Medical Progress

LUNG TRANSPLANTATION

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SINCE the performance of the first successful lung transplantation nearly two decades ago, the procedure has gained widespread acceptance as a therapeutic option for a diverse array of lung diseases. For patients with severe functional impairment and limited life expectancy, lung transplantation offers the possibility of a markedly improved quality of life and longer survival. Nonetheless, complications are frequent and result in constraints on long-term preservation of graft function and patient survival. This article will review the current status of lung transplantation, with particular attention to the selection of patients, achievable outcomes, and complications.

RECENT TRENDS

After the initial technical successes of the early 1980s, both the number of transplantations and the number of candidates awaiting transplantation increased rapidly. Despite the continued growth of the candidate pool, the availability of transplantable donor lungs has remained relatively fixed at a level increasingly insufficient to meet demand. These trends have led to a leveling off of the annual lung-transplantation rate, a doubling of the median waiting time to approximately 18 months, and an increase in the number of candidates who die while awaiting transplantation (Fig. 1).[1] There has been a marked proliferation of lung-transplantation centers in the United States: there are currently almost 90, but only 35 of these programs performed more than 10 transplantations in 1997 (Smith CM, United Network for Organ Sharing: personal communication).

Accompanying the growth in activity has been an expansion of the spectrum of diseases for which transplantation can be offered. Currently, chronic obstructive pulmonary disease (including emphysema due to

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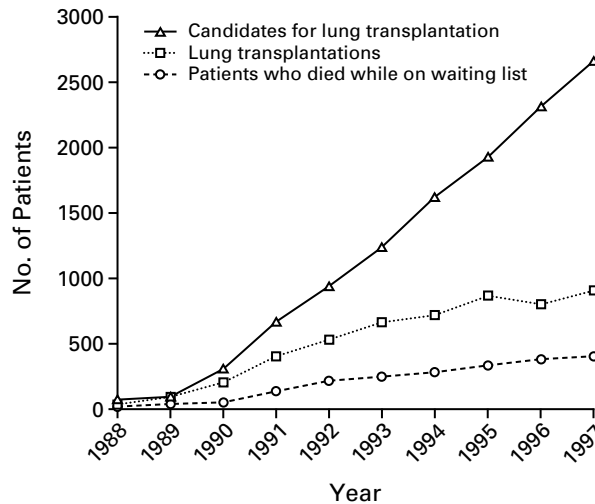
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alpha$_1$-antitrypsin deficiency) is the most common indication, accounting for approximately 45 percent of all lung transplantations.[2] Other common indications include cystic fibrosis, idiopathic pulmonary fibrosis, primary pulmonary hypertension, and Eisenmenger's syndrome. Less frequent indications include sarcoidosis, lymphangioleiomyomatosis, eosinophilic granuloma, drug-induced and radiation-induced pulmonary fibrosis, and pulmonary disease arising from an underlying collagen vascular disorder. Although lung cancer has traditionally represented an absolute contraindication to transplantation, successful transplantation for bronchoalveolar carcinoma has been documented.[3]

TIMING OF REFERRAL

A patient should be referred for transplantation at a point in the course of the disease at which death is considered likely within several years, so that transplantation would be expected to confer a survival advantage. The patient's perception of an unacceptably poor quality of life is an important additional consideration, but the prognosis must be the overriding impetus for referral. Integrated into the decision must be an anticipated waiting time of up to two years, during which the candidate's condition must remain functionally suitable for transplantation. Disease-specific guidelines for timely referral, which are based on available prognostic indexes, have recently been published (Table 1).[4]

SELECTION OF APPROPRIATE CANDIDATES

The use of stringent selection criteria is essential in the identification of candidates for whom transplantation is most likely to be successful. A concerted effort must be made to avoid selecting poor candidates simply because of the desperate nature of their situation. Transplantation should be offered only to patients who have advanced lung disease for which alternative therapies have failed or are unavailable and who have a high risk of death within two to three years. Patients should be functionally disabled but still ambulatory and should be free of clinically significant cardiac, renal, or hepatic impairment. In recognition of the somewhat poorer outcomes among older patients and the rigors of the more extensive surgical procedures, the following age limits have been recommended: 55 years for candidates for heart–lung transplantation, 60 years for candidates for bilateral lung transplantation, and 65 years for candidates for single-lung transplantation.[4]

Absolute and relative contraindications to lung transplantation are listed in Table 2.[4] The latter cat-

Figure 1. Lung Transplantation in the United States, 1988 to 1997.

Despite a steady increase in the number of candidates awaiting lung transplantation, the annual number of transplantations has leveled off because of the limited supply of donor organs. Consequently, an increasing number of candidates die while awaiting transplantation. Data for 1988 to 1996 are from the 1997 Annual Report of the U.S. Scientific Registry for Transplant Recipients and the Organ Procurement and Transplantation Network.[1] Data for 1997 are from the United Network for Organ Sharing.

