
Critical Care Aspects of Lung Transplantation

Christine L. Lau, MD*

G. Alexander Patterson, MD*

Scott M. Palmer, MD, MHS[†]

Lung transplantation currently is the preferred treatment option for a variety of end-stage pulmonary diseases. Remarkable progress has occurred through refinements in technique and improved understanding of transplant immunology and microbiology. As a result, recipients are surviving longer after their transplant. Despite improvements in short- and intermediate-term survival, long-term success with lung transplantation remains limited by chronic allograft rejection, also known as bronchiolitis obliterans syndrome. Despite its long-term limitations, lung transplantation remains the only hope for many with end-stage pulmonary disease, and during the past 20 years, it has become increasingly accepted and used. As a result, clinicians working in an intensive care unit (ICU) are more likely to be exposed to these patients both in the immediate postoperative period as well as throughout their remaining lives. It is thus important that the ICU team have a working knowledge of the common complications, when these complications are most likely to occur, and how best to treat them when they do arise. The main focus of this review is to address the variety of potential graft and life-threatening problems that may occur in lung transplant recipients. Because the ICU is also the most common setting where a potential donor is identified, donor issues will briefly be addressed.

Key words: *lung transplant, immunosuppressive agents, critical care, postoperative complications*

Remarkable progress has been made in the field of lung transplantation since the modern era began in 1983 with the performance of the first successful series of clinical lung transplants by the Toronto Group [1]. Currently, approximately 1500 patients undergo lung transplant operations worldwide

From the *Division of Cardiothoracic Surgery, Washington University School of Medicine, St. Louis, MO, and the †Division of Pulmonary Medicine, Duke University Medical Center, Durham, NC.

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Address correspondence to: Scott M. Palmer, DUMC 3876, Room 128, Bell Building, Duke University Medical Center, Durham, NC 27710, or e-mail: palme002@mc.duke.edu.

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each year. The International Society for Heart and Lung Transplantation (ISHLT) Registry maintains the most complete database of lung transplant volumes and performance, with data on almost 14,000 adult lung transplant recipients [2]. Improvements in organ preservation, surgical techniques, infection prophylaxis, and immunosuppressive medications have resulted in durable and steady improvements in lung transplant outcomes and allowed for expanded uses of lung transplantation. Actuarial survival rates are 83% at 3 months, 73% at 1 year, 57% at 3 years, 45% at 5 years, and 23% at 10 years [2].

Several major challenges, however, limit the applicability and success of lung transplantation as therapy in end-stage lung disease. First, suitable donors remain scarce, thus resulting in longer recipient waiting times and increased death rates on the waiting list especially for the patients with idiopathic pulmonary fibrosis (IPF) and cystic fibrosis (CF) [3-6]. These long waiting times have forced transplant programs to relax previously stringent donor selection criteria in an effort to secure more donor lungs. Second, while improvements in lung preservation strategies have reduced the incidence of serious reperfusion injury, acute lung injury still occurs unpredictably, resulting in increased intensive care unit (ICU) length of stay, morbidity, and mortality. Finally, chronic lung allograft dysfunction known as bronchiolitis obliterans syndrome (BOS) affects the majority of long-term lung transplant survivors and often directly or indirectly results in patient death.

As we enter the third decade of successful clinical lung transplantation, a working knowledge of the common critical care issues facing these unique patients both in the initial perioperative period and throughout their remaining lives is increasingly important to intensivists. This review will focus on the critical care issues that face lung transplant recipients. Addressed in this review will be the disease indication for transplantation, the type of procedure performed, perioperative complications, complications arising from BOS and its treatments,

nonpulmonary complications that may require intensive care stay, and unique concerns arising from a lifetime requirement for immunosuppression. Brief mention of donor issues is also included as the ICU team needs to recognize the potential organ donor and make appropriate referral to the local procurement agency.

Donor Shortage

Despite aggressive measures including the use of marginal donors, national efforts to boost organ donations, and use of lobar and non-heart-beating donors, there remains a critical shortage of donor lungs. Further contributing to this shortage is the estimate that only 10% to 15% of multiorgan donors have lungs suitable for procurement [7,8]. Clearly, there is an important role for the intensivist to first identify a potential donor and introduce the concept of organ donation to appropriate family members. All potential donors without absolute contraindications to organ donation should be referred to the local organ procurement agency. ABO incompatibility between donor and recipient, HIV positivity, active malignancies (outside central nervous system), and active hepatitis infections remain absolute contraindications to donor lung procurement.

The primary reasons why lungs from a multiorgan donor are not suitable for transplantation are pulmonary contusions, pulmonary sepsis, and pulmonary edema [9]. Various techniques have been suggested to increase the recoverability of donor lungs including use of high-dose steroids early during the management of brain-dead patients, maximization of pulmonary toilet, and strict monitoring of ventilator support and fluid administration [8-10]. Thus, in addition to donor identification, the intensivist can facilitate appropriate donor management while working in conjunction with local organ procurement agencies.

The use of non-heart-beating donors to increase the number of lungs available is being used at some centers and should be familiar to the intensivist [11]. In the ICU setting, these potential donors are critically ill patients who do not meet standard brain death criteria but whose family members desire withdrawal of support. They become potential lung donors after the pronouncement of death. Obviously given the significant comorbidities in many of these patients, few actually meet the criteria for donors. We have successfully used lungs

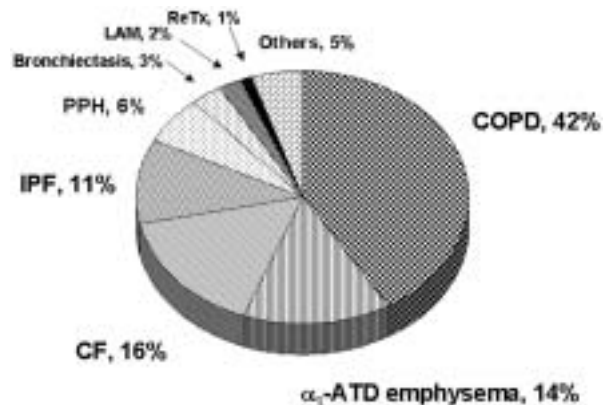


Fig 1. Chart depicting the most common indications for lung transplantation at our center (Barnes-Jewish Hospital). ReTx = retransplant; LAM = lymphangiomyomatosis; PPH = primary pulmonary hypertension; IPF = idiopathic pulmonary fibrosis; CF = cystic fibrosis; α_1 ATD = α -1-antitrypsin deficiency; COPD = chronic obstructive pulmonary disease.

from 2 non-heart-beating donors in the ICU after withdrawal of support when time to death after withdrawal was short (>30 minutes).

Indications for Transplantation

According to the ISHLT registry data, the major indications for lung transplantation are chronic obstructive pulmonary disease (COPD)/emphysema/ α -1-antitrypsin deficiency (48.1%), IPF (17%), CF (16%), primary pulmonary hypertension (PPH) (4.5%), sarcoidosis (2.5%), bronchiectasis (2.1%), congenital heart disease (1.1%), lymphangiomyomatosis (1.1%), and other (8.1%) [2]. In recent years, the majority of recipients for lung transplantation have been in the 50- to 64-year-old age group [2]. In the combined experience of our 2 centers of more than 1100 transplants, emphysema is also the most common indication for transplant (including both COPD/ α -1-antitrypsin deficiency) (Fig 1). In addition to the familiar disease indications, our programs have used lung transplantation in the treatment of a number of less common end-stage lung diseases including pulmonary alveolar proteinosis, Williams-Campbell Syndrome [12], rheumatoid lung disease, eosinophilic granuloma, Kartagener's syndrome, aluminum pneumoconiosis, and silicosis.

Circumstances unique to the disease indication for transplant need to be considered postoperative-

ly by the intensivist. In general, potential transplant recipients should be without significant comorbid diseases. Still, patients with emphysema are older than patients with cystic fibrosis and thus perhaps more at risk for cardiovascular or cerebrovascular events. In contrast, CF patients often have occult renal insufficiency secondary to years of antibiotic therapy, particularly with aminoglycosides. Unique infectious concerns are also seen in the cystic population as these patients are frequently infected with one or more strains of *Pseudomonas aeruginosa* as well as often colonized with mycobacterial or fungal pathogens. Furthermore, cystic patients often have a degree of liver disease and/or pancreatic insufficiency due to the multiorgan system effects of the CF genetic defect. Patients with PPH often initially have residual right heart dysfunction posttransplant and need greater attention to cardiac hemodynamics, often requiring increased right-sided filling pressures for hemodynamic stability. In addition, with the widespread use of intravenous prostacyclin (Flolan), patients with pulmonary hypertension often are in much worse medical condition (eg, florid right heart failure and ascites) as compared to those who underwent transplant prior to the introduction of intravenous prostacyclin.

