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Overview of Lung Transplantation

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Abstract Although significant gains have been made in improving lung function and survival in cystic fibrosis (CF), ultimately respiratory failure is the leading cause of mortality in these patients. For CF patients with end stage lung disease, lung transplantation is an option for treatment. The field of lung transplantation has progressed markedly in the last 20 years. Nonetheless it remains a technically complex and challenging procedure, and patients are at risk for numerous short term and long term complications. Potential transplant recipients must be physically and psychologically prepared for the arduous process involved in lung transplantation. This article will review the history of lung transplantation, indications for transplantation, surgical techniques, and complications of transplantation.

Keywords Lung transplant · Solid organ transplant · Surgery

Introduction

Lung transplantation is acknowledged as a treatment option for selected patients with advanced lung disease that has failed to respond to standard medical and surgical therapy. Despite great advances over the past 100 years, lung transplantation remains a complex and technically challenging procedure. The lung transplant candidate must be ill enough to warrant undertaking this high-risk procedure, yet strong enough to survive the complex surgery. As with other solid organ transplant candidates, prospective lung transplant patients must also have the ability to understand and comply with the complex post-transplant medical regimen. To better understand the current state of lung transplantation, it is helpful to know its historical development.

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Historical background

Research on transplant surgical techniques and immunology during the early part of the twentieth century paved the way for the first attempts at lung transplantation. In 1906, Charles Guthrie and Alexis Carrel successfully placed the heart and lungs of a kitten into the neck of a cat (a heterotopic transplant) [1]. Further animal lung transplant surgery (using canine lobes and whole lungs) was carried out over the next 50 years. Surgical technique development coincided with immunological research in the 1920s and 1930s. These early studies helped delineate the important role of immunosuppression medications in graft survival.

The first human lung transplant was performed in 1963 by Dr. James Hardy at the University of Mississippi [2]. The patient was an adult man with severe emphysema and a left lung carcinoma. It was felt that the patient could not survive lung resection for treatment of the carcinoma. A single lung transplant was successfully performed, but the patient died of renal failure and malnutrition on postoperative day 18. After Hardy's ground-breaking surgery, there were other attempts at human lung transplantation. These attempts included lobar transplantation in 1968 by Shinoi et al. [3] at the Tokyo Medical College and the first heart–lung transplant (in an infant; the first pediatric lung transplant) by Denton Cooley at the Texas Heart Institute in Houston in 1968 [4]. However, none of these lung transplant surgeries achieved long-term patient survival. However, these attempts did advance the knowledge of

surgical techniques and organ preservation, and they highlighted the need for more effective immunosuppression.

The advent of cyclosporine in the 1970s and further refinement of surgical techniques led to the first successful human lung transplant in 1981 by Dr. Bruce Reitz [5]. This surgery was a combined heart–lung into an adult woman with primary ("idiopathic") pulmonary hypertension. In 1983, Dr. Joel Cooper performed the first successful isolated lung (i.e., lung alone rather than heart–lungs) transplant in a patient with pulmonary fibrosis [6]. En bloc double lung transplantation was performed successfully by Patterson in 1988 [7]. But this technique was prone to significant complications, particularly tracheal dehiscence. As a result, sequential bilateral lung transplantation (where the airway anastomosis is not at the trachea but at the mainstem bronchi level) has become the most common surgical procedure used for bilateral lung transplantation. This technique, originally described by Henri Metras in 1950, was reintroduced by Pasque at Washington University in St. Louis in 1990 [8]. In more recent times, live donor lobar lung transplant [9] and cadaveric split-lung [10] techniques are successfully performed in a limited number of transplant centers.

Indications/contraindications

Referral for transplant evaluation can be considered for advanced lung disease patients who have exhausted conventional medical and surgical treatments. The primary diseases of patients referred for lung transplantation is different between adult and pediatric patients (Table 1). The option of lung transplantation should be discussed with the patient/family as early as possible, including the ramifications of lung transplantation and the potential surgical complications (including death). General selection guidelines have been published but for some conditions (Table 2), there are no strict selection criteria [11]. Each lung transplant center has slightly different selection criteria, based upon their experience and preferences. Hence, it is important to contact the lung transplant team at the selected institution to determine if proposed lung transplant candidates meet that particular transplant center's criteria for acceptance. In general, candidates for lung transplantation should be referred if they have a life expectancy of less than 2 years and demonstrate progressive lung function decline and/or fall to New York Heart Association/World Health Organization (WHO) functional class III or IV. Although most centers state that the age limit for lung transplant candidates is 55–65 years (depending on the type of lung transplant), there have been several lung transplants performed on patients more than age 65 years.

