

Concise Clinical Review

Lung Transplantation

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First performed in 1963, lung transplantation is approaching the half-century mark. With more than 32,000 procedures having been performed worldwide, lung transplantation has become the standard of care for select patients with advanced lung diseases of various nonmalignant etiologies. Indications for transplantation have broadened over the years, and selection criteria have become less restrictive. A relatively scarce donor pool limits wider application of this therapy, but this is being addressed in part through relaxation of donor selection criteria, donor management protocols that preserve and optimize lung function, and development of *ex vivo* perfusion techniques to "recondition" suboptimal organs. Bilateral lung transplantation has become the procedure of choice for most indications, although its preferential use in patients with idiopathic pulmonary fibrosis remains controversial. Post-transplantation survival has steadily improved, but significant constraints on long-term survival persist as evidenced by a median survival rate that currently stands at 5.7 years. This has brought into focus the question of whether and for whom transplantation actually confers a survival advantage, a question that in the absence of randomized trials can only be answered with statistical modeling. Primary graft dysfunction, infection, and bronchiolitis obliterans syndrome are common complications encountered by the lung transplant recipient and are major impediments to long-term survival. This review provides an overview of the current status of lung transplantation, highlighting both the many advances that have taken place and the challenges that remain.

Keywords: lung transplantation; complications; mortality; patient selection

Dr. James Hardy and colleagues demonstrated the technical feasibility of human lung transplantation with the inaugural procedure in 1963 (1), but another 20 years passed before meaningful survival was achieved. In the ensuing years, more than 32,000 procedures have been performed worldwide (2). Lung transplantation has evolved from a medical curiosity to the standard of care for select patients with advanced and disabling lung disease. This review surveys the current status of lung transplantation, highlighting the many advances that have taken place and the challenges that remain.

INDICATIONS

The indications for lung transplantation have broadened over time and include a diverse spectrum of pulmonary diseases of the airways, parenchyma, and vasculature. Chronic obstructive

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pulmonary disease (COPD) exclusive of α_1 -antitrypsin deficiency was for many years the most common indication worldwide, accounting for approximately one-third of all procedures performed to date (2). More recently, the number of transplants performed for idiopathic pulmonary fibrosis (IPF) has steadily increased, particularly in the United States, where IPF now represents the leading indication for transplantation (3). Cystic fibrosis (CF) is the third major indication, accounting for approximately 15% of procedures. Other less common indications include emphysema due to α_1 -antitrypsin deficiency, sarcoidosis, non-CF bronchiectasis, and lymphangioleiomyomatosis. Once a leading indication for transplantation, idiopathic pulmonary arterial hypertension (IPAH) currently constitutes only 2% of procedures, reflecting major advances in the medical management of these patients (2).

Some indications remain controversial. Lung disease occurring in the setting of underlying collagen vascular disease raises concerns that extrapulmonary manifestations of the systemic disease could compromise post-transplant outcomes. In particular, the esophageal dysmotility and reflux that frequently characterize scleroderma could increase the risk of aspiration and accelerated graft loss. The demonstration that survival at 1 and 2 years post-transplantation of patients with scleroderma is comparable to other patient populations provides some reassurance that carefully selected patients can benefit from this procedure (4, 5) Use of lung transplantation as a definitive cure for locally advanced bronchioloalveolar carcinoma resulted in a high rate of cancer recurrence, leading the vast majority of centers to exclude this patient population (6).

ISSUES IN CANDIDATE SELECTION

There are surprisingly few remaining absolute contraindications to lung transplantation. There is general consensus that the following contraindicate listing: (1) recent malignancy (other than nonmelanoma skin cancer); (2) active infection with hepatitis B or C virus associated with histologic evidence of significant liver damage; (3) active or recent cigarette smoking, drug abuse, or alcohol abuse; (4) severe psychiatric illness; (5) repeated noncompliance with medical care; (6) absence of a consistent and reliable social support network (7). Infection with HIV is still viewed by most centers as an absolute contraindication, but promising results with liver, kidney, and heart transplantation in HIV-positive recipients, and a recent case report of successful lung transplantation, may soon remove this barrier (8). The presence of significant extrapulmonary vital organ dysfunction precludes isolated lung transplantation, but multiorgan procedures such as heart-lung or lung-liver can be considered in highly select patients (9). Both obesity and underweight nutritional status increase the risk of post-transplant mortality, but cutoffs for exclusion of candidates vary among centers (10). Prior pleurodesis is associated with an increased risk of intraoperative bleeding, particularly when cardiopulmonary

bypass is used, but is **not** a **contraindication** to transplantation in experienced surgical hands (11). The risk posed by other medical comorbidities, such as diabetes mellitus, osteoporosis, gastroesophageal reflux, and coronary artery disease, must be assessed individually based on severity of disease, presence of end-organ damage, and ease of control with standard therapies.

Many transplant centers still define an **age cutoff** for transplant eligibility, typically **65 years**. Supporting this policy, advanced recipient age has been consistently identified as a risk factor for increased post-transplant mortality (2). Nonetheless, there has been a growing trend to **expand** the **age** range, based on the argument that **functional** rather than **chronological** age should be considered. This trend has been most pronounced in the United States, where patients 65 years and older accounted for 19% of transplant recipients in 2008 compared with less than 5% before 2002 (3). Two recent single-center case series involving 50 and 78 patients, respectively, who were 65 years or older found **no difference** in 1-year and 3-year post-transplant **survival** rates compared with younger cohorts (12, 13). However, the United Network for Organ Sharing (UNOS) database of U.S. transplants documents a 10-year survival rate among recipients 65 years or older of only 13% compared with 23% for those 50 to 64 years, and 38% for those less than 50 years of age (3).

An evolving area of controversy centers on the **eligibility** of **ventilator-dependent** patients in the intensive care unit (ICU). Ventilator dependence **before** transplantation has long been recognized as a risk factor for increased short-term post-transplant mortality, although it does not appear to adversely impact outcomes beyond the first year (2). Although transplantation of these patients was previously discouraged, the new lung allocation system in the United States has forced transplant centers to reconsider this philosophy by assigning high allocation scores to ventilator-dependent patients. Many programs are now willing to maintain select ventilator-dependent patients on their active waiting list, anticipating that the high allocation score will expedite transplantation, but reserving the option of de-listing patients who develop intercurrent complications or progressive debility. A recent analysis of 586 ventilator-dependent patients in the UNOS database documents inferior but not necessarily prohibitively poor short-term outcomes; 1-year and 2-year survival rates were 62 and 57%, respectively, compared with 79 and 70% for unsupported patients (14). Even more **controversial** is transplantation of patients on **extracorporeal membrane oxygenation** support, for whom 1-year and 2-year post-transplant survival rates were **only 50** and **45%**, respectively (14).