Transplant Procedure

The decision to perform a single, double, or heart-lung transplant depends on numerous factors including recipient factors (disease, age, comorbidities), institutional biases, organ availability, and emergence of the transplant. Single-lung transplant is an excellent option for pulmonary fibrosis [13]. In fact, the first successful isolated lung transplants were single-lung transplants for pulmonary fibrosis [1,14]. Selected patients with emphysema, specifically those of shorter stature and older age, can also expect good results from single-lung transplantation. We have found single-lung transplant to be an acceptable option for patients with pulmonary hypertension [15]. However, these can be challenging cases during the first few postoperative days [16]. As a result, some programs prefer bilateral lung transplant or even combined heart-lung transplant for patients with pulmonary hypertension. Bilateral transplant is mandatory for patients with cystic fibrosis and bronchiectasis. Both septic native lungs must be excised. Bilateral lung transplant would also be preferred in patients with any native disease with preexisting mycetomas [17]

or other chronic fungal or mycobacterial infections to minimize the risk for recurrent infection posttransplant.

Heart-lung transplant is reserved for patients with end-stage cardiac and pulmonary disease. Usually, this represents patients with Eisenmenger's syndrome who have both pulmonary hypertension and significant left ventricle dysfunction, perhaps due to an uncorrected congenital defect. Annual activity of heart-lung transplants has decreased by >50% since 1995 in part because lung transplant alone is appropriate in many cases but also because a clear survival advantage has not been demonstrated in this population of patients [2].

In cases in which either single or bilateral transplant would be appropriate, the selection of organs depends on institutional basis and regional organ availability and remains an area of controversy. Both our programs favor the bilateral transplant option for all disease categories for several reasons. First, although one theoretical concern might be depriving certain patients of organs, in our experience, this is rarely the case. For patients of uncommon sizes or bloods groups, there simply may not be another matched recipient with whom to pair the transplant. Furthermore, in some cases, if one donor lung is considered "marginal" and not appropriate for single-lung usage, we will take both lungs to provide the recipient with a bilateral transplant. In our experience, outcomes with marginal donors have been acceptable, and there is currently a major effort among the transplant societies to better standardize acceptable donor criteria.

Second, we feel strongly that the overall quality of life and survival benefit with bilateral transplant are quite superior to single-lung transplant. Although registry data demonstrate only a small but statistically significant survival advantage with bilateral transplant, in our experience, in patients transplanted for obstructive lung disease, bilateral lung transplantation provides markedly superior results [18]. In addition, we believe that early postoperative management is made much simpler in the presence of 2 lung grafts, thus reducing the likelihood for certain early complications. Finally, when we recently reviewed risk factors for chronic allograft dysfunction manifest as BOS in 225 lung transplant recipients who survived longer than 6 months, in addition to immunological variables such as acute rejection and histocompatibility leukocyte antigen mismatch, we identified single-lung transplant (as compared to bilateral transplant) as a significant risk for BOS in a multivariate Cox model (hazard ratio = 2.08, $P = .001$) [19].

Although this observation may represent an artifact of the BOS nomenclature, it also may suggest there are immunological advantages to bilateral transplant.

Surgical Techniques

All recipients have routine monitoring devices including a Swan-Ganz catheter, radial and femoral arterial lines, Foley catheter, and a transesophageal echocardiography probe. A heating blanket is placed just under the ribcage, and the patient is securely strapped. Double lumen endotracheal intubation is routine. Following completion of the transplant and closure of the incision, bronchoscopy is performed to inspect the bronchial anastomosis and clear any secretions.

Most adult lung transplants can be conducted without requirement for cardiopulmonary bypass. There are a number of specific indications for institution of cardiopulmonary bypass. Patients with severe primary or secondary pulmonary hypertension are most safely transplanted on bypass. Occasionally, patients with cystic fibrosis will have such voluminous purulent secretions that independent lung ventilation is impossible. In our programs, the most frequent indication for bypass is dysfunction (due to early reperfusion injury) of the first implanted lung. For the pediatric age group, cardiopulmonary bypass is usually required since small airway size in children precludes placement of a double lumen endotracheal tube for independent lung ventilation [20].

Single-lung transplantation. The choice of side of transplant is based on several factors, but when possible, the side with the poorest function determined by preoperative ventilation-perfusion scanning is transplanted, provided the presence of a normal thoracic cavity. In patients with pulmonary hypertension with profound hypoxia or hypercarbia, the right side is preferred because cannulation for cardiopulmonary bypass can be easily performed within the chest. The standard incision is the posterolateral thoracotomy, although some groups have recommended the anterior axillary thoracotomy for emphysema patients [21]. A standard pneumonectomy is performed with care taken to prevent injury to the phrenic and vagal nerves. The pulmonary artery, left atrium, and bronchus are mobilized and dissected back toward the mediastinum to prepare for implantation of the donor lung. The donor lung is placed within the recipient's chest cavity covered by a cold laparotomy

pad. If space permits, we place a layer of slush in the empty chest cavity first. We find it simplest to perform the anastomoses from posterior to anterior in the following sequence: bronchus, artery, and atrium. All 3 anastomoses can be performed in a running fashion. Alternatively, the membranous part of the bronchial anastomosis can be performed in a running fashion while the anterior cartilaginous bronchial anastomosis can be performed with an interrupted figure of 8 sutures. Either way, peribronchial tissues are reapproximated over the anastomosis. When performing the venous anastomosis, sutures are placed using a mattress technique that achieves good intima-to-intima apposition and excludes all atrial muscle. This limits the thrombogenicity of this suture line. The last few sutures in the venous anastomosis are left intentionally loose until the lung is inflated and the pulmonary artery clamp slowly loosened. The left atrial clamp is then opened momentarily to completely deair the atrium. The atrial suture line is then secured and clamps removed completely. All suture lines as well as the cut edges of pericardium are then checked for hemostasis as ventilation and perfusion are restored.

Bilateral sequential lung transplantation. Exposure for bilateral lung transplantation is through either bilateral anterolateral thoracotomies or the trans-sternal bilateral thoracotomy (thoracosternotomy or "clamshell" incision) [22]. Wound healing may be easier with the bilateral anterolateral thoracotomies, but the clamshell incision is often advantageous under the following circumstances: (1) a concomitant heart operation is planned, (2) the patient has pulmonary hypertension with secondary cardiomegaly, and (3) the patient has restrictive lung disease and small chest cavities precluding adequate exposure via bilateral thoracotomies.

To reduce the likelihood of requiring cardiopulmonary bypass, the least functional lung, as determined by preoperative quantitative ventilation and perfusion imaging, is resected and replaced first. An attempt is made to detach all pleural adhesions and fully mobilize the hila of both lungs before the first lung is explanted. This preliminary dissection shortens the time that the first implanted lung is exposed to the entire cardiac output and thus lessens the likelihood of reperfusion edema in that lung. In this respect, both donor lungs should be prepared for implantation prior to removing the recipient's lungs if possible.

The technical aspects for bilateral sequential lung transplantation are similar to single-lung transplantation.

Heart-lung transplantation. The type of incision performed is based on surgeon's preference with either a median sternotomy or an anterotranssternal (clamshell) thoracotomy providing excellent exposure. For cardiopulmonary bypass, the ascending aorta is cannulated, and bicaval cannulation provides venous return. Both pleural spaces are opened, and adhesions are divided. The recipient is cooled to between 28°C and 32°C, and mechanical ventilation is ceased to allow better exposure. The pericardium around the level of the hilum is excised, and the pulmonary artery and veins are mobilized in the intrapericardial space. The right atrium is excised adjacent to the atrioventricular groove anteriorly, and the excision is extended circumferentially along the atrial septum. The aorta is divided above aortic valve and retracted superiorly. The remaining pulmonary arteries, left atrium, and ventricular structures are dissected free from surrounding mediastinal tissue, and the patient's heart is removed.

The bronchi on each side are mobilized and ligated proximally using a surgical stapler. The bronchi are divided beyond the staple line, and both lungs are removed separately. It is important to identify and preserve both phrenic nerves.

The bronchial stumps and tracheal carina are mobilized and the recipient trachea divided immediately above the carina. Care must be taken to ensure that bronchial vessels in the subcarinal space are controlled and that hemostasis is ensured before the graft is placed and anastomoses completed. Exposure to the posterior mediastinum to establish hemostasis after heart-lung implantation is difficult and hazardous. Prior to placement of the graft, the pericardial openings are extended inferiorly and superiorly to create bilateral openings through which each donor lung can be introduced into its respective pleural space.

The donor heart-lung block is brought into the operative field and each lung passed through the opening in the pericardium into the pleural cavities posterior to the phrenic nerve-pericardial pedicles. The tracheal anastomosis is performed first. A running 4.0-monofilament absorbable suture is used.

Following the tracheal anastomosis, the right atrial anastomosis is performed either by the bicaval technique or the right cuff technique described by Shumway and Lower.

The aortic anastomosis is performed last while the patient is being rewarmed. Attention to deairing the heart and aorta is imperative. Transesophageal echocardiography is extremely useful in assessing amount of residual air. After

achieving stable hemodynamics and gas exchange, the patient is weaned from cardiopulmonary bypass and the cannulas removed.