TABLE 1. DISEASE-SPECIFIC GUIDELINES FOR REFERRAL FOR LUNG TRANSPLANTATION.*

Chronic obstructive pulmonary disease
FEV_1 <25 percent of predicted value after bronchodilator therapy
Clinically significant hypoxemia, hypercapnia, or pulmonary hypertension; rapid decline in lung function; or frequent severe exacerbations

Idiopathic pulmonary fibrosis
Symptomatic disease unresponsive to medical therapy
Vital capacity <60 to 70 percent of predicted value
Evidence of resting or exercise-induced hypoxemia

Cystic fibrosis
FEV_1 ≤30 percent of predicted value
FEV_1 >30 percent with rapidly declining lung function, frequent severe exacerbations, or progressive weight loss
Female sex and age of less than 18 years with FEV_1 >30 percent†

Primary pulmonary hypertension
NYHA functional class III or IV
Mean pulmonary-artery pressure >55 mm Hg
Mean right atrial pressure >15 mm Hg
Cardiac index <2 liters/min/m²
Failure of medical therapy, especially intravenous epoprostenol, to improve NYHA functional class or hemodynamic indexes

Eisenmenger's syndrome
NYHA functional class III or IV despite optimal medical management

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*Adapted from Maurer et al.[4] FEV_1 denotes forced expiratory volume in one second, and NYHA New York Heart Association.

†These factors are associated with a poorer prognosis; therefore, early referral may be indicated.

egory, consisting of characteristics requiring individualized consideration, merits further elaboration. Included in this category are chronic medical conditions such as osteoporosis, hypertension, diabetes mellitus, and coronary artery disease, which may worsen after transplantation and are acceptable in a candidate only if they have not resulted in end-organ damage and are well controlled with standard therapy. Preoperative corticosteroid therapy was once considered an absolute contraindication, since it was thought to be associated with impaired bronchial anastomotic healing.[5] Because of improved surgical techniques, transplantation can now be performed safely in patients who take moderate doses of corticosteroids.[6] Although patients receiving mechanical ventilation have undergone successful transplantation, as a group they have a higher mortality rate.[2,7-9]

In patients who have previously undergone thoracic surgery or who have pleurodesis, the procedure is technically more difficult and carries an increased risk of bleeding, particularly if cardiopulmonary bypass is used. Nonetheless, transplantation can be performed successfully in carefully selected patients.[10,11] The approach to patients with underlying collagen vascular disease remains controversial. Short-term survival and functional outcomes appear to be similar to those of other populations, but complications related to the underlying disease process have been reported.[12-14] Currently, many centers are willing to offer transplantation to carefully selected candidates who have collagen vascular disease without clinically significant extrapulmonary manifestations.

Chronic infection of the respiratory tract distinguishes patients with cystic fibrosis from patients with other diseases amenable to treatment by transplantation and has aroused concern about the risk of infection after transplantation. In general, however, the risk of postoperative infection in these patients is no greater than that in other patient populations.[15] Some centers exclude patients with pan-resistant *Pseudomonas aeruginosa,* but recent data demonstrating posttransplantation infection and survival rates similar to those of patients with sensitive strains suggest that this policy is unwarranted.[16] In contrast, the presence of *Burkholderia cepacia* portends a high risk of severe and often lethal postoperative infections and is considered an absolute contraindication by a number of centers.[16,17] Aspergillus is recovered from respiratory tract cultures in up to 50 percent of patients with cystic fibrosis, but its presence is not predictive of subsequent infection in the allograft and should not be considered a contraindication to transplantation.[18]

ALLOCATION OF ORGANS

Several features distinguish the allocation of lung allografts from the allocation of other solid organs. First, in contrast to policies governing the distribution of hearts and livers in the United States, the al-

TABLE 2. GENERAL GUIDELINES FOR THE SELECTION OF LUNG-TRANSPLANT RECIPIENTS.*

Indications

Advanced obstructive, fibrotic, or pulmonary vascular disease with a high risk of death within 2 to 3 years
Lack of success or availability of alternative therapies
Severe functional limitation, but preserved ability to walk
Age of 55 years or less for candidates for heart–lung transplantation, age of 60 years or less for candidates for bilateral lung transplantation, and age of 65 years or less for candidates for single-lung transplantation

