Medical Complications in Lung Transplant Recipients with Pulmonary Fibrosis

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Abstract
Lung transplantation is a therapeutic option for selected patients with severe interstitial disease who continue to have progressive clinical deterioration. There is a survival advantage for selected patients who undergo transplant, but it primarily improves quality of life after transplantation. Unfortunately, patients with IPF have worse outcomes following lung transplantation due to various factors. This review article will describe several common post-operative complications including anastomotic complications, allograft dysfunction, cardiovascular complications, thromboembolic phenomenon, renal failure, neurologic complications and complications related to the native lung in the single lung transplant recipients.

Keywords: Lung transplantation; Pulmonary fibrosis; Complications

Introduction
To date, all the medical therapies evaluated for patients with Idiopathic Pulmonary Fibrosis (IPF) have had no effect on the natural course of the disease. Lung transplantation is a therapeutic option for selected patients with severe interstitial disease who continue to have progressive clinical deterioration. Through June 30, 2011, there have been 39,835 lung transplants performed worldwide [1]. Worldwide, pulmonary fibrosis is the second most common indication for lung transplantation. Unfortunately, the 5-year survival for patients with IPF is the lowest compared to patients with other lung ailments requiring lung transplantation (Chart 1).

As more patients are being transplanted and living a significant distance from the transplant center, more physicians without specific training in transplantation are encountering visits by these patients. To ensure appropriate and timely care for lung transplant recipients, there needs to be increased awareness of common potential complications after lung transplantation. This review article will describe several common post-operative complications that may arise.

Types of Transplant Procedures
Any of four surgical options are available to patients needing lung transplantation; Single Lung Transplant (SLT), Bilateral Sequential Lung Transplant (BSLT), Living Lobar Transplant and Heart-Lung Transplant (HLT). Since the mid 1990s, the number of BSLT has consistently increased for all the major underlying disease categories. This is equally true for recipients with pulmonary fibrosis; rates rose from 20% in 1998 to 50% in 2010.

When viewing the survival rates according to procedure type, BSLT appears to be better than SLT. These survival differences may be influenced by clinical factors such as age, underlying lung disorder, experience of lung transplant center, recipient co-morbidities and characteristics of procured donor allograft [1]. The survival advantage may be more apparent in the in the later years of lung transplantation. The peri-operative mortality has been shown to be higher in the BSLT recipients; 1-month mortality 21% for BSLT versus 10% for SLT [2]. Conditional half-lives (patients surviving at least 1 year) are 9.4 years for BSLT versus 6.5 years for SLT. Short-term and long-term survival rates are also significantly related to recipient age. Patients less than 50 years of age have a 1-year survival of 80% compared to 72% in patients greater than 65 and a 5-year survival of 56% compared to 37% respectively.

Survival comparisons within diagnoses are the lowest in the COPD and IPF groups (6.8 years) compared to other diagnoses (CF 10.4 years; PAH 10.0 years; sarcoidosis 8.6 years; alpha-1 antitrypsin deficiency 8.6 years). Survival did not differ between procedure types in patients with idiopathic pulmonary fibrosis [3]. Improvements in lung respiratory mechanics and an enhanced pulmonary reserve have been proposed reasons for the survival advantage in recipients with BSLT [4]. Lung function assessments; however, are similar between BSLT and SLT recipients. The mean vital capacity before transplantation is approximately 40-45% of predicted. This value increases to 65% within

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3 months following single lung transplantation [5]. Improvements in the lung functions continue for up to one year. On the first anniversary, mean forced expiratory volume in one second (FEV₁) is approximately 2.00 L in SLT recipients compared to 2.25 L in BSLT recipients [6].