A lung transplant evaluation involves a thorough history, physical examination, laboratory tests (blood type, complete blood count, chemistry/liver function tests, 24-h urine for creatinine clearance, urinanalysis, human immunodeficiency virus [HIV], sputum cultures), pulmonary function tests, electrocardiogram/echocardiogram, 6-min walk test, and a psychosocial evaluation. The psychosocial evaluation should include information on backup caregivers, transportation, medical insurance, housing, and ability to comply with complex medical/treatment regimens. There should also be a thorough patient evaluation for significant psychiatric illness and cognitive dysfunction.

Table 1 Indications for lung transplantation

Adult	Pediatric
COPD/emphysema	Cystic fibrosis
Idiopathic pulmonary fibrosis	Idiopathic (primary) PH
Cystic fibrosis	Re-transplant for OB
Alpha-1	Congenital heart disease
Idiopathic (primary) PH	Idiopathic pulmonary fibrosis
Sarcoidosis	OB (non-transplant related)
Bronchiectasis	Re-transplant (not for OB)
LAM	Interstitial pneumonitis
Congenital heart disease	Pulmonary vascular disease
Re-transplant for OB	Eisenmenger's syndrome
OB (non-transplant related)	Pulmonary fibrosis, other
Re-transplant (not for OB)	Surfactant protein B deficiency
Connective tissue disease	COPD/emphysema
Interstitial pneumonitis	Bronchopulmonary dysplasia
Cancer	

Adult and pediatric Diseases. Most common indications listed at the top of each list

COPD chronic obstructive pulmonary disease, *PH* pulmonary hypertension, *OB* obliterative bronchiolitis, *LAM* lymphangiomyelomitosis

Table 2 Criteria for lung transplantation based on disease

Chronic obstructive pulmonary disease/emphysema
Hypoxemia at rest (PaO_2 <55 mmHg)
Hypercapnia
Post-bronchodilator FEV_1 <25% predicted
Cor pulmonale
Rapid clinical deterioration
Increased number of pulmonary exacerbations
Progressive FEV_1 decline
Cystic fibrosis
Baseline FEV_1<30% predicted
Hypoxemia at rest (PaO2<55 mmHg)
Hypercapnia
Female or pediatric patient with rapid clinical decline
Greater than two pulmonary exacerbations per year requiring hospital admission or home IV antibiotic therapy
Idiopathic pulmonary arterial hypertension
New York Heart Association/WHO functional class III or IV
Unresponsive to medical management
Mean right atrial pressure>10 mmHg
Mean pulmonary arterial pressure >50 mmHg
Cardiac index<2.0 l min^{-1} m^{-2}

Potential candidates should not use tobacco or have had no tobacco use for at least 6 months before transplant evaluation and listing. Chronic systemic corticosteroid use can hinder wound healing, particularly of the bronchial anastomosis [12]. Thus, candidates who require systemic corticosteroids should have their dose weaned to <10 mg/day or, for pediatric candidates, to not more than 0.5 mg kg^{-1} day^{-1}.

As noted above, lung transplant centers do not share the exact same acceptance criteria. There is also variability between centers on the relative contraindications. However, most programs agree on the absolute or strict contraindications to isolated lung transplantation (Table 3).

Donor lung

Lung allografts can originate from deceased (i.e., brain dead) donors, non-heart beating (deceased cardiac) donors [13], or from lobes obtained from live donors [14] who are ABO compatible and who "match" the patient for lung/height (Fig. 1). Generally, the donor lungs should be about the same height as those of the recipient, or at least within 4–5 cm. Unlike matching for kidney transplantation, the lung allografts do not need to be human leukocyte antigen (HLA) matched. Lung allgrafts do not tolerate long ischemic times, precluding preoperative tissue typing [15, 16], Yet, several retrospective studies have found relationship between HLA matching (particularly at the HLA-B and HLA-DR loci) and graft survival in lung transplant recipients [17–20].