Absolute contraindications

Severe extrapulmonary organ dysfunction, including renal insufficiency with a creatinine clearance below 50 ml/min, hepatic dysfunction with coagulopathy or portal hypertension, and left ventricular dysfunction or severe coronary artery disease (consider heart–lung transplantation)
Acute, critical illness
Active cancer or recent history of cancer with substantial likelihood of recurrence (except for basal-cell and squamous-cell carcinoma of the skin)
Active extrapulmonary infection (including infection with human immunodeficiency virus; hepatitis B, indicated by the presence of hepatitis B surface antigen; and hepatitis C with evidence of liver disease on biopsy)
Severe psychiatric illness, noncompliance with therapy, and drug or alcohol dependence
Active or recent (preceding 3 to 6 months) cigarette smoking
Severe malnutrition (<70 percent of ideal body weight) or marked obesity (>130 percent of ideal body weight)
Inability to walk, with poor rehabilitation potential

Relative contraindications†

Chronic medical conditions that are poorly controlled or associated with target-organ damage
Daily requirements for more than 20 mg of prednisone (or equivalent)
Mechanical ventilation (excluding noninvasive ventilation)
Extensive pleural thickening from prior thoracic surgery or infection
Active collagen vascular disease
Preoperative colonization of the airways with pan-resistant bacteria (in patients with cystic fibrosis)

*Adapted from Maurer et al.[4]

†These factors are considered on an individual basis. The presence of *Burkholderia cepacia* is considered an absolute contraindication by some centers.

location of lungs is based principally on waiting time without regard for severity of illness or medical urgency.[19] The only exception is a 90-day credit granted at the time of listing to patients with idiopathic pulmonary fibrosis, an acknowledgment of the disproportionately high mortality rate in this group of patients during the waiting period for transplantation.[20] Second, the lung is perhaps the most fragile organ in a patient who is brain-dead and is subject to damage by excessive administration of fluid, aspiration, and ventilator-associated pneumonia as well as by extensive prior cigarette smoking. For this reason, less than 20 percent of cadaveric donors have lungs suitable for harvest.[1] Third, the lung can tolerate only a brief period of ischemia, typically less than six hours. This limits the geographic distribution of lung allografts and precludes routine prospective HLA crossmatching. Instead, donors and recipients are matched on the basis of major blood groups and size and, in some programs, on serologic status for cytomegalovirus.

SURGICAL TECHNIQUES

There are four major surgical approaches to lung transplantation: single-lung transplantation, bilateral sequential transplantation, heart–lung transplantation, and transplantation of lobes from living donors. Indications for each technique are evolving. Heart–lung transplantation was the first procedure to be successfully implemented, but it has largely been supplanted by procedures to replace the lung alone. It is used in patients with Eisenmenger's syndrome and irreparable cardiac defects and in patients with advanced lung disease and concurrent left ventricular dysfunction or extensive coronary artery disease. The presence of cor pulmonale is not an indication for heart–lung transplantation, since recovery of right ventricular function is generally rapid and complete with replacement of the lungs alone.[21,22]

Single-lung transplantation has been the most commonly employed technique. The advantages of single-lung transplantation include technical ease and the fact that one donor can be used for two recipients. This procedure has been successfully used in patients with all types of lung disease except cystic fibrosis and bronchiectasis, although there has been concern about its use in patients with pulmonary hypertension. In patients with pulmonary hypertension, high vascular resistance in the native lung requires the allograft to handle nearly the entire cardiac output, potentially causing exaggerated pulmonary edema due to reperfusion and poor allograft function during the immediate postoperative period. However, a recent study of patients with pulmonary hypertension at the University of Pittsburgh found no difference in perioperative oxygenation, the duration of mechanical ventilatory support, or actuarial survival between recipients of single-lung transplants and recipients of double-lung transplants.[23]

Single-lung transplantation was initially deemed to be physiologically unsuitable for patients with emphysema, because of concern about preferential ventilation of the more compliant native lung, but experience has proved this concern to be largely unfounded. Marked overdistention of the emphysematous lung is occasionally encountered in the early postoperative period as a result of positive-pressure ventilation and has been successfully managed with independent lung ventilation.[24] Progressive hyperinflation can also occur more insidiously, compressing the allograft and contributing to late deterioration in allograft function. In this setting, surgery to reduce the volume of the native lung has been reported to improve lung function.[25,26]

Bilateral sequential transplantation involves the sequential performance of two single-lung transplantations at one time. In the absence of marked pulmonary hypertension, cardiopulmonary bypass can usually be avoided by ventilating the contralateral lung during each implantation — a distinct advantage over

the previous technique of en bloc double-lung replacement. The primary indications for this procedure are cystic fibrosis and other forms of bronchiectasis, which mandate the removal of both infected lungs. For the reasons discussed above, many centers prefer bilateral transplantation for patients with pulmonary hypertension. In addition, some have advocated the routine use of this procedure in younger patients with emphysema, arguing that it offers functional and survival advantages over single-lung transplantation.[27,28]