Chronic infection of the airways is a **universal** feature of CF that raises unique concerns in selecting candidates. Patients harboring panresistant *Pseudomonas aeruginosa* have lower survival rates compared with patients with sensitive strains: 87 versus 97% at 1 year and 58 versus 86% at 5 years (15). Nonetheless, these outcomes compare favorably to those of other non-CF patient populations, arguing that **panresistant P. aeruginosa** should **not** be **viewed** as a **contraindication** to lung transplantation. In contrast, the presence of certain species of *Burkholderia cepacia* complex (BCC) is associated with a high risk of serious and often lethal post-transplant infections. Published series before the subdivision of BCC into individual species documented 1-year survival rates in the range of 50 to 67% for patients with BCC compared with 83 to 92% for those without (16, 17). These negative reports led the vast majority of transplant centers to exclude candidates with BCC from consideration for lung transplantation. However, it has more recently become clear that BCC encompasses a heterogeneous collection of species (previously referred to as genomovars) with varying pathogenicity and impact on post-transplant outcomes. The

observed excessive post-transplant mortality appears largely attributable to *Burkholderia cenocepacia* (genomovar III) and to a lesser extent, *Burkholderia gladioli* (18, 19). In contrast, infection with other BCC species does **not** appear to adversely impact post-transplant survival, and patients harboring these organisms should **not** be excluded from transplantation (20).

TIMING OF LISTING

Listing for transplantation is considered at a time when the lung disease has advanced to a disabling and potentially life-threatening stage, such that survival with transplantation is deemed to be more likely than survival without. In addition to prognosis, decisions to list should take into account the patient's clinical trajectory, functional status, quality of life, and willingness to accept the attendant risks and commitments of transplantation. Disease-specific guidelines for timely listing of patients, based on expert consensus, have been published (Table 1) (7). Early referral to a lung transplant center, even before the need for listing is anticipated, is encouraged to initiate patient and family education, promote familiarity with the transplant team, and identify and address potential barriers to transplantation (e.g., obesity, deconditioning, ongoing smoking).

ORGAN ALLOCATION

Rules governing allocation of organs vary between different countries but typically involve a **time-based** or **need-based** ranking of candidates on the **waiting list**, or some combination of the two. In response to the perceived inequities of an existing time-based system, and under mandate of the federal government, a **new lung allocation system** was implemented in the United States in **2005** that allocates lungs on the basis of both **medical urgency** (i.e., risk of death without a transplant) and "net transplant **benefit**" (i.e., the extent to which transplantation will extend survival). By incorporating this latter concept, the system attempts to avoid the pitfall of preferentially allocating the limited donor organ pool to marginal candidates with an unacceptably high post-transplantation mortality rate.

The new system uses **Cox proportional hazards models**, derived from an analysis of the **UNOS** national database, to predict 1-year survival without and with transplantation (21). Approximately a dozen parameters are incorporated into the models, of which underlying diagnosis is the most influential. These survival projections are used to calculate a candidate's lung allocation score (LAS) as follows: raw LAS = net transplant benefit (1-year survival with transplant – 1-year survival without transplant) minus medical urgency (1-year survival without transplant). This score is then normalized to a 0 to 100 scale for ease of use. Because survival without transplant is factored into both net transplant benefit and medical urgency measures, it has a greater impact on the LAS than post-transplant survival.

In the brief time since its implementation, the LAS system has had a profound impact on the dynamics of lung transplantation in the United States (3). Because there is no longer an incentive to place patients on the active waiting list simply to accrue time, the number of actively listed patients has fallen to approximately one-half of the pre-LAS level. Median waiting time, which had ranged from 2 to 3 years under the time-based allocation system, has decreased to less than 200 days, and one-quarter of patients are waiting less than 35 days. Importantly, there has been a significant reduction in the death rate of patients on the waiting list, one of the main objectives of the new system. By prioritizing patients with more rapidly pro-

TABLE 1. DISEASE-SPECIFIC GUIDELINES FOR LISTING FOR LUNG TRANSPLANTATION

Chronic obstructive pulmonary disease

BODE index of 7–10 or at least one of the following:

History of hospitalization for exacerbation associated with acute hypercapnia (P_{CO_2} exceeding 50 mm Hg)

Pulmonary hypertension or cor pulmonale, or both, despite oxygen therapy

$FEV_1 < 20\%$ and either $D_{LCO} < 20\%$ or homogenous distribution of emphysema

Idiopathic pulmonary fibrosis

Histologic or radiographic evidence of UIP and any of the following:

A $D_{LCO} < 39\%$ predicted.

A 10% or greater decrement in FVC during 6 mo of follow-up

A decrease in pulse oximetry below 88% during a 6MWT

Honeycombing on HRCT (fibrosis score of > 2)

Cystic fibrosis

$FEV_1 < 30\%$ predicted, or rapidly declining lung function if $FEV_1 > 30\%$ predicted (women and patients < 18 yr of age have a poorer prognosis; consider earlier listing) and/or any of the following:

Increasing oxygen requirements

Hypercapnia

Pulmonary hypertension

Idiopathic pulmonary arterial hypertension

Persistent NYHA class III or IV on maximal medical therapy

Low (350 m) or declining 6MWT

Failing therapy with intravenous epoprostenol, or equivalent.

Cardiac index of < 2 L/min/m²

Right atrial pressure > 15 mm Hg

Sarcoidosis

NYHA functional class III or IV and any of the following:

Hypoxemia at rest

Pulmonary hypertension

Elevated right atrial pressure > 15 mm Hg

Definition of abbreviations: BODE = body mass index, airflow obstruction, dyspnea, and exercise capacity; D_{LCO} = diffusing capacity of carbon monoxide; HRCT = high-resolution computed tomography; NYHA = New York Heart Association; 6MWT = 6-minute walking test; UIP = usual interstitial pneumonia. Adapted from Reference 7.

gressive diseases, the LAS system has facilitated transplantation of an increasing percentage of patients with IPF, with a commensurate decline in the percentage of transplants performed for patients with COPD. For similar reasons, the percentage of patients in the ICU at the time of transplant has nearly tripled to approximately 9%.

Despite the changing profile of transplant candidates, overall 1-year post-transplant survival rates have not declined in the LAS era (3). However, recent studies have demonstrated that transplantation of the subset of patients with the highest LAS does come at the expense of increased morbidity and mortality (22, 23). For the 5% of patients with LAS greater than 75 transplanted in 2006 to 2007, half of whom were in the ICU at the time of transplant, 1-year post-transplant survival was 64% compared with approximately 80% for those patients with lower LAS. In addition, these patients had an increased risk of infection and dialysis-requiring renal failure, and an increased length of stay during the initial transplant hospitalization (23). A more extended period of observation will be required to determine the impact of the LAS system on long-term outcomes for all recipient groups.