While there is insufficient time for tissue matching, all recipients and prospective donors are screened for preformed

Table 3 Contraindications to lung transplantation

Strict contraindications	Relative contraindications
Active malignancy	Bilateral pleurodesis
Significant renal or liver disease	Systemic steroid use >20 mg/day
HIV infection	Morbid obesity
Current tobacco smoking	Severe cachexia
Current substance abuse	Severe psychiatric disorders
Left heart failure/dysfunction	History of medical nonadherence
Active Hepatitis B or C infection	History of substance abuse
Other systemic disease which would limit patient or organ survival	Renal or liver insufficiency
Other lung disease which could recur in transplanted lung	Airway infection with *Aspergillus* or *Scedosporium*
	Airway infection with pan- or multi-drug resistant bacteria
	Spinal fusion
	Severe scoliosis
	Short-gut or severe malabsorption

Fig. 1 Lung allograft

antibodies or percent of reactive antibody (PRA). A recipient's PRA level > 25 should trigger a prospective specific crossmatch between the donor and recipient. A positive specific crossmatch suggests anti-donor circulating antibodies that could lead to hyperacute rejection of the allograft. Hence, a positive prospective crossmatch usually leads to cancellation of the transplant for that proposed recipient.

Strict contraindications to lung donation include active malignancy, positive HIV status, hepatitis B or C antibodies, sepsis/bacteremia (e.g., rabies), significant tobacco use, active malignancy, prolonged severe hypotension or cardiac arrest, or deceased donor age >60 years. Recently, there have been several publications on the use of "extended criteria" for donors, such as use of donor lungs that have radiological infiltrates, PaO_2<300 mmHg on FiO_2 1.0 or history of disseminated intravascular coagulation [21–25].

If the donor organ is found to be acceptable after meeting functional and physiological criteria, then it is essential to minimize damage from ischemic–reperfusion injury. This injury is related to the disruption of homeostatic mechanisms in monocyte and endothelial cells caused by reactive oxygen species. Receptors for leukocyte adhesion molecules are upregulated, and leukocyte chemotactic factors are released. This cascade leads to inflammation and then cellular injury. Antegrade and retrograde flush using ice-cold saline or crystalloid flush solutions (e.g., Euro-Collins, University of Wisconsin and Cardiosol), inflation using 100% oxygen, and maintenance of hypothermia to reduce the allograft metabolic demands are methods employed to reduce allograft cellular injury.

Lung transplant surgery

After being notified that suitable lungs may be available for transplantation, the transplant candidate travels to the transplant facility. While awaiting confirmation of organ acceptability, the patient is prepared for surgery. Whether

Table 4 Lung transplant procedures

Single lung
Double lung
Heart–lung bloc
Lobar lung transplant
Split lung
Cadaveric
Living donor lobar
Single
Bilateral

the patient also receives the first doses of immunosuppression medications and/or receives induction therapy before the operating room is program specific. Once the lungs have been inspected by the procurement team and accepted for transplant, then the patient is taken to the operating room for extraction of the diseased lungs.

The thoracic incision depends upon the type of lung transplant to be performed, the patient's primary diagnosis, and the surgeon's experience/preference (Table 4). If there is no prior history of thoracotomy/extensive pleural adhesions, the chest is usually entered through a median sternotomy. If there is a history of previous thoracotomies or cystic fibrosis, then a bilateral anterior thoracosternotomy ("clamshell" incision) is usually performed (Fig. 2). Cardiopulmonary bypass (CPB) may be used for shorter ischemic times and use of leukocyte-depleting filters, although the risk of bleeding, neutrophil activation, systemic inflammation, and reperfusion injury are increased [26–29]. CPB is not necessary if the patient can have selective bronchial intubation.

