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Chapter
Lung Transplantation in Idiopathic Pulmonary Fibrosis

Ryan Goetz, Nitesh Kumar Jain, Humayun Anjum and Thomas S. Kaleekal

Abstract

Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease associated with a high degree of morbidity and mortality in its more advanced stages. Antifibrotic therapies are generally effective in delaying the progression of disease; however, some patients continue to progress despite treatment. Lung transplantation is a surgical option for selected patients with advanced pulmonary fibrosis that increases their overall survival and quality of life. Changes in the Lung Allocation Score (LAS) in 2005 have resulted in increased transplants and decreased waitlist mortality in this population. Indications for transplant evaluation and listing include the clinical progression of the disease and related mortality risk \( \geq 50\% \) at 2 years without a transplant. Patients with clinically rapid deterioration or acute flares needing hospitalization can be bridged to transplant on extracorporeal support while remaining ambulatory and free from mechanical ventilation.

Keywords: Idiopathic lung fibrosis, IPF, Pulmonary fibrosis, Lung transplantation, Single lung transplantation, Double lung transplantation, anti-fibrotics, Interstitial lung disease, survival, GERD, Acute exacerbation of IPF, ECMO, Immunosuppression

1. Introduction

Lung transplantation is a therapeutic option for selected patients with end-stage lung disease that may improve their survival and provide a good quality of life [1].

IPF is a progressive form of interstitial lung disease with characteristic clinical features, imaging, and histologic findings. Clinical features include progressive dyspnea on exertion, chronic dry cough, and fatigue. Physical exam findings include bilateral Velcro-like crackles, clubbing and in late stages sequelae of secondary pulmonary hypertension. Pulmonary function tests demonstrate restriction in the form of decreased lung volumes and decreased diffusion capacity along with resting or exertional hypoxemia [2]. Though therapeutic medications have been approved for the treatment of IPF, a lung transplant is a surgical option in selected cases. Currently, about 4500 transplants or more are being done yearly across the world, mostly in the United States (US), Europe, and Japan. Of these transplants, nearly 33% have a diagnosis of IPF with a clinical, radiological, and pathological pattern consistent with Usual Interstitial Pneumonitis (UIP). Secondary pulmonary fibrosis from Non-Specific Interstitial Pneumonitis (NSIP) in connective tissue diseases, chronic hypersensitivity pneumonitis, post-inflammatory fibrosis (infections, drugs, toxins, inhalational injuries, radiation), sarcoidosis, and other rare interstitial lung diseases also account for 30–35% of lung transplants making fibrotic lung disease the predominant indication for lung transplantation at most centers in the US.
2. Diagnosis and medical therapies

Along with the clinical features described above, computed tomography (CT) of the chest, preferably high-resolution cuts (≤1.25 mm) with inspiratory and expiratory imaging, is the initial diagnostic choice. The radiological findings on CT are used in correlation with the histologic findings to diagnose IPF. The typical UIP pattern is defined by heterogenous para-septal fibrosis, architectural distortion, reticulation, and honeycombing with a peripheral and lower lobe predominance. These findings have a high positive predictive value for UIP and are diagnostic for IPF when autoimmune and hypersensitivity features are not present. There is no requirement to obtain a surgical lung biopsy due to the increased risk of complications like developing a bronchopleural fistula at the surgical site or setting off an IPF “flare.” Current recommendations are to refer these patients to a transplant center at the time of diagnosis for consideration of the transplant evaluation. “Probable UIP” is the nomenclature used for bilateral reticulation with predominance in peripheral and lower lung fields with traction bronchiectasis but without honeycombing. This is also diagnostic for IPF in older adults and does not necessarily mandate a surgical lung biopsy or cryo-biopsy. In patients without these classic imaging findings or “atypical” cases, referral to an interstitial lung disease center is highly recommended for engaging a multi-disciplinary clinical, radiologic, and pathologic approach to diagnosis and management [2].

A full discussion of therapeutics in IPF is covered in other sections. Non-pharmacologic and pharmacologic therapies are essential in the pre-transplant patient. Non-pharmacologic therapies include supplemental oxygen where indicated, cardio-pulmonary rehabilitation, smoking cessation, and appropriate vaccinations (including influenza, pneumococcal, and now novel coronavirus-19 (COVID-19) [2]. Pharmacology therapy has revolutionized IPF care over the past decade. Nintedanib is a tyrosine kinase inhibitor inhibiting vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF). Pirfenidone is an anti-inflammatory/anti-fibrotic agent with various mechanisms, including inhibiting collagen synthesis with decreased fibroblast activity and decreasing tumor growth factor-beta and tumor necrosis factor-alpha activity. These drugs were initially approved with clinical trials demonstrating stabilization of forced vital capacity (FVC), a common marker of disease progression. More recently, meta-analyses have demonstrated mortality benefits with both agents [3].