**Immunosuppression Therapy**

Acute rejection rates are extremely common in the first year after lung transplantation with approximately 30-40% of recipients having at least one episode in the first year after transplant [1]. Standard triple drug immunosuppressive agents are prescribed to minimize this risk. Appropriate dosing must balance the benefits of preventing rejection with the risk of infection. The regimen typically includes prednisone, an antimetabolite (azathioprine or mycophenolate mofetil) and a calcineurin inhibitor (tacrolimus or cyclosporine). Although these medications have unique side effects, the cumulative dose or degree of immunosuppression predisposes individuals to opportunistic infections, malignancies, renal failure, post-transplant diabetes mellitus, hypertension and dyslipidemia. Table 1 reviews common drug interactions that can alter clearance or therapeutic drug levels.

**Allograft Parenchymal Abnormalities**

The lung allograft is subject to a variety of insults resulting in various parenchymal abnormalities. They are broadly classified as infectious and non-infectious in etiology. Infections are the leading cause of morbidity and mortality in the first three years of transplantation [1]. Bacterial pathogens are predominantly implicated, but fungal and viral infections, are also of great concern (particularly Aspergillus and cytomegalovirus).

Unfortunately, radiographic pulmonary parenchymal abnormalities can be nonspecific (Figure 1). Bacterial and fungal infections can be difficult to discern as radiographic features can include consolidation, ill-defined nodules, and cavitation and ground glass opacifications. Viral infections, particularly CMV, may have normal radiographs or show ground-glass attenuation, micronodules, reticulonodular opacities, and/or consolidation. To confound the diagnostic challenges, radiographic features of Acute Cellular Rejection (ACR) can present similar to any of the previously mentioned complications. ACR radiographic features can appear as normal radiograph, ground-glass opacities, consolidation, nodules, alveolar opacities, a new exudative or increasing size of pleural effusion (seen in 43% of patients) [7,8].

As a result of the lack of specificity of imaging studies, broad-spectrum antimicrobial therapy is often instituted in the acutely ill lung transplant recipient. One must maintain a broad infectious disease differential given the triple drug immunosuppression when considering treatment options. Additionally, as acute rejection is on the differential, obtaining a definitive diagnosis is mandatory. Clinical correlation and transbronchial biopsy is generally indicated for obtaining the diagnosis. Infections and number of acute cellular rejections contribute to a higher risk of developing chronic rejection.

**Primary Graft Dysfunction (PGD) accounts for the main cause of death within the first 30 days following lung transplantation (1).** The underlying diagnosis of fibrotic disease is not predictive of developing PGD (restrictive disease with PGD 22.1% versus without PGD 20.3%) [9]. More recently, it has been demonstrated that patients with IPF and associated pulmonary hypertension have a higher incidence of developing PGD [10]. They found a 1.64 increase in the odds of developing the severe form PGD (grade 3) for each 10 mmHg increase in the mean pulmonary artery pressure.

Prompt diagnosis and therapy may contribute to a lower incidence of chronic allograft rejection. Chronic allograft rejection has been observed...
as Bronchiolitis Obliterans Syndrome (BOS) or Restrictive Allograft Syndrome (RAS). BOS usually presents as progressive airflow limitation noted on Pulmonary Function Testing (PFT). Patients are classified into different grades depending on the severity of airflow limitation relative to their best post-transplant FEV1. Typical radiographic appearances include a mixture of hypo- and hyperattenuation (mosaic attenuation) regions produced by air trapping and decreased peripheral vascularity, subsegmental atelectasis and bronchiectasis (Figure 2) [8]. Features of RAS include upper lobe fibrosis. Radiographic features include reticulonodular opacities, traction bronchiectasis, honeycombing, interlobular septal thickening and loss of lung volume (Figure 3). Unlike the obstructive airflow limitation previously described, these patients have restrictive physiology on PFTs [8,11].

The presence of BAL eosinophilia and neutrophilia, airway infection colonization and acute cellular/lymphocytic bronchiolitis episodes are risk factors to develop both BOS and RAS [12]. The underlying disease or ILD does not appear to influence the development of one form of chronic allograft rejection (24% BOS and 20.8% RAS).