When the new lungs have been implanted and perfusion has been reestablished, then chest tubes are placed (bilateral tubes, if double lung transplantation). Before chest closure, flexible bronchoscopy is performed to check the anastomoses, and transesophageal echocardiogram is obtained to confirm good venous and arterial flows. The patient remains intubated and on mechanical ventilatory support while they are transported to the intensive care unit.

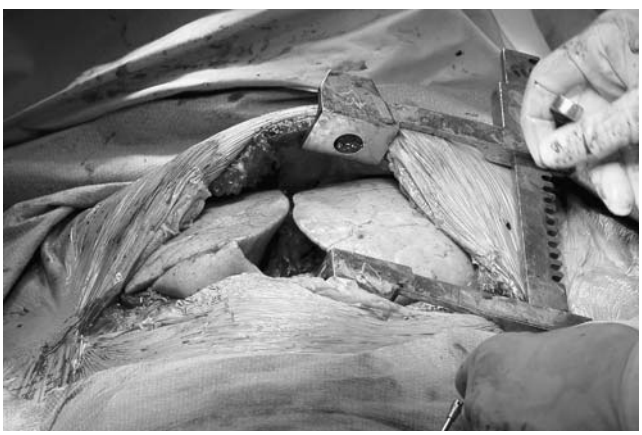

Fig. 2 Bilateral anterior thoracosternotomy ("clamshell" incision)

Postoperative management

Patients generally remain intubated on the ventilator for the first 12–48 h after surgery. Patients have increased pulmonary vascular permeability and resulting pulmonary edema because of the ischemia and reperfusion injury of the new lung as well as from the interruption of the pulmonary lymphatics. Accordingly, the early postoperative care of the lung transplant patient involves maintaining adequate blood pressure/perfusion and gas exchange without sacrificing renal function or prolonging intubation time. This care involves close monitoring of fluid balance and ventilator management. Attention needs to be paid to chest tube output, particularly if it is particularly bloody (which may indicate suture line bleeding) or if the presence of a large air leak. These findings may herald the urgent need to take the patient back to the operating room to repair vascular or bronchial anastomoses.

The number of chest tubes and the length of time they are kept in place is dependent on the patient diagnosis (purulent vs non-purulent lung disease), type of transplant (deceased donor vs lobar transplant), and the size of the patient. The chest tubes are placed to suction until no further air leak is recorded, and the lungs are sufficiently expanded. The amount of suction depends on the type of lung transplant: Deceased donor lung allograft recipients are conventionally on 20 cmH_2O. However, it has been reported that living donor lobar lung transplant patients may experience difficulty with ventilation if the suction is set at that level [30].

The immediate postoperative period is also a time when the patient receives large amounts of immunosuppression medications. While these patients are at increased infection risk, there is no evidence that reverse isolation is more effective than simple hand-washing. Nevertheless, surveillance cultures and aggressive treatment of any suspected infections are required.

New lung transplant recipients are kept intravascularly hypovolemic during the first few days after surgery. Hence, meticulous monitoring of the patient's fluid status is critical. All intravenous medications should be maximally concentrated to avoid excessive fluid intake. Diuretics are part of the routine management of the postoperative lung transplant patient and their use is limited only by hypotension or prerenal azotemia.

The principle goal of postoperative management of the lung transplant recipient is successful early extubation. This goal can be achieved through avoidance of complications such as hypotension, volume overload, infection, or renal dysfunction. Prolonged mechanical ventilation is linked to increase morbidity and mortality.

Complications

Lung transplant complications can occur immediately after surgery or be delayed for several years (Table 5). Strong clinical suspicion and close follow-up of the transplant patient are the strategies to reduce morbidity and mortality in the patients who survive the lung transplant surgery.

Avoiding transplant in patients with elevated PRAs and positive specific cross-match and confirming appropriate ABO matching of donor and recipient have markedly reduced the incidence of hyperacute rejection. Hyperacute rejection is mediated by preformed antibodies in the transplant recipient that recognizes antigens on the donor vascular endothelium. The humoral response triggers activation of inflammatory and coagulation cascades with subsequent development of extensive graft thrombosis and then graft failure and death. While plasmapheresis has been used to ameliorate the effects of hyperacute rejection, the best treatment is prevention of ABO mismatch and transplantation in sensitized individuals.