Postoperative Care

Immediately postoperatively, patients are transported intubated to the ICU for constant monitoring. Once stabilized, a standard ventilator pressure support weaning protocol is initiated. We favor pressure control ventilation to limit peak airway pressures and prevent barotrauma to the bronchial anastomosis. Plateau pressures should be limited to no more than 35 mm Hg. In half of the single or bilateral lung transplant recipients at our institution, liberation from mechanical ventilation occurs within 48 hours of transplantation. Patients typically leave the operating room on high FiO₂, but if the initial postoperative arterial blood gas demonstrates an arterial pO₂ of greater than 70 and/or saturations greater than 90%, then the FiO₂ is weaned, with repeat measurements of arterial oxygenation made after each change, to minimize risks of oxygen toxicity. In most patients without significant reperfusion edema, the FiO₂ can be weaned successfully to 30% or less within the first 24 hours of transplantation. Postoperatively, a quantitative lung perfusion scan to assess for adequate patency and graft flow is usually performed. If a lobar or greater perfusion defect is appreciated, further interrogation for the cause should be undertaken either by catheterization or operative exploration.

In single-lung transplant patients with COPD, zero or minimal positive end expiratory pressure (PEEP) is used, along with an adequate expiratory phase of ventilation to prevent air trapping in the native lung. An expiratory hold maneuver may be useful to detect air trapping in these patients. Careful fluid management is necessary to avoid substantial transplant lung edema, and usually negative fluid balance is attempted within the first 48 hours. Adequate urine output is carefully maintained with combinations of blood, colloid, and diuretics. Recent evidence suggests that lung injury caused by transplantation significantly reduces the ability of the lungs to clear edema fluid [23]. Although often employed in renal doses to facilitate diuresis, the role for low-dose dopamine at 2 to 3 µg/kg/min remains controversial. Overly aggressive diuresis can result in renal insufficiency that may be exacerbated by high postoperative cyclosporine or tacrolimus levels, and careful monitoring of immunosuppressive medication levels

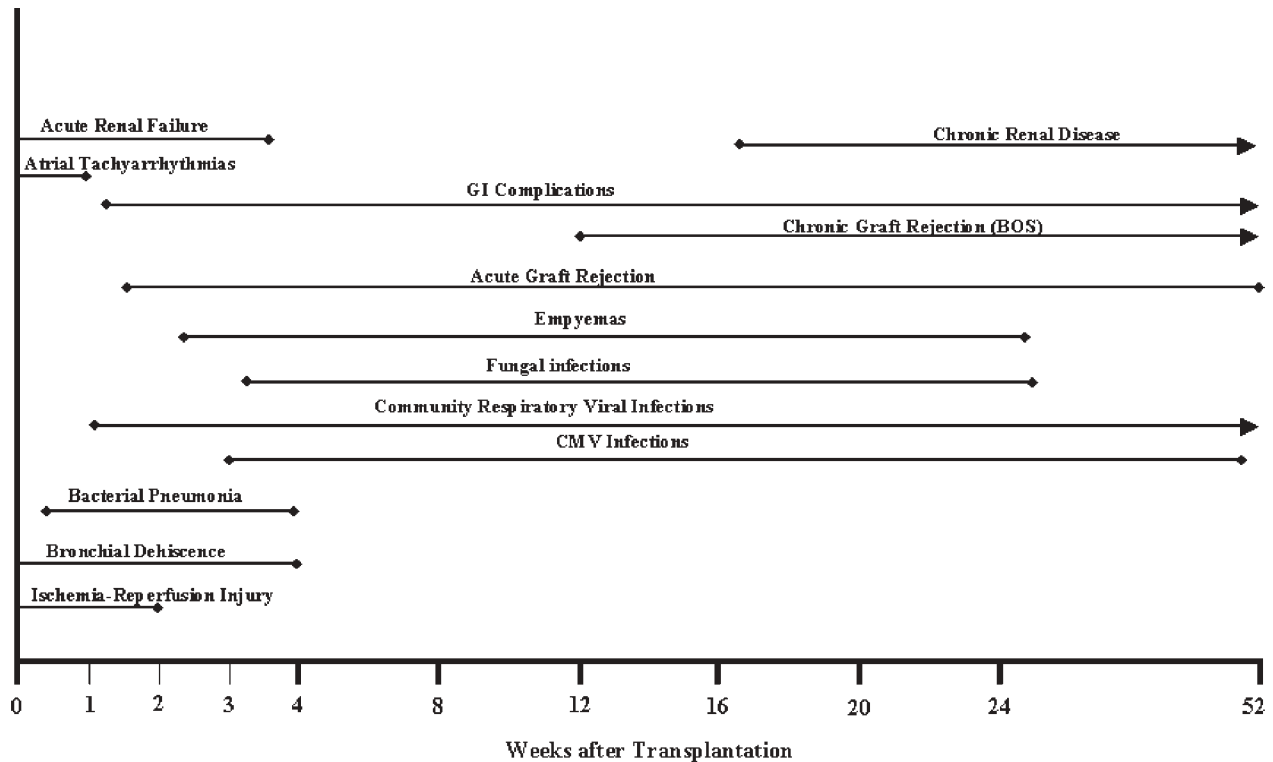


Fig 2. Timeline of complications following lung transplantation that may require intensive care unit treatment. GI = gastrointestinal; BOS = bronchiolitis obliterans syndrome; CMV = cytomegalovirus.

and renal function is essential in the immediate postoperative period.

Prior to extubation, patients undergo bronchoscopy to ensure adequate clearance of secretions. Following extubation, the apical chest tubes are removed in the absence of an air leak, commonly within 48 hours postoperatively. Because of the frequent occurrence and reoccurrence of pleural effusions postoperatively especially in bilateral lung transplant recipients, the basal chest tubes remain for several days, usually being removed on postoperative day 5 to 7 (chest tube drainage <150 ml/24°).

Vigorous chest physiotherapy, postural drainage, inhaled bronchodilators, and frequent clearance of pulmonary secretions is required in the postoperative care of these patients. Early and constant involvement of the physical therapy team ensures that transplant recipients are out of bed to chair, ambulatory with assistance, and using the treadmill or exercise bikes as soon as possible even if they remain intubated. In patients with early allograft dysfunction requiring prolonged intubation, early tracheostomy allows easier mobility and better patient comfort, oral hygiene, and clearance of pulmonary secretions.

Adequate pain control is a necessity to prevent atelectasis from poor chest movement and inadequate coughing effort secondary to postthoracotomy incisional pain. An epidural catheter provides an excellent means of achieving pain control with minimal systemic effects. In one study after lung transplantation, use of an epidural catheter was associated with faster extubation and decreased ICU days as compared to intravenous morphine [24]. Patients often require at least some oral narcotics in the first few weeks after transplantation for pain management. Use of oral narcotics or acetaminophen are preferred to nonsteroidal anti-inflammatory drugs, which could exacerbate renal insufficiency in these patients already on cyclosporine or other potentially nephrotoxic drugs.

Complications

Following lung transplantation, there are numerous complications that can occur. The ones most likely to be encountered by the intensivist are discussed below. A timeline of these complications is shown in Figure 2.

Ischemia-Reperfusion Injury

Ischemia-reperfusion injury represents the most frequent cause of early mortality and prolonged ICU stay. A variety of factors such as poor preservation, prolonged ischemic time, or unsuspected donor lung pathology such as contusion or aspiration play a role in its development. The condition is characterized by noncardiogenic pulmonary edema and progressive lung injury over the first few hours following implantation (Figs 3A, 3B). The process can evolve into severe diffuse alveolar damage (Fig 3C) requiring maximal ventilatory support and even institution of extracorporeal membrane oxygenation (ECMO).

Fortunately, severe reperfusion injury is not so commonly encountered in recent years. Superior strategies of lung preservation have evolved [25]. It is clear from experimental [26,27] and clinical work [28] that low-potassium dextran solution provides superior preservation over high-potassium preservation solutions previously in use. In addition, experimental work suggests that nitric oxide added to the flush solution at the time of harvest provides a preservation advantage [29]. Lung hyperinflation is an excellent model of pulmonary edema. Therefore, we are particularly careful to avoid lung hyperinflation during harvest and storage of the donor lungs. Each of these factors has contributed to a reduction in the frequency of ischemia-reperfusion injury.

Recently, the use of controlled reperfusion in combination with leukocyte depletion [30-36] has shown promise as a preventative strategy for ischemia-reperfusion injury. Lick and colleagues [37] reported a nonrandomized small series in humans using this technique and reported no reperfusion injury. At the time of reperfusion, leukocyte-filtered modified perfusate is pumped at a controlled rate (200 ml/min) and pressure (less than 20 mm Hg) for 10 minutes through the transplanted lung. The lung is ventilated with 50% inspired oxygen concentration during the period.

