocal cord paralysis, which resolved by 4 weeks after transplantation. Two months after transplantation, another recipient suffered a left diaphragmatic hernia through the opening made for omentopexy, which required surgical correction.

Figure 4 compares rates (complications per recipient per month) and types of major pulmonary complications seen in the first month, the second

and third months, and the fourth through 24th months after transplantation.

Extrapulmonary complications

Extrapulmonary infections. A total of 23 extrapulmonary infections were seen after transplantation and are summarized in Table 7. Bacterial infections were the most common, followed by fungal and CMV infections. The majority of bacterial infections occurred in the immediate postoperative period, unlike CMV infections, which occurred more frequently after the first month.

Extrapulmonary noninfectious complications. Table 8 summarizes the noninfectious extrapulmonary complications that occurred during this follow-up period. Recurrent seizures due to high cyclosporine levels were seen in two patients with CF and required anticonvulsant therapy and reduction in cyclosporine dosage. This was perhaps a result of marked variability in cyclosporine absorption frequently seen in recipients with CF; in fact, 7 of 12 major episodes of cyclosporine side effects occurred in recipients with CF.

Transient hemolysis developed in two recipients due to graft-derived antibodies. Both recipients were A-positive; one received a transplant from an O-positive donor, and the other from an O-negative donor. Hemoglobin levels dropped precipitously 1 to 2 weeks after transplantation in association with a positive direct Coombs' test, low haptoglobin levels, and presence of AB-directed antibodies. This ABO incompatibility represents a type of "graft-vs-host" disease and is presumed to be due to production of AB antibodies by donor lymphocytes in the transplanted lung.³² The hemolysis resolved gradually over 1 to 2 weeks without specific treatment.

Functional follow-up

To assess the functional status in the 17 long-term survivors (> 3 months), physiologic parameters were compared for different disease categories before and 3 months after transplantation. Pulmonary function data for patients with interstitial lung disease, COPD, and CF are displayed in Figure 5. One patient with IPF who died of invasive aspergillosis 100 days after transplantation was not included in the follow-up evaluation.

Interstitial lung disease (three patients). The percent of predicted forced vital capacity (FVC) improved from 47 ± 13 before transplantation to 72 ± 11 afterward ($P = .12$).

TABLE 7
EXTRAPULMONARY INFECTIONS FOLLOWING LUNG TRANSPLANTATION

Infection group (n)	Types of infection	Number of infections	Causative organism	Location	Management	Outcome
Bacterial infection (9)	Bacteremia with pneumonia	2	Methicillin-resistant <i>Staphylococcus aureus</i> (1) <i>Pseudomonas cepacia</i> (1)	Intensive care unit	Antibiotics	Resolution
	Bacteremia without pneumonia	1	<i>S aureus</i>	Intensive care unit	Antibiotics	Death from <i>Candida</i> sepsis
	Thoracotomy wound infection (one also had sternal osteomyelitis)	2	<i>Pseudomonas aeruginosa</i>	Intensive care unit (1) Floor (1)	Antibiotics, incisional drainage, debridement	Resolution
	Urinary tract infection	1	<i>Escherichia coli</i>	Following discharge	Antibiotics	Resolution
Cytomegalovirus infections (5)	Asymptomatic	2	Cytomegalovirus	Floor (1) Following discharge (1)	IV ganciclovir	Resolution
	Leukopenia	1	Cytomegalovirus	Following discharge (1)	IV ganciclovir	Resolution
	Retinitis/disseminated	2	Cytomegalovirus	Following discharge (2)	IV ganciclovir	Resolution (1 died of <i>Aspergillus</i> sepsis)*
Herpetic infections (2)	Orolabial/pharyngeal	2	Herpes simplex	Floor (1)	Oral acyclovir	Resolved
				Following discharge (1)		
Fungal infections (7)	<i>Candida</i> sepsis with pneumonia (donor lung origin)	2	<i>Candida tropicalis</i>	Intensive care unit (2)	Amphotericin	Death (2)
	<i>Aspergillus</i> sepsis with pneumonia	1	<i>Aspergillus fumigatus</i>	Following discharge (1)	Amphotericin	Death (1)
	<i>Candida</i> cystitis	1	<i>Candida albicans</i>	Intensive care unit	Change of Foley catheter and amphotericin lavage	Resolved
	Oropharyngeal <i>Candida</i>	3	<i>Candida albicans</i>	Following discharge	Nystatin "swish and swallow"	Resolved