Early graft dysfunction or failure is a rare but serious complication of the early postoperative period. It has been reported in less than 15% of lung transplant patients and is characterized by poor gas exchange without evidence of infection or rejection [31].

Diffuse alveolar damage is found on biopsy. Possible causes of graft failure, such as pulmonary venous anastomotic stenosis or thrombosis, must be investigated. If the graft failure cannot be reversed, then use of extracorporeal membrane oxygenation [32] and inhaled nitric oxide [33] have been used successfully. If the patient fails to respond to these measures, urgent retransplantation must be considered.

Reperfusion injury, also known as reperfusion pulmonary edema, reimplantation response, or graft injury, occurs unpredictably in some lung transplant patients. It presents as radiographic diffuse interstitial infiltrates usually within 24 h after surgery. The edema can be because of ischemic cell injury, oxygen-derived free-radical-induced lipid peroxidation injury, complement cascade-mediated injury, disruption of pulmonary lymphatics, or early rejection. Histologically, there are neutrophilic infiltrates in the alveolar interstitium and the pervascular tissue spaces. In addition to the radiological findings, associated clinical findings can include progressive hypoxemia and frothy pulmonary edema. Factors that have been linked to reperfusion pulmonary edema are poor allograft preservation/preparation, long ischemic times, and use of CPB. Treatment involves judicious application of diuretics, careful fluid management, and supportive care. It is important to avoid using high inspired oxygen concentrations and increased end-expiratory pressures that may actually worsen the injury. If the clinical manifestations resolve within a few days, there is no long-term impact on pulmonary function. However, a few afflicted patients will go on to early graft failure and death.

Bronchial dehiscence or air leak can occur soon after transplant surgery. Airway anastomotic dehiscence should be suspected whenever there are large air leaks from the chest tubes as well as poor blood gases in the new lung transplant recipient. This complication is usually present on admission to the intensive care unit, although it can occur several days after surgery. The air leak can be because of incomplete bronchial anastomosis or to patchy areas of necrosis secondary to airway ischemia. There have been reports of airway dehiscence in patients who received sirolimus as one of the initial immunosuppression agents [34, 35]. Hence, routine use of sirolimus in the new lung transplant patient should be avoided whenever possible. Treatment of bronchial dehiscence is prompt surgical evaluation and repair.

Vascular anastomotic complications can present clinically as hypotension immediately after completion of surgery. Arterial stenosis, venous thrombosis or stenosis, congestive heart failure, and sepsis should be explored as possible causes of persistent or significant hypotension during the

Table 5 Complication of lung transplantation

Early
Hyperacute rejection
Acute rejection
Demyelinating disease (due to tacrolimus or cyclosporine)
Seizure disorder
Ectopic atrial tachycardia (EAT)
Infection
Bacterial (including atypical mycobacteria)
Viral (CMV, adenovirus, RSV)
Fungal (*Aspergillus*, *Scedosporium*)
Other (PCP)
Late complications
Acute rejection
Chronic rejection/bronchiolitis obliterans
Bronchiolitis obliterans syndrome
Colonic perforation
Hyperlipidemia
Infection
EBV
CMV
HHV6 and HHV9
Diabetes
Hypertension
Renal insufficiency/failure
Post-transplant lymphoproliferative disease
Kaposi's sarcoma
Osteoporosis
Photosensitivity

immediate postoperative period. Thrombus formation at the left atrial anastomosis suture line or in the pulmonary veins is a devastating complication of the new lung transplant recipient [36]. Pulmonary vein thromboses can embolize to the systemic circulation and cause fatal cerebral emboli [37]. Transesophageal echocardiography should be employed to evaluate the vascular anastomoses and should be compared to the intraoperative studies.

Airway clearance is hampered in the new lungs because of denervation (leading to depressed cough reflex) and to mechanical impairment to mucocilliary clearance secondary to the interruption at the anastomosis site. Poor mucociliary clearance leads to progressive atelectasis, pneumonia, and hypoxemia in the lung transplant patient. Treatment involves aggressive chest physiotherapy, incentive spirometry, aerosol bronchodilators, and patient exercise.