A number of other concerns have been raised about the LAS system. An analysis by Gries and colleagues calls into question the ability of the LAS model to accurately predict 1-year post-transplant survival based exclusively on pretransplant parameters (24). Similarly, because the LAS model does not include hemodynamic parameters reflecting right ventricular function, its ability to predict the risk of death on the wait list for patients with IPAH has been questioned. Supporting this contention, wait list mortality after LAS implementation decreased for all diagnostic groups except IPAH, suggesting that the LAS model may underestimate the medical urgency measure in this patient population (25). To address these and other concerns, regular review of the LAS models has been mandated to ensure that new factors found to be predictive of outcomes are incorporated

and that current outcomes data are used. Additionally, a Lung Review Board was created to handle appeals for modification of the LAS in individual cases in which the clinician believes the assigned LAS underestimates medical urgency. Because of the particular concerns raised about IPAH, the Lung Review Board recently agreed to increase the LAS to the 90th percentile of all scores nationally for any patient with IPAH who is deteriorating despite optimal therapy, has a right atrial pressure exceeding 15 mm Hg, and has a cardiac index less than 1.8 L/min/m².

DONOR SELECTION AND MANAGEMENT

The **lungs** of a brain-dead **organ donor** are susceptible to a variety of insults, including **volume overload**, acute lung injury, contusion, **aspiration**, and **pneumonia**, as well as to the consequences of prior smoking. To avoid use of compromised lungs, selection criteria were established almost 30 years ago that continue to define the “standard” lung donor to the present day (Table 2) (26). Historically, the vast majority of organ donors have failed to meet these criteria, leading to **lung recovery rates of only 15 to 25%**, the **lowest** of all the major transplantable **organs**. There is compelling evidence that these standard criteria are, in fact, **too stringent**, resulting in significant underuse of viable lungs. In one study, tissue from lungs that had been rejected for transplantation was subjected to histological and microbiological analysis, physiological assessment of alveolar epithelial cell fluid clearance capacity, and measurement of pulmonary edema by extravascular water-to-dry weight ratio (27). **Forty-one percent** of these lungs were found to have minimal or no abnormalities and thus to be potentially **suitable** for use. Additional evidence comes from a multitude of published reports, summarized in a recent review (28), that document outcomes with “extended criteria” donors that are similar to those achieved with donors meeting standard criteria.

TABLE 2. STANDARD LUNG DONOR CRITERIA

Age < 55 yr
 Clear chest radiograph
 $\text{PaO}_2 > 300$ mm Hg on FiO_2 1.0, PEEP 5 cm H_2O
 Cigarette smoking history of < 20 pack-years
 Absence of significant chest trauma
 No evidence of aspiration or sepsis
 No prior thoracic surgery on side of harvest
 Absence of organisms on sputum Gram stain
 Absence of purulent secretions and gastric contents at bronchoscopy
 Negative for HIV antibody, hepatitis B surface antigen, and hepatitis C antibody

No active or recent history of malignancy (excluding localized squamous or basal cell skin cancer, localized cervical cancer, and primary brain tumors with low metastatic potential and in the absence or invasive procedures to the brain and skull)
 No history of significant chronic lung disease

Definition of abbreviation: PEEP = positive end-expiratory pressure.

Use of tailored lung donor management protocols involving judicious fluid management, therapeutic bronchoscopy, and lung recruitment maneuvers has been shown to enhance lung harvest rates, in large part by improving oxygenation parameters in initially unsuitable donors (29, 30). Using such a management protocol, in combination with more liberal donor selection criteria, the Alfred Hospital Lung Transplant Service in Victoria, Australia was able to increase lung harvest rates to an unprecedented 66% without compromising post-transplant outcomes (31). Existing donor management protocols and guidelines recommend use of tidal volumes in the range of 8 to 15 ml/kg (30, 32, 33). However, a recent multicenter, randomized trial demonstrated that use of a low tidal volume, lung-protective ventilatory protocol (6–8 ml/kg; positive end-expiratory pressure, 8–10 cm H_2O) in brain-dead potential organ donors resulted in a doubling of lung harvest rates (54 vs. 27%, $P < 0.005$) compared with a conventional ventilatory protocol (10–12 ml/kg; positive end-expiratory pressure, 3–5 cm H_2O) (34).

The development of *ex vivo* perfusion systems to “recondition” injured lungs before implantation adds a new facet to donor management (35). The perfusate is a hyperoncotic serum that draws fluid out of the extravascular space and leads to dehydration of edematous lungs. Although currently available in only a small number of centers, *ex vivo* perfusion has been shown to significantly improve oxygenation and to permit successful transplantation of lungs initially deemed unsuitable (36). Coupling gene therapy technology with *ex vivo* perfusion, Cypel and colleagues recently demonstrated that transfer of the IL-10 gene to perfused lungs led to improvement in oxygenation, decreased pulmonary vascular resistance, decreased proinflammatory cytokine production, and recovery of alveolar epithelial cell tight junctions (37).

The ongoing shortage of organs has fueled a search for alternatives to the brain-dead donor pool. One emerging source is the donation after cardiac death (DCD) donor (also referred to as non-heart-beating donor) who has undergone a planned (i.e., controlled) withdrawal of life support in the operating room or, less commonly, an out-of-hospital (i.e., uncontrolled) arrest. Preliminary experience with use of controlled DCD lung donors has been promising, with short- and intermediate-term survival similar to that associated with use of conventional brain-dead donors (38, 39).

CHOICE OF PROCEDURE

Single lung transplantation (SLT) and bilateral lung transplantation (BLT) currently make up more than 97% of all pro-

cedures performed worldwide (2). SLT offers a more efficient use of the limited donor pool and is better tolerated by frail patients, but it provides less functional reserve than BLT in the setting of allograft dysfunction, and outcomes may be hampered by complications affecting the native lung. Heart-lung transplantation (HLT), historically the first procedure to achieve successful outcomes, now accounts for less than 3% of all procedures. Its role is restricted largely to patients with Eisenmenger syndrome with surgically uncorrectable cardiac defects. HLT is still occasionally performed in patients with IPAH. However, experience with lung transplantation alone has demonstrated the ability of the dysfunctional right ventricle to recover once pulmonary artery pressures have normalized, obviating the need for concurrent cardiac replacement in all but the most severely decompensated patients. In rare instances, HLT is used for patients with advanced lung disease and coexisting severe left ventricular dysfunction or extensive coronary artery disease. A fourth technique, living-donor bilobar transplantation, was introduced in the 1990s principally as a means of ensuring transplantation for extremely ill candidates deemed unlikely to tolerate a protracted wait for a cadaveric donor. Concerns about donor complications, lack of functional or survival advantage in recipients as compared with conventional cadaveric transplantation, and expedited transplantation of sicker patients provided by the new lung allocation system have led to the virtual abandonment of this procedure. Since 2005, only nine living-donor bilobar transplantations have been reported in the United States (40).