*Role of disseminated CMV infection in contributing to death unclear because CMV "buffy coat" turned negative with ganciclovir treatment

COPD/ α -1 antitrypsin deficiency (seven patients). The percent of predicted forced expiratory volume in 1 second (FEV₁) improved from 18 ± 5 before transplantation to 52 ± 11 afterward (P = .0001).

Cystic fibrosis (four patients). The percent of predicted FEV₁ improved from 13 ± 3 before transplantation to 42 ± 22 afterward (P = .05).

Pulmonary hypertension (three patients). Right

ventricular ejection fraction improved from a value of 22 ± 2.4% before transplantation to 54 ± 12.8% afterward (P = .05) (Figure 6). The systolic pulmonary artery pressure decreased significantly from a value of 109 ± 8 before transplantation to 49 ± 9 immediately afterward (P = .006) and to 35 ± 9 (P = .002) at the time when the Swan-Ganz pulmonary arterial catheter was discontinued (6.7 ± 4.7 days).

An improvement in oxygenation was noted after

TABLE 8
EXTRAPULMONARY NONINFECTIOUS COMPLICATIONS

Category	Types and number of complications
Hematologic	Transient hemolytic anemia secondary to graft-derived antibodies (2) Macrocytic anemia with thrombocytosis (1) Disseminated intravascular coagulopathy from sepsis (2) and graft failure (1) Coagulopathy following cardiopulmonary bypass (2), Thrombocytopenia (3)
Cardiac	Cardiac arrest Following preoperative intubation with recovery (1) Following surgical exploration and cardiopulmonary bypass for hemorrhage from atrial tear resulting in death from coronary air embolism (1) Secondary to subarachnoid hemorrhage resulting in brain death (1) Supraventricular tachycardia (4) Atrial fibrillation (2) Ventricular tachycardia (2) Pulmonary edema or volume overload (9)
Neurologic	Left-sided cerebral vascular accident which resolved (1) Transient lower extremity paresis from epidural catheter for pain control (2) Subarachnoid hemorrhage (1)
Gastrointestinal	Hyperamylasemia (2) Hyperbilirubinemia (2) Prolonged ileus (2)
Renal	Acute tubular necrosis Sepsis (3) Graft failure (1) Gentamicin (1) Transient postoperative rise in creatinine (2)
Drug-related major complications	Cyclosporine Seizures (2) Severe headache (1) Hyperkalemia requiring treatment (1) Hypertension (2) Mild renal failure (4) Hypomagnesemia requiring intravenous replacement (2) Corticosteroids Osteoporosis with vertebral compression fracture (1), Upper gastrointestinal bleeding (1) Delirium (1) Diabetes (2) Azathioprine Leukopenia (2) Cholestatic jaundice (1)
Miscellaneous	Sacral decubitus ulcer (1)

transplantation in all disease categories. In the 17 long-term survivors, the partial pressure of arterial oxygen improved significantly from a value of 59 ± 10 mm Hg before transplantation to 75 ± 12 mm Hg approximately 3 months after transplantation ($P = .0004$). Six of these 17 patients were receiving supplemental oxygen when pretransplantation measurements were taken (3.2 ± 1.3 L/minute). Although all patients required supplemental oxygen

before transplantation, by 3 months only one patient still needed it.