Treatment of ischemia-reperfusion injury includes diuresis and maximal ventilatory support. In most cases, the reperfusion injury will resolve in 24 to 48 hours. We have previously demonstrated that inhaled nitric oxide is of benefit in severe reperfusion injury as it significantly decreases pulmonary artery pressure and improves PaO₂/FiO₂ ratio [38]. Recently inhaled prostacyclin has been investigated and has shown promise as an alternative to nitric oxide [39]. In severe cases, ECMO is a suitable treatment option if employed early [40]. Initiating

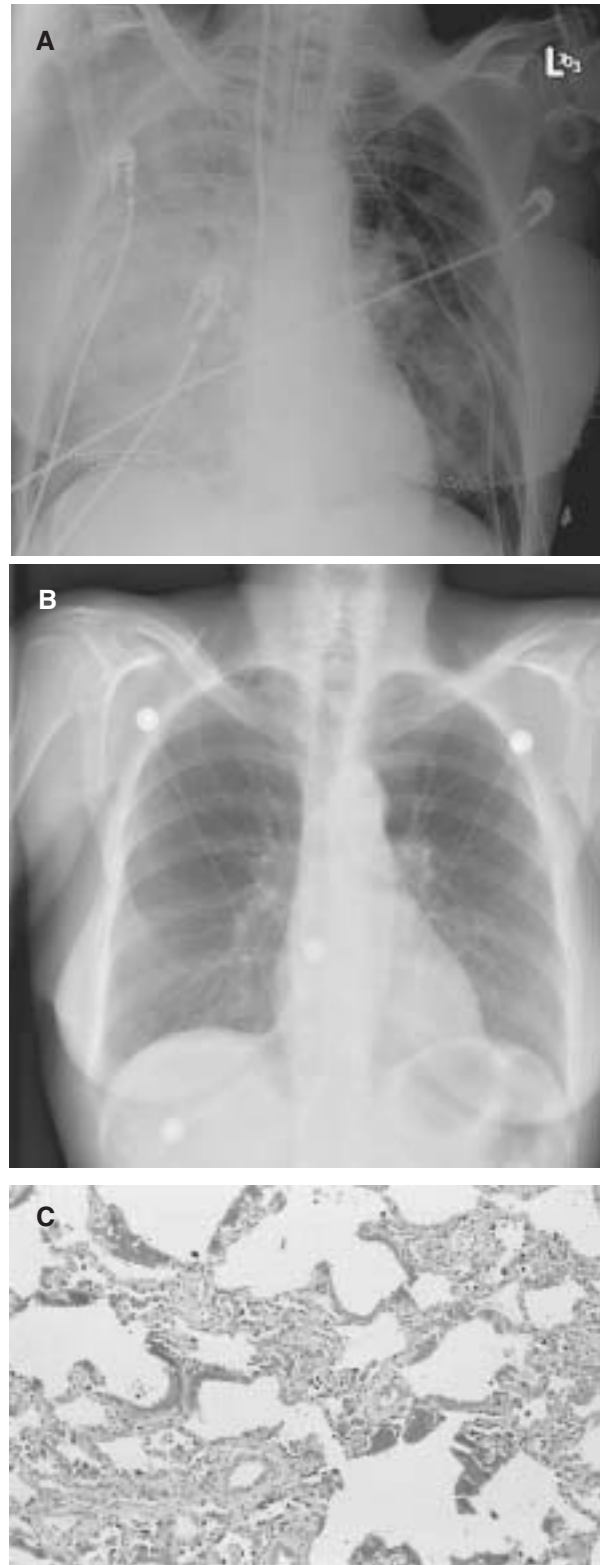


Fig 3. (A) Chest radiograph showing severe right-sided ischemia-reperfusion injury following bilateral lung transplantation. Right lung was implanted first. (B) Chest radiograph of same patient after resolution of ischemia-reperfusion injury. (C) Transbronchial biopsy showing diffuse alveolar damage characteristic of ischemia-reperfusion injury.

use of ECMO more than 24 hours after the injury has been uniformly unsuccessful in our experience.

Ischemia-Reperfusion Injury in Single-Lung Transplant Emphysema Recipients

Initially, it was felt that emphysema patients would not be good candidates for single-lung transplantation because the overly compliant native lung would be prone to hyperinflation resulting in mediastinal shift and compression of the transplanted lung. Despite this concern, successful single-lung transplantation for emphysema was reported in 1989 by Mal and colleagues [41]. When ischemia-reperfusion injury occurs in single-lung transplant recipients with emphysema treatment, dilemmas may arise. Treatment of the ischemia-reperfusion injury with mechanical ventilation and high levels of PEEP can result in overexpansion of the more compliant native emphysematous lung. As a result of overdistention, the native lungs' pulmonary vascular resistance increases, and blood is then shunted to the dysfunctional allograft worsening V/Q mismatch. Furthermore, if the overdistention continues, mediastinal shift with resultant impairment of cardiac return can result in hemodynamic instability.

Awareness of this potential problem and conservative treatment consisting of minimizing tidal volume and lowering PEEP while accepting mild respiratory acidosis often is all that is needed. The patient should be based in the lateral position with the transplant side up, and aggressive chest physiotherapy must be performed on a regular basis. When these measures fail, success has been reported with independent lung ventilation [42,43]. For independent lung ventilation, a double lumen endotracheal tube is placed, and 2 ventilators are used to optimize oxygenation and ventilation to each lung. The ventilator settings for the native, emphysematous lung usually consists of minimal PEEP, high flows, and low tidal volumes, while the allograft receives high PEEP. The use of independent lung ventilation is complicated in the ICU setting for several reasons: the requirement for 2 ventilator systems, the difficulty in removing secretions from the smaller lumen of dual lumen endotracheal tubes, and the ease in which these endotracheal tubes are dislodged from their appropriate position. Because of the complexity and lack of com-

puting data to demonstrate benefit on outcomes, independent lung ventilation is rarely performed in our program.

Noninfectious Airway Complications

Anastomotic complications limited the success of many early attempts at human lung transplantation. Lethal tracheal dehiscence and/or extensive airway necrosis was reported in 4 of the initial 13 bilateral lung transplant recipients at Toronto [44]. Anastomotic complications, however, are now infrequent in modern lung transplantation with improvements in lung preservation, surgical technique, and perioperative management of the recipient [45]. Recently, however, a high incidence of postoperative airway dehiscence has been reported with the early use of sirolimus (Rapamune, rapamycin, Wyeth Laboratories, Philadelphia, PA; and Certican, RAD, everolimus, rapamycin derivative, Novartis, East Hanover, NJ) in lung transplant recipients [46]. In a series of 15 patients treated in the early postoperative period with sirolimus, 4 experienced anastomotic dehiscences and, more concerning, 3 of these 4 died as a result. The use of sirolimus in the early posttransplant period should be discouraged.

Bronchial dehiscence and necrosis can usually be managed by conservative airway debridement. It is remarkable how a significant area of donor airway necrosis and dehiscence will often spontaneously heal and provide a satisfactory result (Figs 4A, 4B). Long-term complication from anastomotic dehiscences including bronchial strictures and bronchomalacia are treated with airway stents [47,48]. Fatality is rare.

Infections

Lung transplant recipients are at increased risk for a variety of infectious complications, due to the chronic immunosuppression and abnormal physiology of the posttransplant lung. Infections with typical bacterial pathogens as well as opportunistic infections such as CMV are common. Collectively, infections represent the leading cause of death in the early postoperative period and remain an important cause of morbidity and mortality throughout the posttransplant period. These infectious complications may result in respiratory failure

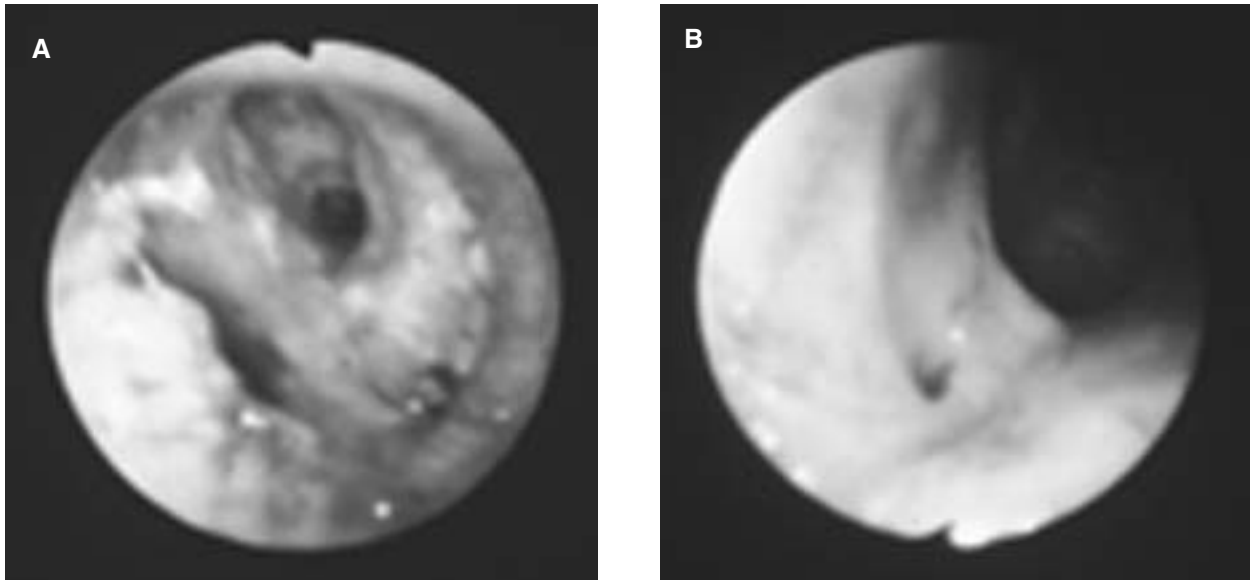


Fig 4. (A) Bronchoscopy findings of right anastomotic dehiscence with a defect present in the membranous wall (arrow). (B) Follow-up bronchoscopy showing closing of the defect with a residual “pinhole,” which ultimately healed.

or sepsis and require ICU stay. Furthermore, evidence suggests many infections may induce immune and inflammatory responses that predispose to either acute or chronic allograft rejection or both. The discussion below will focus on the infections that may be seen by the intensivist taking care of lung transplant patients.