In choosing between SLT and BLT, underlying disease is a major determinant. BLT is the exclusive procedure for patients with CF and other forms of suppurative lung disease because of concerns related to leaving a chronically infected lung in place with SLT. For patients with IPAH and those with severe secondary pulmonary hypertension, SLT poses an increased risk of perioperative allograft edema, since virtually the entire cardiac output must be borne by the freshly transplanted lung. For this reason, the vast majority of these patients now receive BLT. The choice of procedure for patients with COPD and IPF remains a matter of some debate, as both SLT and BLT produce acceptable, albeit not necessarily equivalent, outcomes. Historically, SLT was the predominant procedure for both diseases, but BLT now accounts for two-thirds of all procedures for COPD and just over one-half of procedures performed for IPF (2).

In the case of COPD, this shift may be explained by a growing body of literature suggesting that BLT leads to longer survival than SLT. The survival advantage of BLT in the COPD population was initially documented in several single-center studies, but these studies were limited in size and could not adjust for imbalances in baseline patient characteristics (41, 42). Two studies based on data from the International Society for Heart and Lung Transplantation (ISHLT) registry attempted to deal with these limitations by using larger data sets and adjusting for baseline differences in the groups receiving SLT and BLT. In the first study, Meyer and colleagues analyzed the outcomes of 2,260 patients who underwent SLT or BLT from 1991 to 1997 (43). For recipient age groups 60 years or younger, 5-year actuarial survival rates exceeded 60% after BLT compared with rates approximating 40% after SLT. Multivariate analysis confirmed the favorable survival effect of BLT at least until the age of 60 years, beyond which the analysis was limited by small sample size. In the second study, Thabut and colleagues analyzed data for 9,883 patients with COPD, 36% of whom underwent BLT and 64% SLT between 1987 and 2006 (44). Using a variety of statistical methods to account for possible selection bias, the authors

found that BLT was associated with longer survival than SLT, with an adjusted survival advantage ranging from 4 to 6.3% at 5 years. Again, a survival advantage to BLT could not be confirmed in recipients over the age of 60 years.

It is more difficult to identify a compelling rationale for the increased use of BLT in patients with IPF. Two small single-center studies reported conflicting results on whether SLT or BLT held a survival advantage in this patient group (45, 46). Three studies using large registries suggested that BLT might actually lead to higher mortality than SLT. Meyers and colleagues analyzed the outcomes for 821 IPF transplant recipients and found that survival was higher after SLT than BLT for patients younger than 60 years; no difference in survival was found for recipients over 60 (47). In a second study by Whelan and colleagues, BLT was identified as an independent risk factor for 90-day mortality in an analysis of 830 patients with IPF from the ISHLT registry (48). In the largest study, Thabut and colleagues analyzed the outcomes of 3,327 patients with IPF who underwent SLT or BLT in the United States between 1987 and 2009 and used multivariate risk adjustment, propensity score risk adjustment, and propensity-based matching to account for selection bias (49). The authors found no difference in adjusted survival between SLT and BLT recipients. This was due to offsetting effects: an increased relative risk of death with BLT in the early postoperative period, followed by a reduced relative risk of death several years after transplantation.

A recent study by Nathan and colleagues exposes an additional risk of preferentially using BLT in the IPF population (50). Focusing on a time period after introduction of the LAS allocation system, these authors demonstrated that listing patients with IPF for BLT was associated with longer waiting times and an increased risk of dying on the waiting list compared with listing for SLT. In the absence of a counterbalancing post-transplant survival advantage to BLT, the potential effect of this practice is a net loss of life for the IPF population.

OUTCOMES

As recorded in the ISHLT Registry, the overall median survival for the 24,936 patients who received a lung transplant between 1994 and 2008 was 5.3 years (2). Median survival has improved over time, from 4.0 years in the 1988 to 1994 era to 5.7 years in the 2000 to 2008 era. In the latter era, survival rates were 79% at 1 year, 63% at 3 years, 52% at 5 years, and 29% at 10 years. Disease-specific differences in survival are apparent but may be confounded by differences in severity of illness, comorbidities, and average age among these populations. In descending order, median survival is 7.1 years for CF, 6.1 years for α_1 -antitrypsin deficiency, 5.2 years for COPD, 5.1 years for sarcoidosis, 4.6 years for IPAH, and 4.3 years for IPF.

Given the considerable constraints on long-term survival after lung transplantation, determining whether and for whom this procedure actually extends survival remains problematic. In the absence of randomized trials, statistical modeling has been used to address these pivotal questions. One approach has been to determine whether receiving a transplant is a prognostic factor for survival for patients placed on the waiting list. In this approach, the instantaneous risk of death of patients is analyzed by either a proportional or nonproportional hazards model that includes the transplant event as a time-dependent covariate. The nonproportional hazards model allows for a high initial post-transplantation risk of death followed by an exponential decay in risk to a constant. Because patients who ultimately receive a transplant may differ from those who do not, additional covariates may be entered in the model to adjust for the imbalance

in baseline characteristics. A second approach involves the development of prognostic models to predict the expected survival of patients with and without lung transplantation.

Although some of these models have been validated in a cohort distinct from the one from which they were derived (51), others have either not yet been validated (52) or have not been validated for the specific subgroup of patients with advanced lung disease awaiting lung transplantation (53). Published studies examining the possible survival benefit of lung transplantation are summarized in Table 3 and discussed below.

Five studies, all using time-dependent nonproportional or proportional hazard approaches, have been published assessing the survival benefit of lung transplantation in patients with pulmonary fibrosis (54–58). Given the poor prognosis associated with this disease, it is not surprising that all studies found that transplantation conferred a survival benefit.