All survivors had improved pulmonary symptoms, and based on New York Hospital Association (NYHA) criteria, 14 were in class I and 2 were in class II at 3 months; all had been in either class III or IV before transplantation. Of the two recipients who were in class II at 3 months, one had partial loss of function in the transplanted lung due to severe stenosis from healed dehiscence, and the other was subsequently diagnosed with progressive OB. In the group of survivors who underwent the 6-minute walk test both before and after transplantation, a marked improvement in the total distance walked was noted.

DISCUSSION

Survival following lung transplantation has steadily improved over the last few years. Our 1-year overall survival rate of 65% compares well with the St. Louis International Lung Transplant Registry's (ILTR) survival estimate of 67% ($n = 849$) and with the Toronto Lung Transplant Group's survival rate of 66% ($n = 81$).³³ The actuarial 1-year survival in the SLT recipients at our center was 63%, compared with 68% ($n = 565$) in the ILTR, and 65% ($n = 45$) in Toronto.³³ Six-month survival probability following BLT at our center was 71%, in the ILTR, 70% ($n = 163$), and in Toronto, 76% ($n=37$). Early results from each institution reflect the presence of a learning curve, with newer centers benefiting from the experience of

established centers. This learning-curve effect is apparent from two separate reports by the Washington University Lung Transplant Group, where survival in a more recent period was much better (91.7%) than in an earlier report (79%), or in comparison to all patients receiving lung transplants from the commencement of their program (77%).^{34,35}

Perhaps owing to the small number of patients in each disease group, a statistically significant difference in survival between the four disease groups was not seen. However, a definite trend towards better survival in the emphysema group (100%) and poorer survival in the pulmonary hypertension group (37.5%) followed a similar pattern (76% and 51%, respectively) reported by the Toronto Group.³³ This trend may suggest a disease-specific tolerance for lung transplantation. Clarification of factors contributing to the decreased survival, particularly in patients with pulmonary hypertension, should lead to better patient selection and management. Reimplantation lung injury seems to contribute significantly to mortality in recipients with pulmonary hypertension, and pretreatment with prostaglandin E₁, surfactant, or oxygen-radical scavengers needs to be studied with the goal of reducing or preventing this