Bacterial

Bacterial infections are most common in the early posttransplant period and remain the primary cause of mortality in this period [49]. Most common organisms involved are those colonizing the donor, the recipient, or those known to populate individual institutions' ICUs. Gram-negative pathogens such as *Pseudomonas* spp, *Klebsiella*, and *Haemophilus influenzae* are responsible for most early posttransplant bacterial pneumonias, but gram-positive organisms such as *Staphylococcus aureus* are also causes. Less commonly, *Actinomyces* (Fig 5), *Mycobacterium tuberculosis*, and atypical mycobacterium have been seen in lung transplant recipients [49,50]. Analysis of trends in individual hospital bacterial susceptibilities should guide selection of empiric therapy with adjustments as necessary when sensitivities are available. At our institutions, postoperatively all lung transplant patients receive a 7- to 10-day



Fig 5. Computed tomography scan showing a lung abscess that was aspirated and found to be *Actinomyces*. Patient initially presented with fevers and chills. The patient was subsequently treated with ampicillin, with resolution of the abscess.

course of broad-spectrum antimicrobial prophylaxis (eg, vancomycin and cefepime). This antibiotic regimen is modified depending on results of the cultures obtained from the donor and recipient prior to transplantation (especially in patients with cystic fibrosis who have preoperative pathogens with known sensitivities). Antibiotics may be continued longer depending on the recipient's cultures after transplantation.

We have previously identified blood stream infection (BSI) as an important cause of early postoperative morbidity and mortality. BSI occurs in up to 25% of lung transplant recipients, with *S. aureus* and *P. aeruginosa* as the most common pathogens. Pneumonia and catheter-related infection reflected the most common etiology for posttransplant BSI, and infection was associated with a significantly increased risk for postoperative death. Our results highlight the importance of appropriate antibiotic selection, particularly in CF recipients, and the need to minimize the duration of central lines [51].

Viral

Cytomegalovirus (CMV). CMV disease is the most commonly seen infectious postoperative complication reportedly affecting between 13% and 75% of transplant patients depending on definitions of CMV disease and the type and duration of CMV prophylaxis [52,53]. Lung transplant recipients who are CMV negative and receive CMV-positive donor lungs are at the highest risk of developing severe life-threatening disease from primary infection, while it is not usually seen in donor-negative/recipient-negative transplants [52]. The optimal approach to the prevention of posttransplant CMV infection remains controversial. Most centers, including our own, will employ a regimen of 12 weeks of IV ganciclovir (5 mg/kg qd) posttransplantation in high-risk D+/R- mismatch patients. Some centers employ a shorter course of IV ganciclovir (eg, 4 weeks) in all at-risk lung recipients. In a randomized prospective trial, we have recently demonstrated that hyperimmune globulin against CMV (eg, Cytogam) alone is ineffective in the prevention of CMV viremia or pneumonitis after lung transplant [54]. For our transplants, we use CMV-negative or leukocyte-reduced blood products [52].

CMV infection refers to detection of the virus in the serum or BAL using conventional culture, shell vial assay, or qualitative serum assay (eg, polymerase chain reaction or CMV DNA by hybrid capture). CMV disease is defined by the presence of cytomegalic cells (CMV inclusion bodies or positive immunoperoxidase stain) on tissue biopsies or the isolation of CMV from a tissue specimen in the presence of clinical findings consistent with CMV infection. Most CMV infections respond to 14 to 21 days of IV ganciclovir (5 mg/kg BID). The dose should be adjusted for leukopenia and renal dysfunction. When patients fail to respond to IV ganciclovir therapy, drug resistance should be consid-

ered, and foscarnet or cidofovir therapy may be instituted [55]. However, because of the significant nephrotoxicity of these second-line agents, formal testing for ganciclovir resistance should be performed when suspected. Acute renal failure has been reported in a lung transplant recipient treated with cidofovir [56]. Valganciclovir (Roche, Palo Alto, Calif), an oral ganciclovir derivative with bioavailability comparable to intravenous formulations of ganciclovir, has recently been introduced for use in transplantation. Currently, ongoing prospective studies will define the indications, efficacy, and cost-effectiveness of oral valganciclovir in the lung transplant population.

Community-Acquired Respiratory Viral Infections.

Community-acquired respiratory viral infections, including respiratory syncytial virus (RSV) adenovirus, parainfluenza, and influenza, cause significant morbidity and mortality in lung transplant recipients [57-61]. These viral respiratory infections occur over a broad time range after transplantation, and different mechanisms may account for early and late posttransplant infection. Early viral infection may reflect nosocomial transmission or reactivation of latent virus. In contrast, late posttransplant respiratory viral infection is more likely to be community acquired. A seasonal variation is seen with RSV (January to April), while patients with adenovirus and parainfluenza occurred throughout the year.

The majority of viral infections produce acute symptoms including cough, wheeze, dyspnea, and fever. Presentation of influenza may be atypical, with gastrointestinal (GI) symptoms often predominating. New radiographic findings in lung transplant recipients with viral respiratory infections appear to indicate severe infection and are a marker for poor prognosis [59]. Symptomatic adenoviral infection in particular is typically associated with new radiologic abnormalities and is frequently fatal [59]. In another series, the presence of adenoviral DNA in a series of pediatric lung allografts was associated with an increased incidence of early graft failure or death [62].

Treatment options for respiratory viral infections are limited. Aerosolized ribavirin, although controversial, has shown benefit in the treatment of RSV and parainfluenza infection in children [63]. Intravenous immunoglobulin to RSV has been used in prevention and treatment of RSV infections in infants [64]. While the efficacy of these agents in lung transplant recipients remains unclear, we recommend that all patients with severe symptomatic

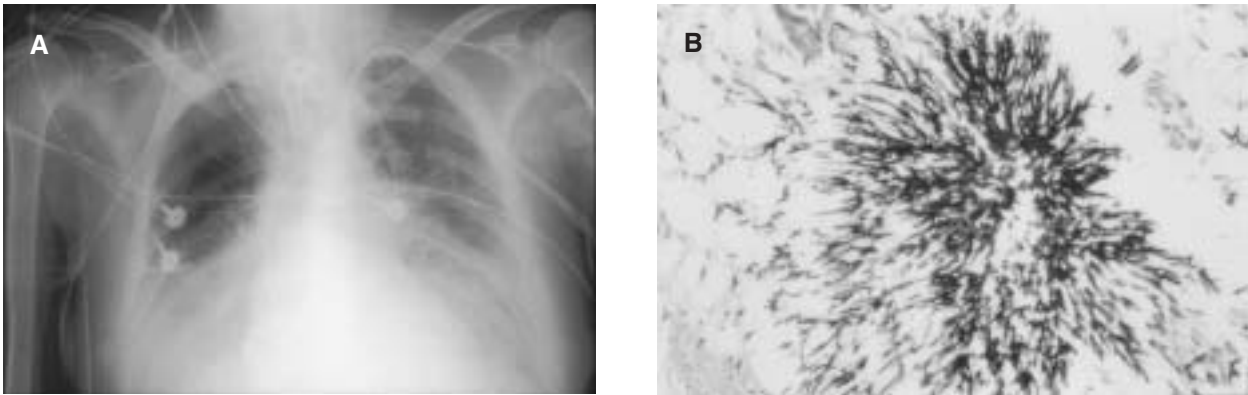


Fig 6. (A) Chest radiograph of patient with invasive pulmonary *Aspergillus*. (B) Histopathologic examination of patient with *Aspergillus* (hematoxylin and eosin, 20X).

RSV or parainfluenza infection receive aerosolized ribavirin. We also recommend its use in patients with radiographic abnormalities and RSV or parainfluenza infection given the increased potential to progress to respiratory failure. Care for adenovirus is currently supportive as there are currently no definitive effective treatments. A trial of decreasing immunosuppression appears worthwhile, although the risk for rejection must be considered. Reports of the use of IV ribavirin or IV immunoglobulin have suggested potential for their use in adenoviral infections in pediatric patients, bone marrow recipients, and AIDS patients [65-68]. Intravenous ribavirin has also been used in a pediatric patient with adenoviral infection after liver transplantation with some success [69]. Treatment for influenza in non-immunocompromised patients consists of several potential drugs including amantadine, rimantadine, and the newer neuraminidase inhibitors, zanamivir and oseltamivir [70,71]. Their use in lung transplant recipients requires further study.