Transplantation of lobes from living donors is a recently developed technique involving bilateral implantation of lower lobes from two blood-group–compatible living donors. The procedure has been performed almost exclusively in patients with cystic fibrosis, though the indications have recently been broadened.[29] The donors should be larger than the recipient so that the donor lobes fill each hemithorax, thus avoiding persistent pleural-space problems in the recipient. Intermediate-term functional and survival outcomes approximate those achieved with conventional transplantation of cadaveric lungs.[30] Although there has been some concern about the potential risks of this procedure to the donor, a clinical series involving 120 donors reported no deaths and only four serious complications necessitating surgical re-exploration.[30] Donation of a lobe decreased lung volumes by an average of approximately 15 percent and was not associated with a long-term limitation in activity.[30]

IMMUNOSUPPRESSION

Immunosuppression is initiated in the immediate perioperative period and continued for the rest of the recipient's life. Standard regimens consist of cyclosporine or tacrolimus, azathioprine or mycophenolate mofetil, and prednisone. Some centers also use antilymphocyte-antibody preparations during the induction phase, but there is no convincing evidence that this approach diminishes the incidence of acute or chronic rejection.[31] Two important issues regarding standard immunosuppressive therapy are the myriad side effects associated with these agents and the numerous interactions with other commonly prescribed medications (Table 3).

OUTCOMES

Survival

According to the registry of the International Society for Heart and Lung Transplantation, 1-year, 3-year, and 5-year actuarial survival after lung transplantation is 70.7, 54.8, and 42.6 percent, respectively, with a median survival of 3.7 years (Fig. 2).[2] Survival rates for lung transplantation have improved only moderately over the past 10 years despite refinements in surgical technique and postoperative care.[2] These rates lag considerably behind those for heart and liver transplantation, for which five-year actuarial survival approximates 70 percent.[1]

Whether lung transplantation truly increases survival over the natural history of the underlying disease remains difficult to ascertain in the absence of randomized trials. One study made a disease-specific comparison of survival after transplantation with the survival of patients awaiting transplantation and found that transplantation offers a survival benefit to patients with cystic fibrosis and pulmonary fibrosis.[32]

TABLE 3. COMMONLY USED IMMUNOSUPPRESSIVE DRUGS.

DRUG	DOSE*	COMMON ADVERSE EFFECTS	DRUG INTERACTIONS
Cyclosporine and tacrolimus	For cyclosporine, the amount needed to achieve a whole-blood trough level of 250–350 ng/ml in the first year after transplantation and a trough level of 200–300 ng/ml thereafter† For tacrolimus, the amount needed to achieve a whole-blood trough level of 10–20 ng/ml	Nephrotoxicity, hypertension, neurotoxicity (tremor, seizures, white-matter disease, headache), hyperlipidemia, hyperkalemia, hypomagnesemia, hemolytic–uremic syndrome, hirsutism and gingival hyperplasia (with cyclosporine), osteoporosis (with cyclosporine), gastroparesis (with cyclosporine), hyperglycemia (with tacrolimus)	Blood levels are increased by macrolide antibiotics, azole antifungal agents, calcium-channel blockers, or gastric-motility agents Blood levels are decreased by anticonvulsant drugs or rifampin
Azathioprine	2–2.5 mg/kg of body weight/day	Leukopenia, macrocytic anemia, thrombocytopenia, hepatotoxicity, pancreatitis, nausea	Enhanced bone marrow toxicity when given with allopurinol
Mycophenolate mofetil	1000–1500 mg twice daily	Diarrhea, emesis, leukopenia, anemia	No clinically significant interactions
Prednisone	0.5 mg/kg/day for 3 months, followed by tapering of the dose to 0.15 mg/kg/day	Hyperglycemia, hypertension, hyperlipidemia, weight gain, osteoporosis, myopathy, mood changes, insomnia, cataracts	No clinically significant interactions

*The doses are based on the protocol used at the University of Pennsylvania Medical Center; the regimens may differ at other transplantation centers.

†Cyclosporine levels are measured by high-performance liquid chromatography.
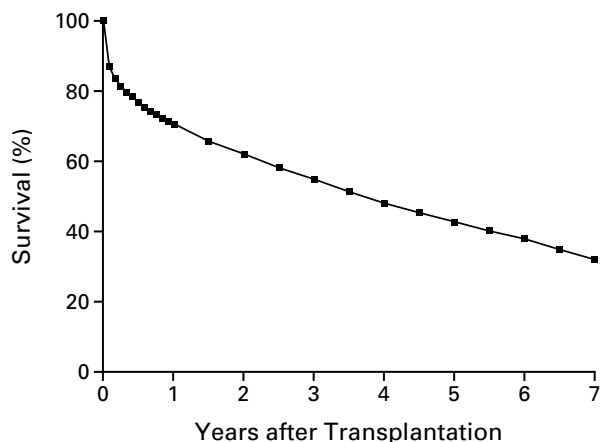
Figure 2. Actuarial Survival after Lung Transplantation.