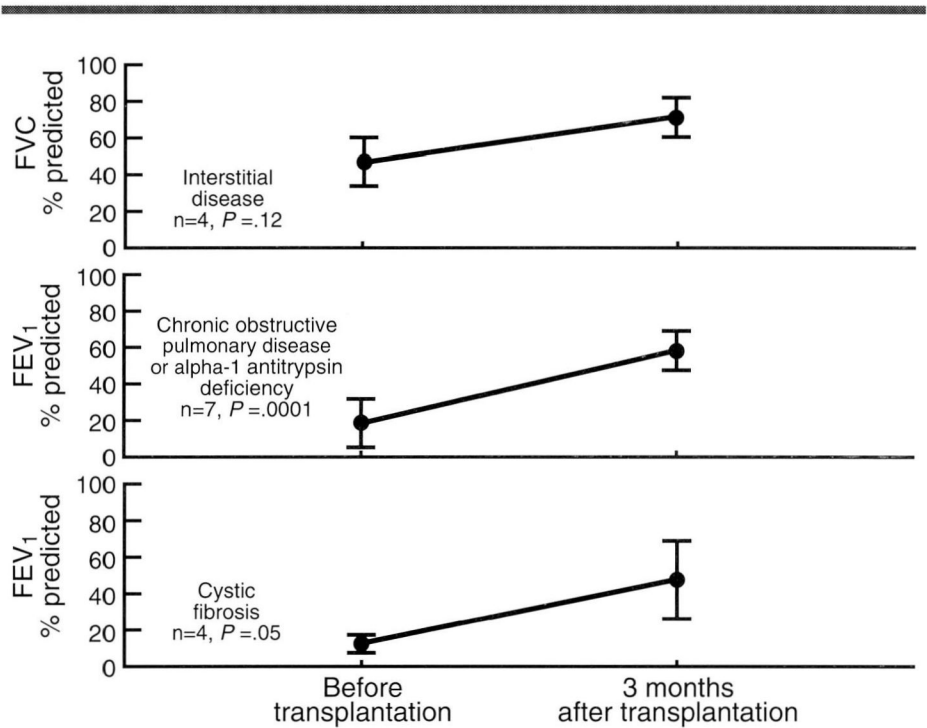


FIGURE 5. Spirometric values before and after transplantation in patients with interstitial lung disease, emphysema, and cystic fibrosis. FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second.

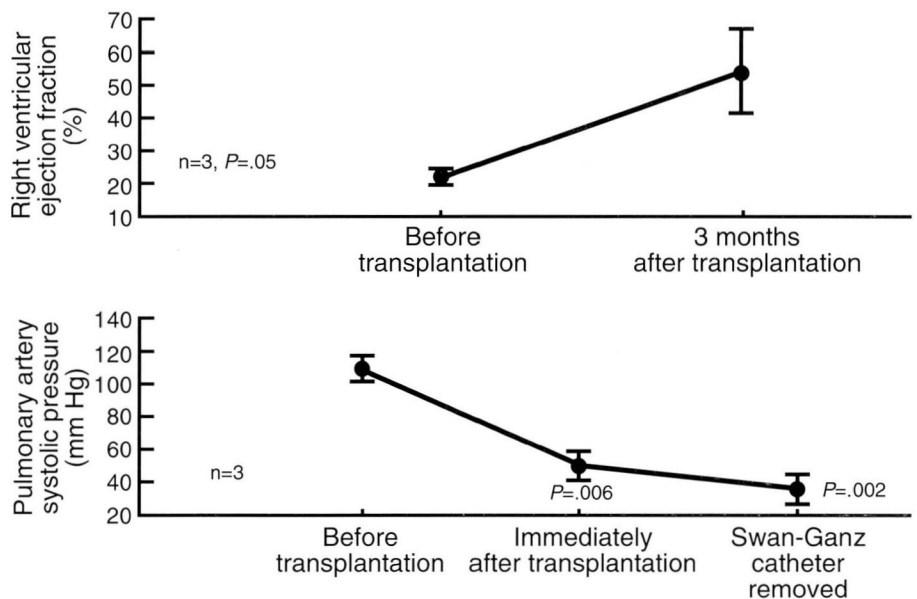


FIGURE 6. Cardiac performance before and after transplantation in survivors with pulmonary hypertension.

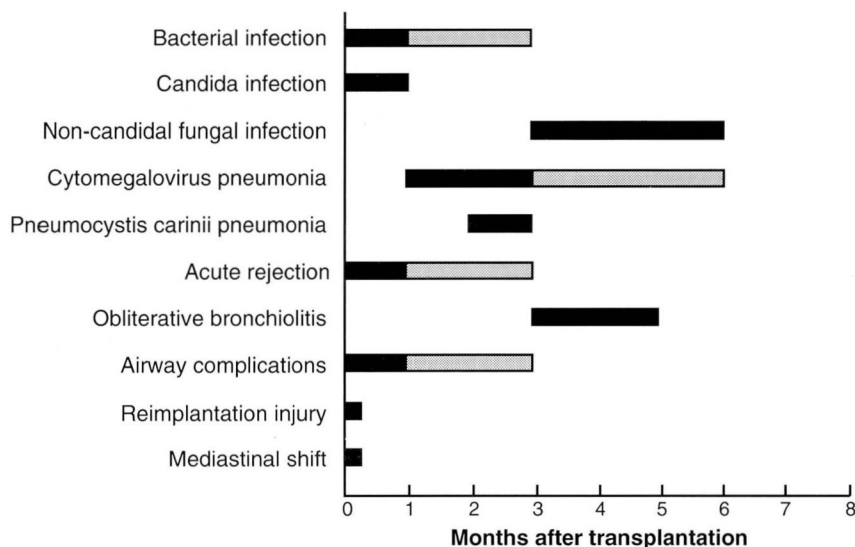


FIGURE 7. Approximate onset of pulmonary complications following lung transplantation. The gray bars indicate a much lower incidence compared with the solid bars. The incidence of obliterative bronchiolitis may increase with duration of follow-up.