The survival benefit of lung transplantation for patients with CF is a more complex issue. Multiple studies using proportional or nonproportional hazards modeling have suggested that transplantation confers a survival benefit for the CF population as a whole (54–57, 59). These results have been challenged by a series of studies by Liou and colleagues, who developed and validated a predictive model of 5-year natural history survivorship for CF (51). Combining this predictive model with a model of post-transplant survival, the authors showed that lung transplantation conferred a survival benefit only for patients older than 18 years, with a predicted 5-year survival less than 50%, and without *B. cepacia* infection and CF-related arthropathy (60). Recently, the same authors used proportional hazards modeling to assess the survival benefit of lung transplantation in 514 pediatric patients with CF on the lung transplant waiting list, of whom 248 underwent transplantation. This analysis revealed that only 5 of the 514 patients were expected to derive a statistically significant survival benefit from transplantation (61). Several authors have challenged the conclusions of this study, pointing out important methodological shortcomings (62, 63). First, the covariates used in the model were obtained up to 3 years before transplantation and could have changed at the time the patient was actually transplanted. Second, the study population was derived from the previous era of time-based allocation in the United States, under which it was common practice to list patients early to allow them to accrue time. Thus, the wait list cohort is likely not truly reflective of patients in imminent need of transplantation. The fact that 57% of the listed children in the study had a predicted survival without transplant of 5 years or more supports this contention. Finally, the transplant recipients in this study had an unusually poor post-transplant median survival approximating 2.8 years. In contrast, an earlier single-center study of pediatric CF recipients from Britain reported a median survival approximating 3.5 years (59), and the ISHLT Registry documents a median survival approaching 5 years in the current era (63). The net effect of using a “healthier” wait list group and a recipient group that experienced excessive post-transplant mortality is the introduction of considerable bias against a survival benefit derived from transplantation.

Because protracted survival is possible even in the advanced stages of COPD, it has been difficult to determine whether transplantation truly extends survival for this patient population. Available studies comparing wait list and post-transplant survival by proportional or nonproportional hazards modeling have yielded conflicting results (54–57, 64, 65). Alternatively, Thabut and colleagues developed prognostic models of survival with and without lung transplantation and applied these models to patients with COPD who were on the UNOS waiting list between 1987 and 2004 (52). These authors found that approx-

TABLE 3. STUDIES ASSESSING THE SURVIVAL BENEFIT OF LUNG TRANSPLANTATION

Study (Reference)	Year	Diseases	Database	Cohort Period	Main Conclusion Regarding the Survival Benefit of LT
Hosenpud <i>et al.</i> (57)	1998	Adult CF, COPD, PF	UNOS registry, U.S.	1992–1994	LT improves survival for patients with CF and PF. No benefit for patients with COPD.
Geertsma <i>et al.</i> (65)	1998	Adult CF, COPD, PF, PAH	Single center, Netherlands	1990–1996	LT improves survival for the recipient group as a whole; disease-specific analysis limited by small sample size.
Aurora <i>et al.</i> (59)	1999	Pediatric CF	Single center, U.K.	1988–1998	LT improves survival for children with CF.
De Meester <i>et al.</i> (54)	2001	Adult CF, COPD, PF, PAH	Eurotransplant registry	1990–1996	LT improves survival for all groups except Eisenmenger syndrome.
Liou <i>et al.</i> (51)	2001	Pediatric and adult CF	UNOS registry, U.S.	1992–1997	LT improves survival for patients with CF with a 5-yr predicted survival < 30%. The majority of patients with CF have equivocal or negative survival effects from the procedure.
Charman <i>et al.</i> (56)	2002	Adult CF, COPD, PF, PAH	Single center, U.K.	1984–1999	LT improves survival for all groups except Eisenmenger syndrome.
Thabut <i>et al.</i> (58)	2003	PF	Single center, France	1988–2001	LT improves survival for patients with PF.
Liou <i>et al.</i> (60)	2005	Pediatric and adult CF	UNOS registry, U.S.	1988–2002	LT improves survival for patients with CF older than 18 yr with a 5-yr predicted spontaneous survival of < 50% and without <i>Burkholderia cepacia</i> or arthropathy. LT does not improve survival for pediatric patients with CF.
Stavem <i>et al.</i> (64)	2006	COPD	Single center, Norway	1990–2003	LT does not improve survival for patients with COPD.
Liou <i>et al.</i> (61)	2007	Pediatric CF	UNOS registry, U.S.	1998–2004	LT improves survival for < 1% of pediatric patients with CF placed on the waiting list.
Thabut <i>et al.</i> (52)	2008	COPD	UNOS registry, U.S.	1987–2004	LT improves survival by at least 1 yr for 45% of patients with COPD undergoing BLT but only 22% undergoing SLT.
Titman <i>et al.</i> (55)	2009	Adult CF, COPD, PF, PAH	U.K. national registry	1995–2006	LT improves survival for all disease groups examined.
Lahzami <i>et al.</i> (53)	2010	COPD	2 Centers, Switzerland	1993–2007	LT improves survival for patients with COPD with a BODE \geq 7.

Definition of abbreviations: BODE = body mass index, airflow obstruction, dyspnea, and exercise capacity; CF = cystic fibrosis; COPD = chronic obstructive pulmonary diseases; LT = lung transplantation; PAH = pulmonary arterial hypertension; PF = pulmonary fibrosis; SLT = single lung transplant; UNOS = United Network for Organ Sharing.

imately 45% of patients would gain a survival benefit of at least 1 year by undergoing BLT; only 22% would derive such a benefit if SLT were used. In addition to procedure type, FEV₁ was a major determinant of the survival benefit. As an example, nearly 80% of patients with an FEV₁ less than 16%, but only 11% of those with an FEV₁ greater than 25%, were predicted to gain at least a year of life with BLT. Finally, a recent study suggests that patients with COPD with a body mass index, airflow obstruction, dyspnea, and exercise capacity (BODE) index greater than 7 derive a survival benefit from transplantation (53).

In addition to its possible survival benefit, lung transplantation is associated with substantial improvements in lung function, exercise tolerance, and hemodynamics. Quality-of-life measures also appear to improve markedly across most domains, although the majority of available studies are limited by their cross-sectional rather than longitudinal design (66). Some authors have suggested that it may be most appropriate to judge the success of lung transplantation by the net gain in quality-adjusted life-years, a composite outcome that takes into consideration both length and quality of survival (66, 67).

COMMON COMPLICATIONS

Primary Graft Dysfunction

Primary graft dysfunction (PGD) describes a form of acute allograft injury characterized by development of noncardiogenic pulmonary edema within 72 hours of transplantation in the absence of identifiable secondary causes (68). PGD is presumed to be a consequence of ischemia-reperfusion injury, but inflammatory events associated with donor brain death, surgical trauma, and lymphatic disruption may be contributing factors.