Because treatment options for community-acquired viral infections in lung transplant recipients are limited, the main goal should be prevention in this population. It is routine for all our lung transplant recipients to receive yearly influenza vaccines. Unfortunately, in solid organ transplant recipients, the response to influenza vaccine has been noted to be impaired, and revaccination does not seem to improve the vaccine response [63]. In a series of heart transplant patients, the efficacy of the influenza vaccine was significantly impaired, but despite being less effective compared to non-immunosuppressed individuals, approximately 50% of patients still reached protective titers against 2 of 3 virus strains [72]. Therefore, routine influenza immunization is still recommended, but serologic

testing for antibody development and booster vaccination may be indicated [60]. Importantly, all close contacts should receive influenza vaccination, hoping to decrease risk of infection to the transplant patient. Lung transplant recipients should be informed to avoid contact with family and friends with respiratory symptoms, especially children, to minimize risks of acquiring community viral infection. Frequent hand washing should be encouraged after contact with infected patients.

Fungal

Fungal infections are a major problem after lung transplantation and occur early and late posttransplant. *Aspergillus* and *Candida* account for the majority of these fungal infections. *Candida albicans* is commonly isolated posttransplant and usually represents colonization [49], but it may also be invasive [73]. *Aspergillus* species can also represent colonization, but because of the potential for invasive life-threatening infections, consideration needs to be given toward prophylaxis or treatment, depending on the clinical situation. In more than 50% of cases, *Aspergillus* colonization and infection occur within the first 6 months after transplantation. Mortality with invasive *Aspergillus* pneumonia or disseminated disease approaches 60% in one series of lung transplant recipients (Fig 6A, 6B) [74].

Because of the inherent ischemia occurring at the bronchial anastomosis after lung transplantation, fungal infections may develop at this site; therefore, careful attention to the anastomosis is required at all posttransplant bronchoscopies. *Aspergillus* and *Candida* have been identified as

potential pathogens that can cause life-threatening bronchial anastomotic infection [75]. Nunley and colleagues [76] identified 15 (24.6%) saprophytic fungal infections involving the bronchial anastomoses in 61 lung transplants. The majority were due to *Aspergillus* species, and airway complications were more frequently seen in the transplant recipients with these anastomotic infections (46.7%) compared to those without infections (8.7%). Complications from fungal infections arising at the bronchial anastomoses included bronchial stenosis, bronchomalacia, and fatal hemorrhage. A variety of interventions including bronchial stenting, balloon dilatation, electrocauterization, laser debridement, and radiation brachytherapy were used to treat these complications. In addition, in this series, 3 fatalities were reported (4.9%) from saprophytic bronchial anastomotic infections.

In general, on bronchoscopic inspection, if extensive anastomotic pseudomembranes are present, we biopsy the site to rule out an invasive fungal infection. Although the optimal treatment of bronchial anastomotic fungal infection is unknown, we favor a combination of systemic and inhaled antifungal agents because aerosolization allows direct drug delivery to the poorly vascularized anastomosis. Debridement of the site may also be necessary. We have previously reported success with such an approach in the treatment of 3 lung transplant recipients with biopsy-proven invasive *Candida* anastomotic infection [77,78].

Although risk factors for posttransplant fungal infection are not well defined, pretransplant colonization or prior infection may identify patients at higher risk for posttransplant infection. In patients with a single-lung transplant, one potential reservoir of persistent *Aspergillus* is the native lung [49,79]. *Aspergillomas* found in the recipient's explanted lungs has been associated with reduced posttransplant survival [17]. Patients with cystic fibrosis who have positive preoperative sputum cultures for *Aspergillus* are at higher risk for postoperative infections [80].

Nocardia species are increasingly recognized as a complication of lung transplantation [81]. While *Nocardia asteroides* accounts for the most transplant-related nocardiosis, we have reported a case of disseminated (pulmonary and bony) infection with *Nocardia brasiliensis* [82] in a single-lung transplant recipient. While the mortality is high for immunocompromised patients with *N. brasiliensis*, prompt diagnosis and early initiation of appropriate therapy may improve outcome.

Reports of other fungal infections such as *Histoplasma*, *Coccidiomycosis*, *Mucormycosis*, *Zygomycetes*, and *Cryptococcus* are also documented [49]. *Scedosporium apiospermum* is an uncommon cause of disseminated infection, but importantly it is inherently resistant to amphotericin B [83]. PCP, now classified as a fungus, is a rare cause of infection because of the routine use of prophylaxis in all lung transplant recipients. Dematiaceous fungi, such as *Mucor*, are also rare causes of postoperative infection.

In summary, invasive fungal infections in patients undergoing lung transplantation are relatively common and have been associated with significant attributable mortality. Treatment is based on infection; amphotericin B has been the drug of choice for *Aspergillus* and *Fusarium*. Newer options that may be at least as effective and associated with potentially less toxicity include liposomal formulations of amphotericin, voriconazole, and caspofungin. Voriconazole, in particular, must be used with caution in lung transplant recipients because of its extensive drug interactions. High-dose azole therapy may be used for *Scedosporium* (itraconazole, voriconazole). *Nocardia* infections are treated with trimethoprim-sulfamethoxazole. Most candidal infections can be treated with fluconazole. Nonalbicans *Candida* species, however, are increasingly resistant to diflucan but can be effectively treated by new azoles such as voriconazole. Single-lung transplant should probably not be performed in patients with mycetomas as adequate removal of fungal organisms cannot be achieved [17]. Prolonged therapy is required for all fungal infections.

Because of the potential morbidity and mortality associated with fungal infections, our group has had an intense interest in developing a safe and effective preventative strategy. Several antifungal prophylactic strategies have been used in lung transplants, often employing either systemic or inhaled antifungal agents (or both in combination) [84]. However, the use of systemic antifungal therapies is limited by lack of in vitro activity against some infections (eg, fluconazole is ineffective against *Aspergillus* and some *Candida* spp), drug interactions (itraconazole, voriconazole have marked interactions with immunosuppressive and other medications), significant treatment-limiting toxicities (particularly renal toxicity with systemic amphotericin B). Furthermore the use of inhaled amphotericin B has been associated with significant intolerance leading to treatment discontinuation in up to 50% of patients [85].

We recently demonstrated the safety and tolerability of inhaled amphotericin B lipid complex (ABLC) (Abelcet®, Elan Pharmaceuticals) in more than 50 lung transplant recipients. Because of the lipid properties, we hypothesized ABLC would be more effectively nebulized with greater pulmonary deposition than conventional amphotericin B. Consistent with this hypothesis, we saw very low rates of intolerance and very low rates of fungal infection in those patients who received nebulized ABLC, as compared to our prior experiences [86]. Although further study is needed, nebulized ABLC seems a promising approach to prevent of fungal infections after lung transplantation because systemic toxicities are avoided.

Pleural Space Infections

Empyema is an uncommon complication following lung transplantation, but its occurrence is associated with a significant mortality. Nunley and colleagues performed a retrospective review of 392 transplant recipients and found empyema documented in 14 patients (3.6%) [87]. In this series, empyemas tend to occur early in the posttransplant period, and 28.6% (4 patients) with empyemas died secondary to related infectious complications. There was no predominant organism isolated in empyemic fluid with gram-positive, gram-negative, and saprophytic organisms seen. There was no relationship to type of transplant performed or whether the transplant was done for a septic or nonseptic lung diagnosis. We have observed empyema in the native lung of single-lung transplant recipients (Fig 7) and also found a high associated mortality.

Rejection

Both acute and chronic lung allograft rejection contribute substantially to morbidity seen in lung transplant recipients. Chronic lung transplantation remains the major limitation to long-term success in lung transplantation today. Hyperacute rejection has been only anecdotally reported in the literature [88-90]. Saint Martin and colleagues [91] performed immunofluorescence with C3, immunoglobulin M, and immunoglobulin G and found no evidence of humoral rejection in 106 biopsies; in this report, only 1 patient had a high pretransplant panel reactive antibody (PRA). We have reported immunohis-



Fig 7. Chest radiograph showing empyema of the native lung following single-lung transplantation.

tochemical findings of humoral injury in some recipients with high PRA [92]. Interestingly, Magro and colleagues [93] have recently reported evidence that a frequently occurring septal capillary injury syndrome may represent humoral injury in lung allografts.

The section below focuses on acute and chronic rejection. Although it is unlikely that an isolated acute rejection episode will require ICU care to treat, its occurrence commonly complicates ICU admission for other reasons such as infections especially when immunosuppression regimens are altered. Additionally, acute rejection may present in the early postoperative period when the patient is still in the ICU. Complications arising from the declining lung function seen in progressive chronic allograft rejection, also known as bronchiolitis obliterans syndrome (BOS), may present the intensivist with challenging treatment dilemmas.