Data were derived from the registry of the International Society for Heart and Lung Transplantation and reflect the collective international experience with 7021 single-lung and bilateral procedures performed from 1985 to 1997.[2] Actuarial survival at one, three, five, and seven years is 70.7, 54.8, 42.6, and 31.9 percent, respectively.

No such advantage could be demonstrated for patients with emphysema, a disease that typically follows a protracted course even in the advanced stages.[32]

The rate of death is highest in the year after transplantation, with infection and primary graft failure representing the leading causes of early death.[2] Factors identified by multivariate analysis as portending an increased risk of early death include a pretransplantation diagnosis of pulmonary hypertension (either primary or due to Eisenmenger's syndrome), dependence on a ventilator before transplantation, an age of more than 50 years in the case of recipients, and an age of more than 50 years in the case of donors.[2] In contrast, a pretransplantation diagnosis of emphysema is associated with a reduced risk of early death, a finding that most likely reflects the technical ease with which transplantation can be performed in patients with this disease.[2]

There is no significant difference in actuarial survival between recipients of single-lung transplants and recipients of double-lung transplants.[2] In both groups, long-term survival is limited principally by the development of bronchiolitis obliterans, the lethal effects of which may be manifested as progressive respiratory failure or by an attendant increase in the risk of infection. Advanced age of recipients (55 years or older) and a diagnosis of idiopathic pulmonary fibrosis are associated with somewhat poorer rates of long-term survival.[2]

Pulmonary Function and Gas Exchange

When performed in patients with obstructive or restrictive lung disease, both single-lung and bilateral transplantation dramatically improve lung func- tion. The peak effect of transplantation on lung function is typically achieved within three to six months, at which point the limiting effects of such surgically related factors as postoperative pain, altered chest-wall mechanics, respiratory-muscle dysfunction, and acute lung injury have dissipated. After bilateral lung replacement, normal pulmonary function is usually achieved. In contrast, lung function improves but does not completely normalize after single-lung transplantation, and the particular pattern of residual impairment reflects in part the pathophysiology of the remaining native lung, which participates to a limited extent in ventilation.[33] After single-lung transplantation for chronic obstructive pulmonary disease, the forced expiratory volume in one second increases to approximately 50 to 60 percent of the predicted value.[27,28] In analogous fashion, single-lung transplantation for pulmonary fibrosis leads to a marked but incomplete improvement in lung volumes, with persistence of a mild restrictive pattern.[33,34]

After an uncomplicated procedure, arterial oxygenation rapidly returns to normal. Supplemental oxygen is usually no longer necessary by the time of hospital discharge. For patients with emphysema and preoperative hypercapnia, hypercapnia associated with a blunted ventilatory response to carbon dioxide may persist for several weeks after transplantation.[35] Its presence beyond this time should prompt a search for other causes, such as a poorly functioning allograft or diaphragmatic dysfunction due to phrenic-nerve injury.[36,37]

Hemodynamics

For patients with pulmonary vascular disease, both single-lung and bilateral lung transplantation result in immediate and sustained normalization of pulmonary vascular resistance and pulmonary arterial pressures.[23] This is accompanied by an immediate increase in cardiac output and by more gradual remodeling of the right ventricle, with a decrease in ventricular-wall thickness. In one study of 34 patients, the right ventricular ejection fraction increased, as assessed by radionuclide ventriculography, from a mean of 22 percent preoperatively to 53 percent by three months postoperatively, with sustained improvement throughout a four-year follow-up period.[38]

Exercise Capacity

Exercise capacity improves sufficiently to allow the majority of transplant recipients to resume an active and unencumbered lifestyle. By the end of the first year after transplantation, approximately 80 percent of recipients report no limitations in activity.[2] At the other extreme, only 4 percent require total assistance. On average, after transplantation, the distance a patient can cover during a standard six-minute walk test is double that achieved preoperatively. Re-

cipients of bilateral lung transplants can walk farther in six minutes than recipients of single-lung transplants,[27,28] but this difference may reflect the younger age of the bilateral-transplant recipients.

Peak exercise performance, as assessed by progressive cardiopulmonary exercise testing, is characteristically reduced in lung-transplant recipients, independent of the type of procedure or the underlying disease. Suboptimal exercise performance persists in patients tested as late as one to two years after transplantation.[39] In these patients maximal oxygen consumption is typically only 40 to 60 percent of the predicted value despite the absence of clinically significant cardiac or ventilatory limitations on exercise.[39,40] The finding of an abnormally low anaerobic threshold in conjunction with evidence of impaired peripheral oxygen utilization suggests a defect at the level of the skeletal muscle, possibly resulting from cyclosporine-induced impairment in muscle mitochondrial respiration.[41-45]

Quality of Life

Despite the availability of highly reproducible tools to assess the quality of life, information on the effect of lung transplantation on this outcome measure is limited. The available studies document dramatic global improvement in all quality-of-life measures within several months after transplantation, but reassessment after the first year was not done.[46-48] A study of 18 lung-transplant recipients followed longitudinally beyond 18 months after transplantation[48] found that quality-of-life indexes remained stable for the 13 patients with an uncomplicated course but declined substantially in the 5 patients in whom bronchiolitis obliterans developed.