A number of risk factors for development of PGD have been identified. Donor-related risk factors include female sex, African-

American race, older age, and low donor PaO₂/FiO₂ ratio (69–71). An elevated level of interleukin-8 in bronchoalveolar lavage (BAL) fluid recovered from the donor has been associated with the development of severe PGD, supporting the notion that inflammatory events preceding organ harvest may play a role (72). Recipient risk factors include an underlying diagnosis of IPAH as well as elevation of pulmonary artery pressures independent of diagnosis (69, 71). An association between graft ischemic time and PGD has not been consistently demonstrated. A possible explanation for this is that ischemic time may become a factor only when it exceeds a certain threshold, suggested by one study as beyond 6 hours (73).

Diagnosis of PGD is based on (1) the presence of radiographic opacities in the allograft(s) within 72 hours of transplantation, (2) hypoxemia, and (3) exclusion of secondary causes, such as volume overload, pneumonia, rejection, atelectasis, or pulmonary venous outflow obstruction (68). A grading system is commonly used to classify the severity of PGD based on the PaO₂/FiO₂ ratio (74). In most cases, the process is mild and transient, but in approximately 10 to 20% of cases, injury is sufficiently severe to cause severe hypoxemia (PaO₂/FiO₂ < 200; PGD grade 3) and a clinical course analogous to acute respiratory distress syndrome (75, 76).

Treatment of severe PGD is supportive, relying principally on low-stretch mechanical ventilatory strategies. Under some circumstances, independent lung ventilation, extracorporeal life support, or inhaled nitric oxide can successfully stabilize critically ill patients. Results of emergent retransplantation in this setting have been poor (77). Severe PGD is a leading cause of death in the perioperative period, with short-term mortality rates in the range of 30 to 40% (75, 76, 78). The risk of death remains excessive even beyond the first year, suggesting that the adverse consequences of PGD persist well beyond resolution of the acute event (76, 78). Recovery among survivors is often

protracted and incomplete, although achievement of normal lung function and exercise tolerance is possible. There appears to be an increased risk of bronchiolitis obliterans syndrome (BOS) in survivors of PGD, but the mechanistic link between these two events remains uncertain (79, 80).

Airway Complications

Lung transplantation is **unique** among solid organ procedures in that **no attempt** is routinely made to **reestablish systemic blood flow** to the allograft, in this case via the **bronchial** arterial circulation. As a consequence, the **donor bronchus** is largely dependent on **retrograde blood flow** through **low-pressure pulmonary venous** to **bronchial vascular collaterals**, placing the airway at **risk** for **ischemic** injury. Lending support to this concern, Dhillon and colleagues recently demonstrated by computed tomography (CT) angiography that **bronchial** arteries often **fail** to **regrow** distal to the bronchial anastomosis and that bronchial mucosal oxygen saturation measured distal to the anastomosis is **significantly** lower than that recorded in the native airways (81).

Rarely, airway ischemia can result in bronchial anastomotic **dehiscence** that, when extensive, can lead to mediastinitis, pneumothorax, hemorrhage, and death. Initiation of **sirolimus** in the immediate postoperative period has also been associated with bronchial **dehiscence** and its use should therefore be **avoided until** complete anastomotic **healing** has been documented (82). Surgical treatment of severe airway dehiscence is risky and often unsuccessful. More recently, success has been reported with temporary placement of a bare metal airway stent across the dehiscence to provide scaffolding on which granulation tissue can form (83). For lesser degrees of dehiscence, conservative management with reduction in corticosteroid dosing and chest tube evacuation of associated pneumothorax will often lead to successful healing. Other early manifestations of airway ischemia are necrosis of the anastomotic cartilage without frank dehiscence, and the appearance of patchy areas of bronchial mucosal necrosis and pseudo-membrane formation. These devitalized areas can serve as a nidus for subsequent fungal superinfection (*see below*).

The most common airway complication is **bronchial stenosis**, which may occur **at** or **distal** to the anastomosis, and which is believed in most cases to be a delayed manifestation of an initial **ischemic insult**. The reported prevalence ranges from **4 to 24%** in contemporary series (84–86). Narrowing is most commonly due to fibrotic stricture, but bronchomalacia or excessive granulation tissue can also be factors. Airway narrowing typically develops several weeks to months after transplantation. It may be clinically silent or marked by focal wheezing, recurrent bouts of pneumonia or purulent bronchitis, or suboptimal spirometry demonstrating airflow obstruction and flattening of the flow-volume loop. Bronchoscopy both confirms the diagnosis and permits therapeutic interventions, including balloon dilatation, laser debridement, endobronchial brachytherapy, and stent placement. Although most cases can be successfully managed in this way, some patients experience recurrent strictures of the anastomosis or distal airways, necessitating repeated interventions and leading to compromised functional outcomes.

Infection

Infection is an **ever-present** threat to the lung transplant recipient and a leading cause of both early and late deaths. A comprehensive discussion of infectious complications is beyond the scope of this article; only the most common pathogens are discussed.

Bacterial pneumonia is by far the most frequently encountered infection, with a peak incidence in the first post-transplant

month (87). Although passive transfer of occult infection from the donor is a concern, factors related to the recipient are more likely responsible for the increased risk. These include the **immunosuppressed** status of the recipient, need for prolonged mechanical ventilatory support, blunted **cough** due to postoperative pain and weakness, **surgical disruption** of **lymphatics**, aspiration related to postoperative swallowing dysfunction, and impaired mucociliary clearance associated with airway ischemic injury. *P. aeruginosa* is the predominant organism, followed by *Staphylococcus aureus*. Bacterial infections, in the form of purulent bronchitis, bronchiectasis, and pneumonia reemerge as a late complication among patients who develop BOS.

Cytomegalovirus (CMV) is the most common **viral** pathogen encountered after lung transplantation. Even with standard **prophylactic** measures, up to **one-third** of at-risk lung transplant recipients **develop** CMV disease within the **first** year (88). Infection can arise from acquisition of virus from the donor or from reactivation of latent virus remotely acquired by the recipient. Seronegative recipients who acquire organs from seropositive donors are at greatest risk for developing infection, and these primary infections tend to be the most severe. Although donor-positive/recipient-negative mismatching has been identified as a risk factor for increased mortality in the ISHLT Registry (2), this may no longer be the case with the current widespread use of effective prophylactic regimens (89).

CMV disease may present as a **mononucleosis-like** syndrome of fever, malaise, and leukopenia (CMV syndrome), or as tissue-invasive infection of the lung, gastrointestinal tract, or central nervous system. Peripheral blood viral load quantification by either the pp65 **antigenemia** assay or by **polymerase chain reaction** techniques is commonly used as a diagnostic test, but correlation with events at the tissue level is not absolute. A **definitive diagnosis** of **CMV pneumonia**, the most common manifestation of invasive disease in the lung transplant recipient, requires demonstration of characteristic **viral inclusion bodies** or viral antigens in **lung biopsy specimens** or **cells obtained** by BAL (90). **Caution** must be exercised in interpretation of a positive culture of BAL fluid because **shedding** of virus into the respiratory tract can occur in the **absence** of tissue **invasion**.