complication. Interestingly, three survivors in the pulmonary hypertension group have lived longer than 1 year after transplantation, with the longest-surviving patient completing 21 months recently. Our short-term experience suggests that the first month after transplantation is critical to long-term survival.

Figure 7 shows the approximate time of onset of common pulmonary complications. Acute rejection, bacterial infection, and airway complications were the most common pulmonary complications. Seventy-four percent of the episodes of acute rejection occurred in the first 3 months after transplantation; thereafter, the incidence decreased but still occurred as late as 2 years later. OB has not been a major factor in our recipients, with only one documented case. As our patients survive longer, this problem may become more common. The relatively high incidence of acute rejection indicates that the current immunosuppression regimen still needs improvement. Several alternative forms of immunosuppressive therapy are being developed, and we hope these will enable us to further reduce morbidity and improve survival.

The timing of pulmonary infections in our transplant population (bacterial, fungal, CMV) was similar to that previously reported for lung,^{30,35,36} heart-lung,^{37,38} bone marrow,³⁹ and renal transplan-

tation.⁴⁰ However, lung- and heart-lung transplant recipients are at a much greater risk of infection compared with other organ transplant recipients, perhaps as a result of constant exposure to the environment in a setting of immunosuppression, and breached defense mechanisms such as impaired lymphatic drainage and mucociliary clearance.^{30,41} Infection in the transplanted lung is difficult to differentiate from rejection and pulmonary edema, given the similar radiographic picture, especially in the perioperative period. If pulmonary edema is excluded on clinical grounds,

our approach is to perform a bronchoscopy for bronchioalveolar lavage, protected specimen brush, and transbronchial biopsy. Initial treatment is selected based on bronchioalveolar lavage stains. Patients whose bronchioalveolar lavage reveals no organisms are treated for rejection pending culture and transbronchial biopsy results.

Although bacterial pulmonary infection can occur at any time after transplantation, its occurrence is most common in the first month (71.4%), with gram-negative organisms (especially *Pseudomonas*) and staphylococci being the predominant pathogens. *Pseudomonas* infection is particularly troublesome in recipients with CF, but surprisingly, no deaths in this group were attributed directly to bacterial infection, again reflecting our small numbers. The Toronto group reported four of five deaths in patients with CF were related to septic complications involving *Pseudomonas cepacia*.³³ Overall, the incidence of bacterial infection in our series was higher in patients with CF compared with non-CF patients, probably related to chronic colonization of the proximal airways and sinuses.

CMV pneumonia was not seen in the first month following transplantation, and the majority of the episodes occurred in the second and third months. Although other centers^{33,42} have reported a higher incidence of CMV pneumonia in CMV-negative

patients who receive organs from CMV-positive donors, in our series this infection was more common in CMV-positive patients receiving organs from CMV-positive donors. From our limited, nonrandomized experience, it appears that prophylactic ganciclovir may be helpful. Randomized trials using prophylactic ganciclovir and CMV hyperimmunoglobulin are currently being done at other centers⁴² to assess the role of these agents in preventing the development of CMV pneumonia, but the value of such strategies remains unclear. Perhaps with prophylactic regimens, CMV immune status may not be an important factor in lung matching; this is particularly important because of a limited supply of donor organs. No cases of herpes simplex pneumonia and only one case of *P carinii* pneumonia were reported, probably due to the use of prophylactic acyclovir and the combination of trimethoprim and sulfamethoxazole. An unrecognized benefit of the latter is its possible role in preventing infection due to other susceptible bacteria such as, *Nocardia*, *Listeria*, and perhaps *Toxoplasma*.⁴³