Ischemic injury and bacterial or fungal infection of the airway can lead to bronchial stenosis. The incidence of airway complications is more frequent in pediatric lung transplant recipients, with an estimated range from 9% up to 27% in published series [38–40]. The bronchial stenosis can occur as an early and as a late complication of lung transplantation. Symptoms may be absent or minimal in mild stenosis. Wheezing and dyspnea with hypoxemia will develop with progressive narrowing of the anastomotic site. There may be diminished breath sounds on the effected side or audible wheezing on auscultation. Most bronchial stenoses are secondary to progressive fibrosis and narrowing at the anastomosis site, but other causes are hematomas, "telescoping" of the bronchus during surgical implantation, and infection (particularly with *Aspergillus*). Diagnosis can be established by bronchoscopy with airway cultures. Airway infections should be treated aggressively with appropriate antimicrobials. Extrusion of sutures can predispose the transplant patient to chronic/recurrent airway infection, and so, these sutures should be removed. If significant stenosis is found, bronchial dilatation is recommended. Stent placement is indicated only if the stenosis is too extensive to be effectively treated with serial bronchial dilatations.

The risk for serious infection in lung transplant patients starts in the perioperative period. Infection is the major cause of morbidity and mortality during the first 6 months after transplant surgery [41]. Primary sources of the infection can arise from the donors or from the transplant recipients themselves. Denervation of the new lung, immunosuppression agents, impaired mucocilliary clearance, interruption of bronchial and lymphatic circulations, and impaired recruitment of antibody-forming cells in the transplanted lung all combine to increase both the risk of acquiring infection and the severity of the infection once it is acquired [42, 43]. Prophylactic antimicrobials against bacteria, viruses, and fungi are used in most transplant programs, but the regimens vary widely between centers. Antimicrobial treatments should be given perioperatively based on donor cultures and most common hospital pathogens. However, unusual bacterial infections (*Bordetella bronchiseptica, Nocardia, Clostridium difficile,* etc.) should always be suspected in these immunocompromised patients. Prophylaxis against *Pneumocystis jiroveci* (previously *P. carinii*) is routine in almost all postoperative lung transplant regimens.

Respiratory viral infections can be relatively mild to life threatening in the transplant recipient. While human herpes viruses (particularly HHV6), Epstein–Barr virus (EBV), and adenovirus cause significant morbidity and mortality, cytomegalovirus (CMV) remains the most commonly encountered serious viral infection in lung transplant patients. Onset of CMV pneumonitis after lung transplant is reported to have a strong correlation with subsequent development of bronchiolitis obliterans, which in turn leads to graft dysfunction and death. The highest risk for CMV pneumonia is in seronegative patients who receive lungs from seropositive donors. This increased risk persists even when the seronegative lung transplant patients receive aggressive prophylaxis.

Fungal or mold infections are less frequent than bacterial and viral infections in the lung transplant recipient. However, fungal infections carry the highest mortality risk. The most common fungal infections are *Aspergillus* and *Candida* sp. However, *Coccidiomycosis*, *Histoplasmosis*, *Scedosporium*, and even *Candida* sp. are not uncommon and can cause life-threatening illness in the immunosuppressed transplant patients.

Patient education (hand-washing, etc.), immunization updates, and aggressive monitoring/surveillance studies can help reduce infection risk. Frequent consultation with infectious disease specialists is often necessary. It is often difficult to differentiate between pneumonia and acute rejection in the lung transplant patient. While it is important to treat acute rejection, inadequately treated pneumonia or sepsis can result in death within only a few hours. Hence, aggressive antimicrobial therapy should be started immediately upon any suspicion of infection in these patients.

Like infection, organ rejection risk begins at the time of transplant surgery and remains high for the life of the graft and recipient. Lung transplant patients have a higher incidence of rejection than isolated heart, liver, or kidney transplant patients. In fact, early studies of heart–lung patients reported a much higher rate of rejection of the lungs rather than the heart in the same recipient [1]. Rejection can be classified as hyperacute (see above), acute, or chronic. Histological grading of pulmonary rejection is based upon the 1996 published guidelines produced by the Lung Rejection Study Group [44]. The grades are based on the intensity of cellular infiltration and the presence or absence of eosinophilic hyaline fibrosis. T

cell lymphocytes are believed to be the primary effector cells of acute rejection. Acute rejection is diagnosed by both clinical and histopathological criteria. While histological examination of a lung biopsy is the gold standard for the diagnosis of acute rejection, its sensitivity is dependent on the number of biopsies obtained and the experience of the pathologist/reviewer.