Standard **treatment** of CMV disease consists of **ganciclovir** or, in milder cases, oral valganciclovir, administered for a minimum of 2 to 3 weeks and ideally until documentation of two consecutive negative viral load assays (90). The addition of CMV hyperimmune globulin is of unclear benefit but should be considered in treatment of severe disease. Administration of oral valganciclovir as secondary prophylaxis after completion of definitive treatment is a common practice, but its impact on relapse rates is uncertain.

Numerous prospective, randomized trials have documented the efficacy of **antiviral prophylaxis** in reducing the incidence and severity of CMV disease in transplant recipients (91). **Oral valganciclovir** has largely replaced intravenous ganciclovir as the prophylactic agent of choice, due to its excellent bioavailability, ease of administration, and demonstrated efficacy (92). Universal prophylaxis of all donor-seropositive/recipient-seronegative patients is recommended because the risk of CMV disease is high (90). Although universal prophylaxis is also commonly used in seropositive recipients (independent of donor status), preemptive strategies that selectively target only those patients demonstrating a rising peripheral blood viral load have been suggested as an alternative. Consensus guidelines recommend a minimum of **6 months** of prophylaxis for donor-positive/recipient-negative patients and 3 to 6 months for recipient-positive patients (90). However, a recent randomized, controlled trial of at-risk lung transplant recipients (either donor- or recipient-seropositive)

demonstrated a marked reduction in the incidence of CMV disease with use of a 12-month course of valganciclovir prophylaxis compared with a 3-month course (4 vs. 32%) (88). Additional studies are required to determine whether 12 months is necessary or excessive, and whether all at-risk subgroups require the same regimen.

The other commonly encountered opportunistic pathogen in lung transplant recipients is *Aspergillus*. Infection can involve the airways, lung parenchyma, or extrapulmonary sites. Airway infections occur in approximately 5% of lung transplant recipients, typically within the first 6 months post-transplantation (93). In most cases, infection is localized to the bronchial anastomosis, but it may also present as a more diffuse ulcerative bronchitis with pseudomembranes. Airway infections are often asymptomatic and detected only by surveillance bronchoscopy. Treatment with an oral azole or inhaled amphotericin, at times coupled with bronchoscopic debridement, is usually successful. Rarely, infection of the bronchial anastomosis may erode into the adjacent pulmonary artery, leading to massive hemoptysis and death. An increased risk of bronchial stenosis or bronchomalacia has also been reported, but it is unclear whether this is a consequence of the infection or of an underlying ischemic injury to the bronchus that predisposed to infection (94).

Invasive aspergillosis is encountered in approximately 5% of lung transplant recipients, most often within the first year, and represents a far more serious form of infection (93). The lung parenchyma is involved in the majority of cases, but extrapulmonary disease can accompany pneumonia or occur independently. Radiographically, pulmonary aspergillosis may appear as single or multiple nodular or cavitary opacities or as alveolar consolidation. Diagnosis of pulmonary aspergillosis can be problematic. The relatively high prevalence of airways colonization in lung transplant recipients can make it difficult to interpret the significance of positive fungal stains and cultures derived from BAL specimens. Conversely, BAL studies are negative in up to 40% of patients with invasive disease (95). Performance characteristics of the galactomannan assay have not been fully established in the lung transplant population but preliminary experience suggests an unacceptably low sensitivity for both serum and BAL, though specificity appears to be high (96, 97). Ultimately, the clinician must decide whether the clinical scenario is sufficiently suggestive to justify initiation of an empiric trial of antifungal therapy or whether biopsy confirmation (transthoracic needle or surgical lung biopsy) is needed.

Voriconazole is the mainstay of therapy for invasive aspergillosis; echinocandins and parenteral lipid formulations of amphotericin B are second-line options. Surgical resection of localized pulmonary infection is sometimes used as an adjunct to medical therapy in progressive or refractory cases. Despite the availability of effective antifungal therapy, invasive aspergillosis is associated with a mortality rate in the range of 60% (93).

Acute Rejection

According to the ISHLT Registry, 36% of lung transplant recipients experience at least one episode of acute cellular rejection (ACR) within the first year, although rates as high as 75% are reported in published series analyzing transbronchial lung biopsy results (2, 98). Beyond the first year, the incidence of ACR declines markedly. Risk factors for ACR remain poorly defined. The degree of HLA discordance between donor and recipient has been identified as a risk factor in some (99, 100) but not other studies (98, 101). Polymorphisms in toll-like receptor 4 that down-regulate recipient innate immune responsiveness are associated with a lower incidence of ACR (101).

ACR may be clinically silent in up to 40% of cases (98). When present, clinical manifestations include malaise, low-grade fever,

dyspnea, cough, and leukocytosis. A decline in oxygenation and/or spirometric parameters, and the presence of opacities on chest X-ray or CT scan provide additional, albeit nonspecific, clues. Transbronchial lung biopsy is the gold standard for diagnosis. The histologic hallmark of ACR is the presence of perivascular lymphocytic infiltrates that, in more severe cases, spill over into the adjacent interstitium and alveolar airspaces. Lymphocytic bronchiolitis may accompany the parenchymal involvement or may be an independent feature. A histologic classification system has been universally adopted to grade the severity of ACR on a 0 (absent) to 4 (severe) scale (102).

Conventional treatment of ACR consists of a 3-day pulse of intravenous Solu-Medrol, often followed by a tapering course of prednisone. In most cases, this results in rapid improvement in symptoms, pulmonary function, and radiographic abnormalities, but follow-up biopsies show histologic evidence of persistent rejection in 26% of patients (103). Asymptomatic patients with minimal (A1) rejection have typically been observed without treatment, but data demonstrating progression to a higher grade of ACR in one-quarter of cases and an increased risk of developing BOS have challenged this approach (104).

There is emerging evidence for a second form of acute rejection, mediated by donor-specific anti-HLA alloantibodies that develop *de novo* after transplantation (105, 106). The clinical presentation can be indistinguishable from ACR, with dyspnea, hypoxemia, and diffuse radiographic opacities. Hemoptysis should raise suspicion of this entity but is present in only 25% of cases (105). The suggested diagnostic criteria for acute antibody-mediated rejection are: (1) presence of circulating donor-specific anti-HLA antibodies, (2) histopathological evidence of capillaritis, and (3) detection of endothelial cell C4d deposition. Less than one-half of patients in the largest case series responded to corticosteroids alone; the addition of plasmapheresis was beneficial in the majority of steroid-refractory cases (105). Intravenous immunoglobulin and anti-CD20 monoclonal antibodies have also been used as adjunctive therapy (106).