Candida infection is particularly troublesome in the first month after transplantation and may be donor-induced. In view of the mortality and morbidity associated with this pathogen, prophylactic strategies such as aerosolized amphotericin or oral fluconazole need to be examined. In our series, fungal pneumonias caused by *Aspergillus* or *Cryptococcus* or both were reported after the first 3 months following transplantation. The relatively high mortality rate associated with fungal infection demands a high index of suspicion to facilitate early diagnosis and aggressive treatment. In addition to prophylactic antimicrobials, other approaches are also necessary to reduce the morbidity associated with bacterial infection and rejection. Daily spirometry using a hand-held spirometer has been shown to be useful in detecting early decrements in FEV₁, vital capacity, or peak expiratory flow rates associated with rejection and infections.⁴⁴ If a patient experiences a sustained and consistent fall ($\geq 10\%$) in these measurements on home spirometry, and if this trend is confirmed by conventional pulmonary function testing, transbronchial biopsy with histologic examination can be carried out to distinguish between infection and rejection.⁴³ Early diagnosis is particularly important, as some studies suggest that both infection and rejection may play a role in the development of OB.^{45,46}

Airway complications were fairly common in the

first month after transplantation. However, dehiscence and stenosis did not contribute to mortality in any of our patients, and the role of omental wrap, muscle wrap, or telescopic anastomotic technique without wrapping in preventing dehiscence and stenosis could not be assessed because the anastomotic technique was individualized for each patient. Our current policy has been to use the end-to-end anastomotic technique along with steroids in the immediate postoperative period, and this approach has not resulted in an increased incidence of bronchial dehiscence or stenosis. In addition to bougie dilatation via a rigid bronchoscope and endobronchial stent therapy, laser therapy can also play a role in treating stenotic lesions or suture granulomas.

Maintenance of immunosuppression is particularly difficult in transplant recipients with CF. Impaired fat absorption and altered metabolism of cyclosporine results in fluctuating blood levels, thus leading to either potentially toxic or subtherapeutic levels. In theory, it is possible that recipients with CF may develop chronic rejection more frequently compared with recipients without CF because of inherent problems with immunosuppression and increased incidence of infection, as was seen in the only documented case of OB in our series. However, preliminary data from Stanford University suggest that OB is less prevalent at 1 year in recipients with CF (19%) compared with recipients without CF (41%).⁴⁷

All patient groups in our series showed improvement in pulmonary or cardiac functional status, oxygenation, and NYHA functional class, with the overall outcome comparing favorably with other transplant centers.⁴⁸

CONCLUSION

In summary, lung transplantation is one of the most rapidly evolving modalities in the field of transplantation, and despite the associated morbidity, mortality, and cost, the future of lung transplantation is bright. Though numerous, the complications seen with lung transplantation are usually manageable and, in general, do not result in long-term morbidity.

Following transplantation, a careful and close follow-up by a dedicated transplantation team is essential. In our experience, the outcome is excellent in patients with emphysema, and they may be the best

candidates for transplantation. However, several questions remain to be answered: (1) how to identify factors that contribute to poorer survival in patients with pulmonary hypertension; (2) how to maintain optimal cyclosporine levels in patients with CF; (3) the role of prophylactic antibiotics, anti-CMV, and antifungal therapy in the immediate postoperative period; (4) whether patients with alpha-1 antitrypsin deficiency should receive replacement therapy after transplantation; and (5) whether all patients with lung transplants eventually develop OB or underlying lung diseases such as CF, IPF, or LLM.

We believe that with more experience and with improved surgical techniques, organ preservation, postoperative care, chemoprophylaxis, and immunosuppression, such issues will be resolved and survival following lung transplantation will continue to improve, eventually approaching that for other, more established vital organ transplantations.

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