Improvements in the quality of life and performance status do not have a substantial effect on the employment patterns of lung-transplant recipients: fewer than 40 percent work either full time or part time.[2,46,48,49] Factors that may contribute to this low rate include a potential reluctance to hire persons with a complex medical condition, the potential loss of disability income or medical benefits as a result of employment, and the assignment of a lower priority to employment than to other post-transplantation goals.[49]

COMMON COMPLICATIONS

Primary Graft Failure

Mild, transient pulmonary edema is a common feature of the freshly transplanted allograft. In approximately 15 percent of cases, the injury is sufficiently severe to cause a form of acute respiratory distress syndrome termed primary graft failure.[50] Primary graft failure is presumed to reflect ischemia–reperfusion injury, but surgical trauma and lymphatic disruption may be contributing factors. The diagnosis rests on the presence of widespread

infiltrates on chest radiographs and severe hypoxemia within 72 hours after transplantation and the exclusion of other causes of graft dysfunction, such as volume overload, pneumonia, rejection, occlusion of the venous anastomosis, and aspiration. Treatment is supportive, relying principally on conventional mechanical ventilation. Independent lung ventilation, inhaled nitric oxide, and extracorporeal membrane oxygenation have been used as adjunctive measures.[50-52] Mortality rates of up to 60 percent have been reported, and among those who survive, the recovery period is often protracted, but achievement of normal allograft function is possible.[50,53] The results of emergency retransplantation in such cases have been poor.[54]

Airway Complications

Once a common cause of morbidity and mortality, airway complications now occur in less than 15 percent of patients — a reduction that reflects improved surgical techniques.[55-57] Complete dehiscence of the bronchial anastomosis, now rare, mandates immediate surgical correction or retransplantation. Partial dehiscence is managed conservatively, with evacuation of the associated pneumothorax and a reduction in the dose of corticosteroids. Anastomotic stenosis is the most common airway complication and typically occurs several weeks or months after transplantation. Clues to the presence of clinically significant airway stenosis include focal wheezing, recurrent lower respiratory tract infections, and suboptimal pulmonary function. Narrowing may be caused by stricture, granulation tissue, or bronchomalacia, all of which are amenable to correction with stent placement by bronchoscopy.[56]

Infection

The rate of infection among lung-transplant recipients is several times as high as that among recipients of other organs and is most likely related to the exposure of the allograft to the external environment.[58] Bacterial infections of the lower respiratory tract predominate and have a bimodal distribution. In the early period after transplantation, bacterial pneumonia is common. In addition to immunosuppression, predisposing factors include blunted cough due to postoperative pain and lung denervation, poor lymphatic drainage, impaired mucociliary clearance as a result of diffuse ischemic injury to the bronchial mucosa, narrowing of the bronchial anastomosis, and passive transfer of organisms with the donor lung. Bacterial infection of the lower respiratory tract reemerges as a late complication of transplantation among patients in whom bronchiolitis obliterans develops.[58] Such patients may have recurrent episodes of purulent tracheobronchitis that are often associated with radiographic evidence of bronchiectasis. In both early and late infections, gram-negative organ-

isms, and in particular *P. aeruginosa,* are most often isolated.[58,59] Despite the persistence of virulent bacterial pathogens in the sinuses and upper respiratory tract, lung-transplant recipients with cystic fibrosis do not have a greater risk of lower respiratory tract infections than do patients who receive lung transplants for other reasons.[15]

Although cytomegalovirus infections can now usually be treated successfully with ganciclovir, they contribute substantially to post-transplantation morbidity. Patients who are seronegative for cytomegalovirus before the procedure and in whom primary infection occurs as the result of the transplantation of an organ from a seropositive donor are at greatest risk for severe infection, particularly pneumonitis.[60] A seropositive recipient can be reinfected with a new strain of virus from the donor organ, or a latent infection can be reactivated after transplantation, but in either case the severity of infection tends to be mitigated by the presence of intrinsic immunity.