Augmenting immunosuppression or altering medications within therapeutic classes has been advocated when patients develop chronic rejection. There is clearly a small subset of patients who may respond to this therapy, however, it does increase the risk of reemerging opportunistic infections and development of malignant processes. This must be carefully considered when pursuing this approach to treatment of chronic rejection with increased immunosuppression. One alternative therapy for BOS that is becoming more routinely used is chronic azithromycin treatment. Several small series as well as one prospective, randomized, double blind, placebo-controlled trial have suggested a potential benefit for the use of azithromycin in lung transplant recipients [13-15]. This benefit is for both the prevention of development of BOS, as well as successful treatment for a subset of patients who have already developed BOS. Although the mechanism for the positive effect of azithromycin is not well elucidated, it is believed that the drug's anti-inflammatory properties are likely the cause. Chronic azithromycin therapy appears to be well tolerated although there is an increased risk of gastrointestinal side effects, QTc prolongation and auditory disturbances. In addition, the potential effects of antimicrobial selection are not well understood. Clinicians should be aware that this medication is often taken chronically and ensure this is considered when choosing antibiotics for an acute respiratory infection.

**Anastomotic Complications**

**Airway**

Currently, the bronchial anastomosis is created in an “end-to-end” fashion without an omental wrap. Bronchial artery circulation is lost during the harvesting and not routinely reestablished in the implantation process making the donor bronchus and anastomosis dependent solely on the poorly oxygenated pulmonary artery rendering the area to be ischemic. Early complications (<3 months) from ischemia include necrosis and wound dehiscence. During the healing and remodeling phase, typical complications are airway stenosis, granulation tissue formation and malacia which can occur later (>3 months). Graft rejection, immunosuppression, and bronchopulmonary infections, particularly bacterial and fungal organisms, have also been associated with airway complications. These lung transplant related airway complications occur in up to 30% of patients [16,17]. Management strategies include laser photoresection, cryoablation, airway dilation and silicone or self-expandable metallic stents. The stents are generally placed when respiratory symptoms ensue and are refractory to the other mentioned modalities (Figure 4). Although most patients benefit with improvement in symptomology and lung functions, complications can arise from this therapeutic intervention as well. Mucus plugging, obstructive granuloma, fracture of the stent, migration and infectious colonizations are routinely assessed.

**Vasculature**

Vascular anastomotic complications are relatively uncommon, but have a high morbidity and mortality associated with it. Pulmonary arterial stenosis is more common, whereas stenosis at the atrial cuff and pulmonary vein are rare. When it occurs, this complication is generally early following transplantation [18]. Symptoms include dyspnea, cough, increasing oxygen requirement, persistent elevation in pulmonary artery pressures and pulmonary edema. We present a case of a 67 year-old man who developed dyspnea, hypoxemia and hypercapnea 3 months following a single lung transplant for IPF. Investigations indicated a pulmonary artery stenosis (Figure 5).

Potential contributing factors for the development of pulmonary artery stenosis includes small chest wall size, small recipient artery and difficulty accessing the vessel thereby causing stenosis or kinking of the vessel and the anastomotic site. Diagnostic strategies include utilization of a quantitative perfusion scan, CT pulmonary angiogram
Complications of Native Lung Disease in Single Lung Transplant Recipients

Clinicians should be mindful that patients’ native lung disease progression is not halted with the contralateral lung transplantation despite triple drug immunosuppression. Recipients are still at risk for progression of disease and related complications arising from the native lung. The average percentage of native lung ground glass opacification or fibrosis remains unchanged or increases for the majority of single lung transplant recipients with IPF [19]. Annually, IPF patients are noted to lose 10.8% of native lung volume and an 11% increase in fibrosis for the first four years following SLT [20]. At the time of transplantation, 52% of the native lung had evidence of fibrosis, compared to 92% at four years.