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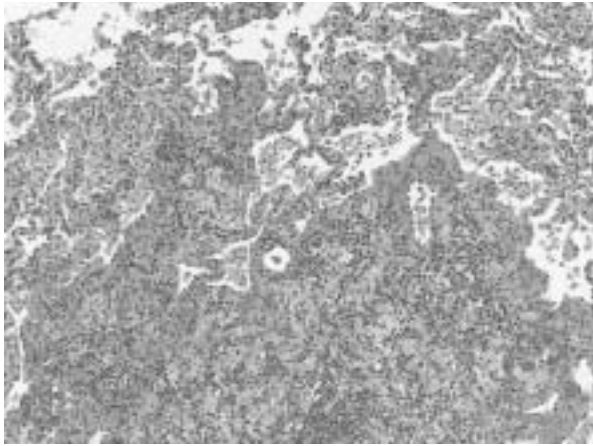


Fig 8. Histopathologic examination of acute rejection, International Society for Heart and Lung Transplantation grade 3 (hematoxylin and eosin, 20X).

the heightened immunosuppression frequently used in the treatment of chronic lung rejection may require ICU admission.

Acute Rejection

Acute allograft rejection is one of the most common complications following lung transplantation. Most recipients experience at least 1 episode of acute rejection within the first year following transplant [94,95]. In 1990, the Lung Rejection Study Group developed a system to characterize lung allograft rejection based on histologic criteria found on biopsy, with emphasis on perivascular and interstitial infiltration of mononuclear cells (Fig 8). Note is also made of the coexistence of airway inflammation [96]. Modest revisions in this system were described in 1995 [97]. In recent years, airway-centered inflammation (lymphocytic bronchitis/bronchiolitis) had been associated with subsequent development of chronic lung allograft dysfunction characterized by the pathologic lesion of bronchiolitis obliterans [98]. In addition, it is clear that there is an association between frequency and severity of acute rejection episodes and subsequent development of bronchiolitis obliterans [98]. Thus, early detection of acute rejection and alteration of immunosuppression to deal with this problem may have a significant impact on subsequent reduction of chronic lung allograft dysfunction.

In the early lung transplant experience, clinical parameters were often used to establish a clinical diagnosis of acute rejection. Unfortunately, dyspnea, low-grade fever, perihilar infiltrates, leukocytosis, hypoxia, and response to intravenous bolus

doses of corticosteroid are rather nonspecific findings. Pathologic assessment of multiple transbronchial biopsy specimens has proven to be the gold standard for the diagnosis of acute lung allograft rejection [96,99,100]. Indeed, many programs including ours have adopted a program of prophylactic surveillance of transbronchial biopsy [95,99,101-104]. However, this strategy is controversial and has been abandoned by a number of active lung transplant programs [105,106].

Since acute rejection is a predictor of BOS, induction and maintenance immunosuppression regimens as well as treatment strategies for documented acute rejection are subjects of intense interest. Induction therapy with either a cytolytic agent or an interleukin-2 receptor (IL-2R) blocker has been shown to reduce early rejection rates [107]. Due to the ease of administration, fewer side effects, similar efficacy, and potentially fewer secondary infections, IL-2R blockers are becoming the agents of choice for centers adhering to an induction protocol.

Treatment of acute rejection episodes basically has 2 goals: to deal with the acute problem and to reduce the likelihood of further episodes. Conventional therapy has been intravenous methylprednisolone in a dose of 10 to 15 mg/kg for 3 to 5 days [108]. While resolution of perivascular infiltrates is often accomplished by this strategy, airway-centered inflammation has been more refractory to therapy. Depending on the maintenance steroid dose, 2 to 3 weeks of an oral steroid taper is usually prescribed. As acute therapy is initiated, the maintenance immunosuppression regimen should be scrutinized. A frequent first adjustment from maintenance cyclosporine is a switch to tacrolimus in the event of cyclosporine toxicity or acute rejection episodes despite adequate cyclosporine dosage [109,110]. The role of newer agents such as sirolimus (rapamycin, Rapamune, Wyeth, and RAD rapamycin derivative, Novartis) or leflunomide (Arava), a pyrimidine synthesis inhibitor, is evolving in lung transplantation based on success in other solid organ transplants [111-114]. Low calcineurin inhibitor drug levels warrant investigation, especially for new medications activating the cytochrome P450 enzyme pathway and enhancing calcineurin inhibitor metabolism (eg, dilantin, rifampin, nafcillin) [115].

Chronic Allograft Rejection/BOS

The descriptive term *bronchiolitis obliterans syndrome* (BOS) has been used to describe a late

decline in FEV₁ from postoperative baseline that is not attributable to acute rejection, infection, or mechanical obstruction due to a bronchial anastomotic complication. The pathologic lesion is bronchiolitis obliterans. A working formulation was created to characterize and grade BOS [116] and has been recently revised by the ISHLT [117].

BOS is a very common condition following lung transplantation [118]. Most observers believe that every recipient will develop some degree of BOS over time in long-term follow-up. In our program, actuarial freedom from BOS at 1, 3, and 5 years posttransplant is 82%, 42%, and 25%, respectively [22].

The cause or causes of BOS are not clear. Evidence suggests that both alloimmune and non-alloimmune mechanisms are important [119]. It is accepted that recipients who have more frequent and severe episodes of acute allograft rejection are more likely to develop subsequent BOS [98]. However, nonimmune mechanisms may also be important. Lung transplant recipients appear to have a high incidence of gastroesophageal reflux disease (GERD). In our experience, patients without GERD have a much lower incidence of BOS than those who have uncorrected GERD. We also have noted improvement of BOS in recipients with GERD who underwent fundoplication [120]. Until we have a better understanding of the molecular and cellular mechanisms of BOS, we are not likely to make much progress in its treatment. This goal is hampered by the lack of a suitable experimental model of the bronchiolitis obliterans lesion. A definitive solution for chronic allograft rejection may come in the future through the development of strategies to promote immune tolerance or permanent acceptance of the graft by the recipient without the need for immunosuppression.

Nonpulmonary Complications

Although lung transplant recipients can experience multiple nonpulmonary complications following lung transplantation, certain of these complications are more likely to require the input of the ICU team and are discussed below.

GI Complications

GI complications are frequent in lung transplant recipients, occurring in as many as 50% of patients

in some series [121]. Frequently reported nonsurgical GI complications include esophagitis, pancreatitis, gastric atony, adynamic colonic ileus, gastroesophageal reflux, peptic ulcer disease, gastritis, gastrointestinal bleeding, CMV hepatitis, CMV colitis, diverticulitis, cholecystitis, and clostridium difficile colitis/diarrhea. The majority of these nonsurgical GI complications occur in the first month postoperatively, and most respond to conservative therapy [121]. Acute abdominal processes requiring surgical intervention have a reported incidence of 4% to 17% in lung transplant recipients and include, in decreasing occurrence, bowel perforation, appendicitis, cholecystitis, colitis, and pneumatosis intestinalis [122]. Posttransplant lymphoproliferative disease may present as an acute abdominal process, secondary to intussusception or bowel perforation. Surgical GI complications can occur at any time after transplantation, and a high index of suspicion is needed because their severity may be masked initially by immunosuppression. Emergent operative exploration when required has significant morbidity and mortality associated with it. Elective procedures, however, can be performed safely in this population with acceptable morbidity [123].

Atrial Tachyarrhythmias

Atrial tachyarrhythmias (ATs) are common following lung transplantation in the adult population. Both of our centers have addressed the incidence, clinical predictors, and effect on outcomes of postoperative AT in the lung transplant population. The incidence of early postoperative ATs following lung transplantation appears to be between 34% to 47%. AT occurred postoperatively after a mean of 4.7 ± 2.3 days in one series and 3.8 ± 3.0 days in another. Age has been independently associated with AT in both our series, with older patients at increased risk. In one series, significant predictors of atrial fibrillation (AF) also included IPF coronary disease, enlarged left atrium on echocardiogram, and number of postoperative vasopressors.

Mean ICU stay and mean hospital stay are significantly longer in patients with atrial arrhythmias (Barnes series 28 days; range 7-233 days for patients with AT compared to 16 days; range 1-232 days without AT, $P < .0001$; Duke series 32.4 ± 60.0 vs 17.5 ± 24.1 days, $P = .04$). In one series, hospital mortality was not different between the 2 groups (+AT 2/71, 3%; versus -AT 7/139, 5%; $P = .7$). In contrast, in the other series, patients with AF

had more in-hospital death (odds ratio = 5.7, $P = .0005$) than did those without AF.

The majority of ATs can be treated medically. In one series, 63 patients with AT were treated medically (89%), and 8 required cardioversion (11%). Efforts to reduce the incidence of supraventricular tachycardia might result in improved short-term morbidity. Additional prospective studies designed to prevent posttransplant AT are needed.