In an attempt to minimize the effect of cytomegalovirus infection, many centers have adopted prophylactic strategies. The most effective strategy for seronegative recipients is the use of seronegative donors and screened blood products. Although it reduces the risk of infection to negligible levels, this strategy is associated with increased waiting times before transplantation, since the majority of donors have been exposed to cytomegalovirus. An alternative strategy that can be employed when either the donor or the recipient is seropositive is the initiation of ganciclovir prophylactically at the time of transplantation or preemptively when an increasing viral burden is detected. The efficacy of such a strategy remains uncertain; current data suggest that prophylaxis may delay the onset and attenuate the severity of infection.[61,62]

As a ubiquitous organism acquired by inhalation, aspergillus frequently colonizes the airways of lung-transplant recipients, but clinical infection develops in only a minority of patients.[18,63,64] The devitalized cartilage and foreign suture material of the fresh bronchial anastomosis create a vulnerable site for aspergillus infection. Aspergillus may also infect the airways more diffusely, causing mucosal edema, ulceration, and the formation of pseudomembranes.[65] Although usually responsive to oral itraconazole or to intravenous or inhaled amphotericin B, airway infections have in rare cases been associated with widespread dissemination and with fatal erosion into the pulmonary artery.[65,66] In contrast to airway infection, invasive disease of the lung parenchyma and disseminated aspergillosis are associated with a high mortality rate despite therapy.

Rejection

Acute Rejection

Aggressive surveillance protocols involving bronchoscopic lung biopsy have shown that most trans-

plant recipients have at least one episode of acute rejection. Preliminary data suggest that the degree of HLA mismatching, particularly at the HLA-DR and HLA-B loci, is a risk factor for acute rejection.[67,68] The incidence is greatest within the first 100 days after transplantation, steadily declining thereafter to a low but not negligible rate after the first year.[69] Transbronchial lung biopsies in patients who are asymptomatic and functionally stable have demonstrated histologic evidence of rejection in up to 39 percent, typically of minimal-to-mild grade.[70-72] When present, clinical manifestations are nonspecific and include malaise, low-grade fever, dyspnea, cough, impaired oxygenation, and leukocytosis. The chest radiograph may demonstrate alveolar, nodular, or interstitial opacities or pleural effusions, but episodes of rejection after the first month are more likely to be undetectable radiographically.[73] A fall in spirometric values in excess of 10 percent commonly accompanies bouts of rejection and has prompted the widespread practice of daily spirometric monitoring at home as a means of early detection.[74] The technique fails to distinguish rejection from infection, however, and appears to be of more limited value in recipients of single-lung transplants, in whom fluctuations in native-lung mechanics can influence spirometric values.[71]

Although at times unavoidable, the practice of diagnosing acute rejection on the basis of clinical criteria alone is imprecise and runs the risk of needlessly subjecting the patient to an augmented regimen of immunosuppression or failing adequately to address the possibility of an alternative process. In one series, acute rejection was confirmed histologically in only 66 percent of the instances in which it was suspected on clinical grounds.[72] Bronchoscopic lung biopsy offers a safe and accurate means of diagnosing acute rejection and has emerged as the procedure of choice. The histologic hallmark of acute rejection is the presence of perivascular lymphocytic infiltrates, which in more severe cases, spill over into the interstitium and alveolar air spaces. In order to optimize the yield and accuracy of transbronchial biopsy, at least five pieces of alveolated parenchyma, each containing bronchioles and more than 100 air sacs, should be obtained.[75]

Treatment of acute rejection consists of a three-day course of 10 to 15 mg of intravenous methylprednisolone per kilogram of body weight per day, followed in some centers by a transient increase in and a subsequent tapering of the maintenance dose of prednisone. The vast majority of patients with histologically proved acute rejection in the first months after transplantation have a brisk clinical, physiologic, and radiographic response, though follow-up biopsies show evidence of persistent rejection in approximately one third of such patients.[72,76] The likelihood of a therapeutic response is substantially lower in pa-

tients in whom the diagnosis is based exclusively on clinical criteria, particularly after the first six months, when chronic rejection commonly contributes to observed declines in lung function.[76,77]

Chronic Rejection

Chronic rejection is a pervasive problem after lung transplantation and accounts for the poorer rates of long-term graft and patient survival as compared with those for other solid-organ procedures. It is manifested histologically as bronchiolitis obliterans, a fibroproliferative process that targets the small airways, leading to submucosal fibrosis and luminal obliteration. In contrast to the case with acute rejection, with chronic rejection, histologic confirmation of bronchiolitis obliterans by transbronchial lung biopsy is problematic, with a reported sensitivity as low as 17 percent.[78] In recognition of this difficulty, the entity of "bronchiolitis obliterans syndrome" has evolved whose diagnosis rests on the physiologic demonstration of airflow limitation rather than on histologic findings. Specifically, bronchiolitis obliterans syndrome is defined as an otherwise unexplained and sustained fall in the forced expiratory volume in one second to a level of 80 percent or less of the peak value after transplantation.[79] Although easily applied, this definition suffers from its inability to identify subclinical disease that may potentially be more amenable to therapy.