3. The natural course of the disease

Before the availability of antifibrotic therapies, the median survival following IPF diagnosis was quite dismal at 3.8 years. While there was considerable variability in the clinical course, many patients experience a decline in their lung function with associated shortness of breath at rest, exertion, and supplemental oxygen dependency. The chronic hypoxic state induces secondary pulmonary hypertension and right ventricular strain, dysfunction, and eventually failure. Acute exacerbations of IPF (AE-IPF) are also a common etiology of morbidity with mortality varying from 50 to 85% with hospitalization [4].

4. Lung transplantation

Lung transplantation is the only curative modality for end-stage IPF with both survival and quality of life benefits. The first lung transplant in humans was performed by J.D. Hardy at the University of Mississippi in 1963 on a patient with lung
cancer [5]. Dr. Joel Cooper performed the first successful single lung transplant in IPF in 1983 [6]. In 2019, a total of 4500 lung transplants were performed, and nearly 33% of these had a primary diagnosis of IPF (UIP pattern), making this one of the most common indications for a lung transplant [1]. Prior to 2005, patients with Chronic Obstructive Lung Disease (COPD) were the most common recipients of lung transplants as the transplant waitlist was based on a queue system with the time of the list as the primary determinant for allocation. Many IPF patients expired while awaiting potential donors on the waitlist. In the US, the Organ Procurement and Transplant Network (OPTN) is the organization entrusted with the responsibility to optimize organ allocation in line with the ethical principles of utility, justice, and respect for persons. In 2005, due to a recognition of high lung transplant waitlist mortality, the LAS system was implemented by the OPTN to optimize the allocation of donor’s lungs with the intent to balance the urgency of transplant need with the post-transplant survival benefit. The clinical parameters, underlying diagnosis of the recipient, and statistical modeling determine the waitlist urgency and post-transplant benefit, thereby generating the LAS for the recipient and the subsequent allocation of available donor lungs. Additional changes in the allocation system were implemented by the Department of Health in November 2017 after a lawsuit in New York challenged the allocation system. The emergency action changed allocation priority from the local Donor Service Area (DSA) to regional priority resulting in patients with the highest LAS within a 250 nautical mile radius of the donor center being eligible for allocation. Before this change, the DSA would offer the donor lungs first to all listed local patients irrespective of their LAS before expanding offers to sicker patients outside the service area. As a result of this change, higher LAS patients in the region are receiving more access to donors’ lungs, and listed IPF patients are benefiting from these changes with an increasing number of transplants [7].

5. Criteria for referral and transplantation in IPF

Conceptually, lung transplantation should be considered in patients with a high risk of death (quantified as >50%) within 2 years if lung transplantation is not performed. High (defined as >80%) likelihood of 5-year survival post-transplant from a general medical perspective (Table 1) [1, 8].

### Indications for Referral
- At the time of diagnosis irrespective of starting antifibrotic therapies
- FVC ≤ 80% predicted or DLCO ≤40% predicted
- Decline in FVC ≥ 10% or decline in DLCO ≥15%
- Decline in FVC ≥ 5% with clinical or radiological progression
- Supplemental oxygen requirements at rest or with exertion

### Indications for Listing
- Decline in FVC ≥ 10% or ≥ 5% with radiological progression or decline in DLCO ≥10% within a 6-month period
- Desaturation to ≤88% on the 6 Minute Walk Test (6 MWT)
- The decline of ≥50 m walk the distance on the 6MWT
- Diagnosis of secondary pulmonary hypertension
- Hospitalization for acute exacerbations or other respiratory complications

Table 1.
Indications for transplant referral and listing [8].
Idiopathic Pulmonary Fibrosis

6. Contraindications to transplant

The International Society for Heart and Lung Transplantation (ISHLT) categorizes contraindications to transplantation as absolute, high risk, and standard risk factors. Absolute contraindications are factors that generally preclude successful lung transplantation. The ISHLT recommends that most transplant centers avoid transplantation in patients with these features, except under “very exceptional or extenuating circumstances.” Importantly, these criteria include patients with severe extrapulmonary organ dysfunction who are not candidates for multi-organ transplants (Table 2) [1, 8].

Next are patients with risk factors associated with high or substantially increased risks. Patients with these features can be considered in centers with experience and expertise in addressing the underlying factors. Lung transplant centers with a higher volume of transplants per year (typically centers ≥40 lung transplants per year) may have better outcomes with these groups of patients. Modifiable risk factors like obesity, malnutrition, deconditioning, treatable infections, coronary disease amenable to stenting or percutaneous interventions, etc., need to be optimized as best possible before listing active for transplantation. If several of these factors are present, the risk factors are multiplicative for the poor post-transplantation outcome (Table 3).

Finally, standard risk factors may predispose patients to poor transplant outcomes in the short and long term. Again these factors are considered to be multiplicative (Table 4) [1, 8].