Renal Failure

Renal failure is a common complication following lung transplantation because of the necessary use of calcineurin inhibitors. Ishani and colleagues [124] reviewed the course of 219 lung and heart-lung transplant recipients surviving at least 6 months posttransplant and found by 6 months, 200 patients (91.3%) had a decrease in their renal function. Doubling of patient's creatinine from pre-transplant baseline occurred in 34%, 43%, and 53% at 1, 2, and 5 years, respectively. End-stage renal disease (ESRD) occurred in 16 lung transplant recipients (7.3%) at a median duration of 28 months. The majority of recipients who developed ESRD had received cyclosporine (13/16) compared to only 3 that had received tacrolimus. Of the patients that developed ESRD, 44% (7) received hemodialysis alone and 56% (9) received kidney transplants. Risk factors associated with time to doubling of creatinine by multivariate analysis were serum creatinine at 1 month posttransplant (relative risk [RR] = 1.30, $P = .03$) and number of cumulative follow-up periods with the diastolic blood pressure greater than 90 mm Hg (RR = 1.28, $P = .02$). Compared to cyclosporine, the use of tacrolimus in the first 6 months following transplantation was associated with a decreased risk for time to doubling of serum creatinine (RR = 0.38, $P = .009$). It is apparent that prevention of subsequent renal failure in lung transplant recipients requires preserving renal function early in the course of transplantation. Early identification of high-risk recipients for renal dysfunction should prompt aggressive blood pressure control in these recipients and consideration of change in immunosuppressive protocol [125]. Other studies have found the underlying pulmonary diagnosis to be a risk factor for the subsequent development of renal insufficiency. Broekroelofs and colleagues [126] found recipients with cystic fibrosis had the greatest impairment in renal function and recipients with pulmonary hypertension the least impairment.

Hyperammonemia

Hyperammonemia following lung transplantation has been reported as a potentially fatal complication [127-129]. The development of hyperammonemia appears to occur early in the posttransplant period. In one recent study, 6 (4.1%) of 145 lung transplant recipients developed hyperammonemia, all within the first 26 days after transplantation [127]. A high mortality rate was seen in the population that developed hyperammonemia (67% vs 17%, $P = .01$). The majority of patients with hyperammonemia develop neurologic symptoms including encephalopathy, lethargy, agitation, seizure, tremors, and coma. Risk factors for the development of hyperammonemia include major GI complications, use of total parenteral nutrition, and lung transplantation for primary pulmonary hypertension. Treatment includes multiple treatment modalities including discontinuation of exogenous nitrogen (TPN), high caloric intake to depress catabolism, lactulose, neomycin, agents used to treat hyperammonemia in congenital urea cycle defects (sodium phenylacetate, sodium benzoate, and arginine hydrochloride), and use of hemodialysis [130].

Thrombotic Thrombocytopenic Purpura—Hemolytic-Uremic Syndrome

An infrequent but potentially serious complication following lung transplantation is thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. More common in other solid organ transplants, especially kidney transplants, these syndromes are characterized by microangiopathic hemolysis, thrombocytopenia, and renal failure [131]. It is most common within the first 3 months posttransplantation, and 96% of cases occur within the first year. It is associated with the use of calcineurin inhibitor therapy. The critical component of treatment is prompt initiation of plasma exchange, but in addition to plasma exchange aspirin, dipyridamole, or glucocorticoids can be used [132]. Hemodialysis or renal transplantation is required in lung transplantation patients who develop renal failure from this syndrome. Mortality is in the range of 13% [131].

Pharmacology

When a lung transplant recipient is admitted to the ICU, their immunosuppressive regimen needs to be

Table 1. Basic Mechanisms of Action of Common Immunosuppressive Agents Used in Lung Transplantation

Generic Name	Trade Name	Mechanism of Action
Cyclosporine	Neoral (alternatives: Gengraf, SangCya, Sandimmune)	T-lymphocyte inhibitor via suppressed interleukin-2 (IL-2) production
Tacrolimus	Prograf	T-lymphocyte inhibitor via suppressed IL-2 production
Rapamycin (sirolimus)	Rapamune	Blocks IL-2 mediated T cell activation
Azathioprine	Imuran	Inhibits lymphocyte proliferation via inhibition of nucleotide synthesis
Mycophenolate	CellCept	Inhibits lymphocyte proliferation via inhibition of nucleotide (purine) synthesis
Prednisone	Deltasone	Removes lymphocytes from intravascular space, inhibits lymphokine-mediated amplification of macrophages and lymphocytes
Methylprednisolone	Solu-medrol	Removes lymphocytes from intravascular space, inhibits lymphokine-mediated amplification of macrophages and lymphocytes

examined and often modified based on their indication for admission. For this reason, it is imperative that intensivists are knowledgeable of basic pharmacotherapy of the common agents used. The majority of lung transplant recipients are treated with a combination of a calcineurin inhibitor plus a purine synthesis antagonist (80%) [2]. The vast majority also receive steroids as part of their maintenance immunosuppression. Sirolimus (rapamycin) is included in the maintenance regimen in 6.3% and 4.6% of recipients at 1 and 5 years, respectively [2]. The basic mechanisms of action of the common immunosuppressive agents used in lung transplantation are listed in Table 1 [133].

When treating lung transplantation, a general knowledge of the multiple drug interactions that can occur between new drugs given in the ICU and the patient's maintenance drugs is important (Table 2) [133]. Immunosuppressive medicines may require alterations but must be continued during critical illnesses. In addition, immunosuppressive drug pharmacokinetics, distribution, and clearance are often affected by severe illnesses, and therefore when available, drug levels must be checked and optimized (Table 3) [133]. These agents should be given on a consistent time schedule. Alternative routes of administration are needed if patients are unable to eat to during their illness. For example, in the early postoperative period, we routinely employ sublingual tacrolimus, intravenous azathioprine, and intravenous methylprednisolone until patients are able to tolerate oral medications. Cyclosporine can be given as a continuous IV infusion if used as a primary immunosuppressive agent instead of tacrolimus. Although there is little published experience with sublingual tacrolimus, in

Table 2. Agents That Increase or Decrease Cyclosporine, Tacrolimus, and Sirolimus Levels

Agents That Increase Cyclosporine, Tacrolimus, and Sirolimus Levels	Agents That Decrease Cyclosporine, Tacrolimus, and Sirolimus Levels
Fluconazole	Phenytoin
Itraconazole	Phenobarbital
Ketoconazole	Carbamazepine
Erythromycin	Nafcillin
Clarithromycin	Rifampin
Amiodarone	St. John's Wort
Metoclopramide	
Allopurinol	
Nefazadone	
Fluvoxamine	
Verapamil	
Diltiazem	
Nicardipine	
Grapefruit juice	

our experience, this route of administration provides reliable trough levels in the early postoperative period. Once converted to oral tacrolimus, the dose is usually doubled. Furthermore, during severe illnesses, the absorption of drugs via the oral route may be altered, and this needs to be considered. Generally, input from a transplant pharmacist is quite helpful in dealing with these complex drug issues.

Conclusions

Treatment of lung transplant recipients often poses unique challenges to the intensivist and the ICU

Table 3. Immunosuppressive Drug Pharmacokinetics, Distribution, and Clearance

Generic Name	Delivery Routes	Half-Life ($t_{1/2}$)	Metabolism	Excretion	Target Trough Value	Usual Maintenance Dose	Acute Toxicities
Cyclosporine	PO, IV	8-10 hours	Hepatic (cytochrome P450-3A4)	Fecal >> urine	200 to 300 ng/ml	Adjusted per trough	Nephrotoxicity, hypertension, tremors, confusion, seizures, hyperkalemia, hemolytic-uremic syndrome, hyperlipidemia
Tacrolimus	PO, IV, SL	8-10 hours	Hepatic (cytochrome P450-3A4)	Fecal >> urine	8-12 ng/ml	Adjusted per trough	Nephrotoxicity, hypertension, tremors, confusion, seizures, hyperkalemia, hemolytic-uremic syndrome, hyperglycemia
Rapamycin (sirolimus)	PO	60 hours			5-10 ng/ml	Adjusted per trough	Hyperlipidemia, bone marrow suppression, hemolytic-uremic syndrome, bronchiolitis obliterans organizing pneumonia
Azathioprine	PO, IV	1-3 hours (for active metabolite 6-mercaptopurine)	Hepatic and red blood cells	Urine	NA	1-2 mg/kg/day	Bone marrow suppression, hepatotoxicity
Mycophenolate	PO, IV	18 hours	Hepatic glucuronyl transferase	Urine >> feces	NA	1-3 g/day	Bone marrow suppression, diarrhea
Prednisone	PO	30-36 hours			NA	Variable	Hyperglycemia, hypokalemia, fluid retention, impaired wound healing, psychosis, promoting gastric ulceration
Methylprednisolone	IV	18-36 hours			NA	Variable	Hyperglycemia, hypokalemia, fluid retention, impaired wound healing, psychosis, promoting gastric ulceration

team. Knowledge of the potential complications that these patients can develop at various time points after their transplant helps guide treatment. Familiarity with immunosuppressive regimens is important to prevent iatrogenic-induced complications. Clearly, a multidisciplinary approach is best that involves input from transplant physicians, intensivists, and ancillary staff on these complex patients. Successful ICU treatment from a multidisciplinary team is essential to allow lung transplant recipients to realize their potential for dramatically improved survival and quality of life after transplant surgery.

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