BOS

Chronic allograft dysfunction due to bronchiolitis obliterans represents the major impediment to long-term graft and patient survival. Bronchiolitis obliterans is a fibroproliferative process that narrows and ultimately obliterates the lumens of small airways, resulting in progressive and largely irreversible airflow obstruction. Because the characteristic histology is difficult to demonstrate by transbronchial biopsy, the FEV₁ is used as a surrogate marker, and the term BOS is applied to this functionally defined disorder (Table 4) (107). Approximately 50% of lung transplant recipients develop BOS by 5 years and 75% by 10 years (2). As originally conceived, BOS was defined as an otherwise unexplained and sustained fall in FEV₁ by at least 20% from post-transplant baseline. Concern that this definition might delay diagnosis beyond a stage amenable to treatment prompted the more recent introduction of a BOS zero-potential (BOS 0-p) stage, defined as a decline in FEV₁ by 10 to 19% or in a forced expiratory flow, midexpiratory phase (FEF₂₅₋₇₅) by at least 25%. The FEV₁ criterion for BOS 0-p has a positive predictive value of 60% for progression to a higher stage of BOS within 1 year and 80% for progression within 4 years (108, 109). The positive predictive value of the FEV₁ criterion is lower in SLT recipients with native lung emphysema, likely because of the confounding impact of native lung hyperinflation on lung function (109). The FEF₂₅₋₇₅ criterion suffers from a low positive predictive value in all recipient populations and is of questionable clinical usefulness (108, 109).

ACR and lymphocytic bronchiolitis have been consistently identified as the major risk factors for development of BOS,

TABLE 4. GRADING SYSTEM FOR BRONCHIOLITIS OBLITERANS SYNDROME

Stage	Spirometric Criteria
0	FEV ₁ > 90% of baseline and FEF ₂₅₋₇₅ > 75% of baseline
0-potential	FEV ₁ 81-90% of baseline and/or FEF ₂₅₋₇₅ ≤ 75% of baseline
1	FEV ₁ 66-80% of baseline
2	FEV ₁ 51-65% of baseline
3	FEV ₁ ≤ 50% of baseline

Definition of abbreviations: FEF₂₅₋₇₅ = forced expiratory flow, midexpiratory phase.

fostering the view that BOS is a manifestation of chronic rejection (110). Additional alloimmune (100, 111), autoimmune (112), and nonimmunologic factors (80, 113-117) have also been implicated (Table 5), suggesting that BOS may actually represent the end result of a wide array of insults to the airway epithelium.

Onset of BOS occurs within the first 2 years after transplant in one-third to one-half of cases (early-onset BOS) (118, 119). The decline in FEV₁ that heralds the onset of BOS may be either insidious or abrupt. Dyspnea, weight loss, cough, and recurrent bouts of purulent bronchitis, with recovery of *P. aeruginosa* from sputum cultures, are accompanying clinical features. Chest radiographs are usually unrevealing, but high-resolution CT commonly demonstrates air trapping, tree-in-bud opacities, and/or bronchiectasis. The natural history of BOS is highly variable; those with early or abrupt onset generally experience more rapid decline in lung function and higher mortality (118, 119). Median survival from diagnosis is 1.5 years and 2.5 years for those with early- and late-onset BOS, respectively (118).

Previous treatment strategies focused on augmentation of immunosuppression, but the benefits of such an approach are questionable and the risk of infection is considerable. More recently, interest has focused on the possible therapeutic role of macrolides, the potential benefits of which relate to their ability to suppress airway inflammation. Several retrospective studies have documented short-term improvement in FEV₁ in approximately 30 to 40% of patients with BOS treated with azithromycin, although not all responses were sustained (120, 121). Responders demonstrated higher levels of BAL neutrophilia at the time of initiation of treatment, suggesting a greater degree of airway inflammation. Responders also experienced better survival compared with nonresponders. Performance of surgical fundoplication to control gastroesophageal reflux has been

TABLE 5. RISK FACTORS FOR BRONCHIOLITIS OBLITERANS SYNDROME

Immune-initiated
Acute cellular rejection (110)
Lymphocytic bronchiolitis (110)
Presence of anti-HLA antibodies (particularly donor-specific) (111)
Anti-type V collagen autoimmunity (112)
Donor-recipient HLA mismatching (100)
Nonimmune-initiated
Gastroesophageal reflux/silent aspiration (113)
CMV pneumonitis (114)
Community-acquired respiratory viral infection (115)
Pseudomonas airway colonization (116)
Aspergillus colonization (117)
Primary graft dysfunction (80)
Airway ischemia (81)

Definition of abbreviations: CMV = cytomegalovirus; HLA = human leukocyte antigen.

Numbers in parentheses denote references.

associated with improvement in lung function in some patients with BOS (122). Retransplantation remains the only definitive treatment for advanced BOS.

The development of strategies to prevent BOS is an area of intense interest. In recognition of the established link between acute rejection and BOS, most transplant centers routinely perform surveillance lung biopsies to detect and treat clinically silent acute rejection, but the impact of this strategy on risk of BOS remains uncertain (123). Early identification of recipients with gastroesophageal reflux and aggressive correction with fundoplication may delay or prevent onset of BOS (124). Initiation shortly after transplantation of inhaled cyclosporine (125) or azithromycin (126) improved BOS-free survival in recent small, single-center randomized, placebo-controlled trials, but larger, multicenter studies will be required to corroborate these findings. In light of the possible link between donor-specific anti-HLA antibodies and BOS (127), a multicenter trial is planned in the United States to assess the impact of therapies directed at preemptively clearing these circulating antibodies in asymptomatic lung transplant recipients.

FUTURE DIRECTIONS

As human lung transplantation approaches the half-century mark, two major hurdles remain that constrain its clinical usefulness: donor organs are scarce, and current immunosuppressive strategies fail to ensure long-term allograft function. Expanded use of DCD donors and *ex vivo* reconditioning of marginal organs are emerging strategies to increase the availability of organs, but more dramatic solutions await advances in stem cell and tissue engineering research (128). The solution to limited graft survival resides in part in research efforts to promote immune tolerance, a state of selective graft acceptance in the absence of global immunosuppression (129). It is hoped that the next half-century will bring about the necessary advances to allow lung transplantation to fulfill its potential as a safe, effective, and durable treatment option.

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