Lung transplant recipients are at high risk for acute cellular rejection within the first few months after undergoing transplant surgery. There are several hypotheses for this increased risk including the extensive pulmonary vasculature with a large population of immunologically active cells (macrophages, lymphocytes, dendritic cells) as well as the fact that the lungs are exposed to antigens from the external environment. Clinical signs of acute rejection are similar to those of infection or reperfusion injury. Patients can be asymptomatic or have a mild drop in arterial oxygenation, new onset or increase in radiological lung infiltrates, development of pleural effusion, and may even have a low-grade fever. Bronchoscopy with transbronchial biopsy should be performed in all stable lung transplant recipients who have a significant drop in their expiratory flow rates or who develop new radiological infiltrates. At least five biopsy specimens are taken from each lung allograft along with bronchoalveolar lavage [45]. Many centers perform scheduled surveillance biopsies of the lung allografts. They report occult rejection or infection in 17% to 25% of transbronchial biopsies on asymptomatic lung transplant patients. This rate of positive biopsy specimens increases in symptomatic patients, with a cited incidence of 50% to 72% of biopsy specimens with either rejection or infection [46]. Histologic findings of acute rejection show lymphocytic perivascular infiltrates that extends into the interstitium with increased severity of rejection. The importance of detecting and treating acute rejection has led to efforts to develop noninvasive alternatives to transbronchial biopsy. High-resolution computerized tomography (HRCT) has been used to detect acute lung rejection. There are reports of "ground-glass" densities on HRCT that have a sensitivity of 65% for detecting lung rejection [47].

After infection has been eliminated as the primary cause of the clinical changes, use of pulse steroids is the usual treatment. The most acute rejection episodes, if caught early, respond favorably to conservative therapy. If the rejection episode does not respond (persistent lung infiltrate, no improvement in expiratory flow rates, etc.) to steroid therapy, then other treatment options include use of OKT3 monoclonal antibody or antithymocyte globulin (ATGAM). While acute rejection is not a significant cause of death for lung transplant recipients, early and more numerous episodes of acute cellular rejection are associated with higher risk of developing obliterative bronchiolitis (OB).

OB is the major obstacle to successful long-term outcome of lung transplant recipients. It is a form of chronic rejection that was first noted in heart–lung transplant patients and then was found to also occur in isolated lung transplant recipients [48]. It has been reported that 70% of deceased-donor heart–lung and lung transplant patients have signs of OB by the fifth postoperative year [49]. There is a lower incidence of OB in living donor lobar lung transplant recipients that seems to be associated with shorter ischemic times compared to deceased donor lung transplant patients at the same facility [50]. Nevertheless, OB occurs in all types of lung transplantation. Transbronchial biopsy is the "gold standard" for the diagnosis of OB. The sensitivity of the transbronchial biopsy to diagnoses OB varies greatly and is dependent with the number of specimens taken from each allograft. The current recommendation is for at least five biopsy specimens from each allograft [51]. However, OB is not uniform throughout the allograft, and a transbronchial biopsy can easily be falsely negative. The small airways are the chief locations of OB. The airway lumens of the small airways (terminal and respiratory bronchioles) are partially or totally obliterated by dense eosinophilic submucosal fibrotic tissue. Clinically, this obliteration of the small airways causes lower oxygen saturation and an increase in airways obstruction. Patient symptoms are nonspecific at the onset of OB, with nonproductive cough and mild dyspnea as the most commonly reported changes. As there is a high risk for false negative transbronchial biopsies for OB, a standardized formulation for clinical diagnosis of OB was developed by the International Society for Heart and Lung Transplantation. Lung transplant patients with a decline of 20% or more in their FEV_1 from baseline and who are without evidence of active infection are diagnosed with bronchiolitis obliterans syndrome (BOS) irrespective of pathological confirmation of OB [51]. The etiology of OB is suspected to be injury of the bronchial epithelium by infection (particularly CMV), chronic inflammation, and immunological mechanisms [24]. These factors cause airway epithelial damage and subsequent exaggerated healing response. There is also increased expression of major histocompatibility class II antigens in the bronchial epithelium. Early and frequent episodes of acute rejection along with detection of lymphocytic bronchitis and bronchiolitis have been found to be linked to the later development of OB [52]. There is no effective treatment for OB. Current management of OB is based on prevention and early detection. Lung transplant patients who experience a drop in their expiratory flow rates without identified infection or other causes should be suspected of having onset of OB or BOS. Augmentation of immunosuppressive therapy is the chief therapy for BOS. Although the pulmonary function tests may stabilize after augmentation