The pathogenesis of bronchiolitis obliterans remains poorly understood. However, the identification of acute rejection as the single most important risk factor substantiates the hypothesis that this disorder is immunologically based.[80-82] Other proposed risk factors include cytomegalovirus infection, airway ischemia, and HLA mismatching.[60,67,80,82-84]

Bronchiolitis obliterans syndrome is uncommon in the first six months after transplantation, but its prevalence subsequently increases steadily, and it is found in 60 to 70 percent of patients who survive for five years.[80-82] The onset of disease is typically insidious and marked by dyspnea and cough. Chronic colonization of the airways with *P. aeruginosa* is common and leads to recurrent bouts of purulent tracheobronchitis. Spirometry shows evidence of progressive airflow obstruction, with a fall in midexpiratory flow rates (forced expiratory flow at 25 to 75 percent of forced vital capacity) often preceding the characteristic decline in the forced expiratory volume in one second and in the ratio of forced expiratory volume in one second to forced vital capacity.[85] Standard chest radiographs are unrevealing, but high-resolution computed tomography may demonstrate decreased peripheral vascular markings, peripheral bronchiectasis, and evidence of air trapping on expiratory images.[86,87]

The pace of the decline in lung function is highly variable and may be characterized by periods of relative stability.[85] The treatment of chronic rejection centers on augmentation of immunosuppression. A wide range of treatments have been used, including high-dose corticosteroids, antilymphocyte antibodies, tacrolimus, inhaled cyclosporine, and methotrexate, but no single approach has proved superior.[88-91] At best, treatment appears to slow the rate of decline in lung function rather than to arrest the process.[88,90] The overall prognosis is poor, with a mortality rate of 40 percent within two years after the diagnosis.[88] Retransplantation is the only definitive treatment for severe bronchiolitis obliterans syndrome. When retransplantation is performed at experienced centers in carefully selected patients, the outcomes now approximate those after initial transplantation.[92] In the light of the current scarcity of donor organs, however, the role of retransplantation in this setting remains controversial.

In the absence of effective treatment for bronchiolitis obliterans syndrome, attention has focused on preventive strategies. Many centers perform frequent lung biopsies for surveillance during the first year after transplantation in the hope that early detection and treatment of clinically occult acute rejection will decrease the risk of chronic rejection. This approach has been called into question by a recent report showing that the prevalence of bronchiolitis obliterans syndrome did not increase when the practice of surveillance biopsy was abandoned.[93] Prophylaxis against cytomegalovirus infection has been reported to delay the onset of chronic rejection but not to affect its overall prevalence.[61,62] Finally, a single prospective trial comparing cyclosporine with tacrolimus as the initial immunosuppressive agent suggested that tacrolimus therapy decreased the prevalence of chronic rejection, but the majority of the patients were followed for less than two years.[94]

FUTURE DIRECTIONS

Lung transplantation has reached its current clinical plateau largely through refinements in the selection of patients, operative techniques, and postoperative care. Two major hurdles must be overcome to increase the applicability of lung transplantation and improve long-term results: the supply of donor organs must be increased to meet the demand, and chronic rejection must be more effectively prevented.

Xenotransplantation — the use of animal organs for transplantation in humans — offers a potential solution to the shortage of donor organs. A major obstacle to xenotransplantation is the presence of preformed human antibodies that bind to specific carbohydrate moieties on xenograft endothelium, activating the complement cascade and precipitating hyperacute rejection.[95] Research focused on the creation of genetically engineered animals, in which the offending endothelial antigens are removed or complement-inhibiting proteins are actively expressed,

may ultimately allow xenotransplantation to become a clinical reality.

Current immunosuppressive strategies subject the recipient to a high risk of infection while failing to prevent chronic rejection. New drugs that are being tested clinically, including sirolimus and leflunomide, may be more efficacious and less toxic than the drugs currently in use.[96] A more definitive solution, however, consists of strategies to promote immune tolerance, a state of permanent acceptance of the graft by the recipient without the need for lifelong treatment with immunosuppressive agents. Two such strategies are currently under investigation. One involves the infusion of donor bone marrow as an adjunct to solid-organ transplantation in order to facilitate engraftment of donor-derived immunomodulatory stem cells capable of attenuating the responsiveness of the recipient to alloantigens. This mixed chimeric condition has been achieved experimentally in animals and results in donor-specific tolerance of lung allografts.[97] Clinical trials conducted at the University of Pittsburgh suggest that this technique is safe and that bone marrow engraftment is achieved, but its effect on the incidence of lung-allograft rejection and the need for exogenous immunosuppression remains uncertain.[98] An alternative strategy, entailing the blockade of T-cell costimulatory activation pathways at the time of transplantation, has also proved successful in inducing tolerance in preclinical studies.[99,100]

It is only through the continued success of research initiatives in transplantation immunobiology that lung transplantation will fulfill its potential as an effective and enduring treatment option for patients with advanced lung disease.

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