Typical complications reported in IPF patients include bacterial or fungal bronchopulmonary infections, pneumothoraces, retention of secretions causing bronchial obstruction and atelectasis [21]. In addition, acute exacerbation of IPF is being increasingly recognized. This is an abrupt worsening of underlying lung disease potentially evoked by a pneumothorax, pulmonary infection or embolism [22]. Bronchogenic carcinomas have been reported at higher rates in single lung transplant recipients. Significant contributing risk factors include advanced recipient or donor age, smoking history (>60 pack years), and COPD or IPF as the underlying lung disease [23].

Cardiovascular Complications

During lung transplantation, a cuff of the donor atrial cuff surrounding the pulmonary veins is sewn into the recipient atrium. This incision should technically block (ablate) electrical conduction between the pulmonary artery and atrium and reduce the risks of supraventricular tachcardias (atrial flutter and fibrillation). Nonetheless, 20–46% of lung transplant recipient develop post-operative atrial arrhythmias primarily on the second to fourth post-operative day, but can develop up to six weeks following surgery [24,25]. Significant risk factors include prior history of coronary artery disease with greater than 50% vessel stenosis, number of post-operative vasoressors and inotropes, age greater than 50 years, presence of an enlarged left atrium, undergoing concurrent Coronary Artery Bypass Graft (CABG), having a high sympathetic tone, and being diagnosed with IPF as the underlying lung disease (55.9%). The higher atrial arrhythmias prevalence in IPF patients may be related to older recipient age (age-related structural heart disease) and a more technically challenging operation (underlying parenchymal fibrosis and adhesions) [24].

The general approach to treatment is similar to patients in the general population as they have risks for hemodynamic instability, embolic cerebral vascular accidents and increased mortality. It is imperative to restore normal sinus rhythm after lung transplantation. Patients poorly tolerate the consequences of shortened chamber filling, particularly lung allograft congestion. Treating these arrhythmias can be challenging. Combination pharmacological therapy has been required to restore normal sinus rhythm. Beta-blockers, amiodarone or calcium channel blockers are the drugs of choice. Approximately one-third of patients may require electrical cardioversion. Calcium channel blockers should be used judiciously with an understanding of the potential drug/drug interaction with calcineurin inhibitors and ensure appropriate drug levels are maintained. Although pharmacological agents can easily control the rate or rhythm, the clinical outcome for patients with atrial arrhythmia are worse compared to those without it. Patients with atrial arrhythmias have a higher likelihood of hospitalization and overall survival is decreased. The 1-year survival for patient without atrial fibrillation is reported to be 90% compared to 70% [24].

Thromboembolic Disease

The incidence of Deep Vein Thrombus (DVT) and Pulmonary Emboli (PE) in the lung transplant population occurs in up to 29% of recipients. Of these events, almost two-thirds will develop in the first year of transplantation with 20% of these occurring within the first month. Clearly, reduced mobility from functional limitations and recent surgery are risk factors; however, we also know that inflammation inhibits anticoagulant factors [26,27]. Other risk factors include increased age, episodes of pneumonia, male gender, diabetes mellitus, utilization of cardiopulmonary bypass and, in particular, an underlying disease of IPF [28-30]. Most of the pulmonary emboli occur within the allograft (86%) [29,31].

Postulated mechanisms include the thrombogenic surface of the vasculature anastomosis and increased perfusion to the allograft, along with a lower pulmonary vascular resistance in single lung transplant recipients. The native lung, however, is still not exempt from developing a PE [29]. The median time of developing PEs are 5.8 months following lung transplantation. Some centers advocate prophylactic anticoagulation for up to 6-9 months. Fortunately, the majority of patients tolerate an embolic event from the hemodynamic parameters even in the presence of large clot burden. In addition, the clot burden has not translated into any loss of lung allograft functions [32].