of immunosuppression medications, most of the lung transplant patients with BOS or OB do not have significant improvement. Sadly, the median survival of lung transplant patients is 3 years after diagnosis of BOS or OB. This mortality is caused by relentless disease progression as well as by the increased infection rate associated with augmented immunosuppression. Retransplantation is the only treatment option for advanced OB with respiratory failure. While survival after retransplantation for OB is better than for other retransplant reasons, the survival is worse than for those who undergo first-time lung transplant.

Post-transplant lymphoproliferative disease

Post-transplant lymphoproliferative disease (PTLD) is a poorly differentiated B cell lymphoma that occurs most frequently with new onset EBV infection. The solid tumor can present as a mass in the lung allograft as well as in the tonsils, adenoids, intestinal tract (in the Peyer's patches), as well as in the central nervous system. Highest risk for PTLD is in those EBV naive patients who get EBV infection within the first year after transplant, particularly within the first 6 months [53]. In addition, tacrolimus immunosuppression is also associated with higher PTLD incidence. Early detection of PTLD improves prognosis. Up to 50% of PTLD cases present with fever, pharyngitis, and/or adenopathy. Finding an asymptomatic lung mass on chest radiograph or the recurrent symptoms of abdominal pain/constipation, weight loss, anemia, dysphagia, or snoring should be more fully evaluated with a computerized axial tomography study with contrast. Whenever possible, biopsy and cytological examination of the mass/lymph nodes should be performed. Treatment usually consists of reduction in immunosuppression. If there is no improvement in tumor size, then use of rituximab or other chemotherapy should be started.

Outpatient clinical follow-up

After hospital discharge, patients are seen frequently by their transplant team in the outpatient setting. The clinic intervals and length of routine follow-up by the transplant team varies by transplant center and clinical condition of the patient. Diagnostic studies, to include assessment of immunosuppression drug levels, serum creatinine, liver enzymes, lipid profile, pulmonary function tests, and chest radiograph, should be obtained at regular intervals. Each routine transplant clinic visit should include the above laboratory studies as well as a physical examination with vital signs (particularly blood pressure and oxygen saturation recording) and a review of the patient's medications. As medical nonadherence has a significant negative impact on patient survival, it is important to monitor for any signs of patient noncompliance. The warning signs of patient medical nonadherence are: widely fluctuating immunosuppression blood levels, missed appointments, poor patient follow-up, and patient depression.

The lung transplant recipient has frequent transplant clinic visits during the first 6–12 months post-transplant. Thereafter, they will be followed by their referring physician for routine non-transplant medical care. Therefore, it is important that the lung transplant patient continues outpatient follow-up by the referring medical team soon after hospital discharge. Explanation and listing of the patient's transplant medications and dosing regimens and monitoring must be transmitted to the primary and referring physician. Frequent and open communications between the transplant team and the referring physician (via telephone, fax, copies of clinic notes) are important factors that have a significant impact on the long-term outcome of the transplant patients.

Conclusions

Lung transplantation continues to be a treatment option for adults and children with advanced lung disease. The technical surgical challenges along with the complex medication regimens and numerous possible complications mandate a medical care team whose members can communicate clearly with each other as well as with the transplant patient and family members. This joint effort, along with continued research into xenotransplantation, stem cells, chimerism, and development of less toxic but effective immunosuppression medications, will help us move forward in improving survival and quality of life for our lung transplant patients.

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