Renal Failure

A quarter to half of all lung transplant recipients develop some degree of renal dysfunction within the first year of transplantation [1,33]. Patients predominantly develop chronic kidney disease stage III (glomerular filtration rate 30-59 cc/min). The accumulation of drug-induced nephrotoxicity (calcineurin-inhibitors and anti-viral agents), hypertension, diabetes mellitus and dyslipidemia are common etiologic factors. Early post-operative insults will also increase the likelihood of chronic renal failure. Such factors include; hypotension, hemodynamic...

Figure 5: 62 year old male 3 months following a right single lung transplant for IPF developed dyspnea and hypoxemia. CT angiogram of the chest found focal web-like or shelf-like stenosis in the right pulmonary artery at the level of the anastomosis. The pre-stenotic segment measured 3.1 x 2.9 cm. At the level of stenosis the lumen narrowed to 1.1 x 1.0 cm. Distal to the stenosis, the artery measured 2.6 x 2.2 cm and/or transesophageal echocardiography. Treatment options include observation, re-operation or angiography with or without stent deployment.
shifts, reduced kidney perfusion and the aggressive use of diuretics. The development of chronic kidney disease leads to a four to five-fold increase risk of death [34]. Older recipient age (greater than 50 years) predicted a shorter period to the development of renal dysfunction [33].

Management strategies to reduce the risk of renal failure include optimizing blood pressure control, dyslipidemia, and diabetes mellitus. Other challenges include the individual tailoring of administration of antiviral agents and balancing the calcineurin inhibitor therapeutic drug levels between renal failure and risks of allograft rejection. On occasion mTOR inhibitors (eg. sirolimus) have been used to reduce calcineurin inhibitor levels or adjunct therapy as a “calcineurin inhibitor sparing” agent [35]. Less than 3% of patients will have progressive renal failure to the point where hemodialysis is required. Considerations are also taken into account for kidney transplantation, but only 0.5% of all patients with renal failure ever receive it [1].

Neurologic Complications

Lung transplants recipients are at risk of developing some form of neurologic complications, such as encephalopathy, headaches, tremors, peripheral neuropathy or critical care myopathy, central nervous system infections, seizures and cerebrovascular accidents [36,37]. Hyperammonia has also been recently linked to etiology of patient confusion [38,39]. Interestingly, this complication may not be a drug class effect. Some individuals experience these signs and symptoms with tacrolimus, but resolve while on therapeutic dose of cyclosporin and vice versa.

Recipients appear to be most susceptible in the first year following transplantation. The majority of these complications have been primarily linked to the adverse events related to older recipient age, undergoing BLST, Calcineurin Inhibitors (CNI), tacrolimus and cyclosporine, or infections. The median recipient age was 50.8 years in 2008 with substantial increased number of transplants being performed in patients over the age of 60 [1]. Although the underlying lung disease could not predict the development of neurological complication, IPF patients are generally older and should be closely monitored. Diagnostic work-up is similar to the general population. When reviewing brain MRI and CT scans, it should be known that bilateral white matter abnormalities (leukoencephalopathy) in the posterior region have been noted and associated with calcineurin inhibitor neurotoxicity [40].

Conclusion

Lung transplantation is a viable therapeutic option for patients with pulmonary fibrosis who are refractory to medical therapy. Although the worldwide cumulative survival rates are improving with more recent eras of practice, pulmonary fibrosis patients continue to have the worst survival following lung transplantation. Despite this, there is a survival advantage for selected patients who undergo transplant [41,42]. In addition, quality of life improves after transplantation. The ISHLT registry data shows lung transplant recipients have better general health, quality of life and return to work. 30% of patients are working either part-time or full-time at 1-year with this measure increasing to 50% at 5 years. Multiple other investigators have consistently demonstrated improvements in several aspects of quality of life as well [43-46].

Lung transplantation is not benign however. Transplant recipients are fully informed of significant risks for various complications as outlined within the text. All measures should be taken to reduce risk factors before and after the procedure that can potentially improve long-term outcomes. As more lung transplant recipients receive treatment by physicians outside the transplant institutions, an increased awareness of all the considerations is imperative for these patients.

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