Social issues:
• Lack of patient willingness/acceptance of transplant
• Limited functional status (i.e., not ambulatory), the poor potential for rehabilitation
• Recurrent non-adherence
• Active substance use (tobacco, vaping, marijuana, IV drug use)

Systemic infections:
• Septic shock
• Active disseminated infection
• Active tuberculosis
• HIV with detectable viremia

Extra-pulmonary organ dysfunction (if not a candidate for multi-organ transplant):
• Renal dysfunction with glomerular filtration rate < 40 mL/min/1.73m²
• Liver cirrhosis
• Acute liver failure
• Acute renal failure (with a low likelihood for recovery)

Other significant illnesses with resultant mortality risk/morbidity:
• Recent cerebrovascular accident
• Malignancy with a high risk of recurrence/death
• Progressive/severe cognitive impairment
• Other severe uncontrolled conditions in which patient is expected to have limited long term survival

Table 2.
Absolute contraindications for lung transplantation [1, 8].
Lung Transplantation in Idiopathic Pulmonary Fibrosis
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Age > 70 years
Cardiac issues include:
• Severe coronary disease requiring coronary artery bypass grafting at transplant
• Reduced left ventricular ejection fraction < 40%

Untreatable hematologic issues:
• Bleeding diathesis
• Thrombophilia
• Severe bone marrow suppression

Significant cerebrovascular disease
Severe esophageal issues, i.e., dysmotility
Re-transplant:
• < 1 year following initial transplant
• For restrictive chronic lung allograft dysfunction (CLAD)
• For AMR as etiology of CLAD

Extra-corporeal support
Hepatitis B or C with detectable viral load and liver fibrosis
Infection:
• Mycobacterium abscessus
• Lomentospora prolificans
• Burkholderia cenocepacia or gladioli

Social issues:
• Lack of understanding of disease and/or transplant despite education
• Poor caregiving plan/social support

Weight: BMI < 16 or > 35 kg/m²
Functionally limited with potential for rehabilitation post-transplant

Table 3.
Relative contraindications or high-risk conditions for transplant.

<table>
<thead>
<tr>
<th>Age 65–70 years</th>
<th>Non-pulmonary organ dysfunction:</th>
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<tr>
<td>Non-pulmonary organ dysfunction:</td>
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<tr>
<td>• Chronic kidney disease with a Glomerular filtration rate of 40–60 mL/min/1.73 m²</td>
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<tr>
<td>• Mild to moderate coronary artery disease</td>
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<tr>
<td>• Severe coronary artery disease amenable to percutaneous intervention prior to transplant</td>
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<tr>
<td>• LVEF 40–50%</td>
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<td>• Peripheral vascular disease</td>
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<tr>
<td>• Severe gastroesophageal reflux disease</td>
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<tr>
<td>• Esophageal dysmotility</td>
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<tr>
<td>• Poorly controlled diabetes</td>
<td></td>
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<tr>
<td>• Bone marrow suppression with thrombocytopenia, anemia, or leukopenia</td>
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<tr>
<td>• Hypoalbuminemia</td>
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<tr>
<td>Connective tissue disease (scleroderma, lupus, inflammatory myopathy)</td>
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<tr>
<td>Retransplant &gt; 1 year for obstructive chronic lung allograft dysfunction (CLAD)</td>
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<tr>
<td>Mechanical ventilation pre-transplant</td>
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Surgical issues:
• Prior pleurodesis
• Previous thoracic surgery

Infections:
• HIV with undetectable viral load
• Scedosporium apiospermum

Frailty
Weight: BMI 30–34.9 or BMI 16–17 kg/m²

Table 4.
Other general risk factors for poor post-transplant outcomes.
7. Listing considerations

7.1 Age

The issue of candidacy for patients with advanced age is controversial in lung transplantation. Historically older patients had worsened outcomes, with multiple case-control studies showing worsened long and short-term mortality in patients over 60 years of age [9]. However, more recently, an increasing number of lung transplants are being performed on older patients, with a database showing that 11.1% of patients being above age 70 from 2006 to 2013. In this study, survival at 1 year was similar in patients in 60s vs. 70s. However, 3 and 5-year survival was worsened in the group in 70s [10]. Successful transplantation has even been reported in an 80-year-old patient [11]. UNOS registry showed similar outcomes up to age 74, but worsened survival between ages 75 and 79. Various complications are more common in patients over 65, including infections, rejection, venous thromboemboli, malignancy, and drug toxicity [12].

7.2 Obesity

Overweight and obese patients (defined as body mass index >25 kg·m\(^{-2}\) and > 30 kg·m\(^{-2}\) respectively) had a higher risk of death post-transplant (15 and 22% higher respectively on the multi-variate analysis) [13]. Weight loss both improves pre-transplant symptoms and post-transplant survival with dose-response improvements [14]. We refer these patients for nutritional counseling and pulmonary rehabilitation. We use a threshold of BMI >35 as an absolute contraindication to transplant.

7.3 Medical frailty

Medical Frailty can be characterized as declining physiologic and functional reserve leading to a general susceptibility to physiologic insults, leading to potentially deleterious outcomes. The prevalence of frailty increases with age. The decline in lean body mass, strength, endurance, balance, walking performance, and low activity are markers of medical frailty [15].

Multiple tools have been developed to assess and quantify medical frailty. Previous work in IPF has utilized the Fried Frailty Phenotype (FFP) score. This score includes 5 components: Unintentional weight loss, exhaustion, slowness, physical activity, and weakness. Table 5 further describes these features. Each component is scored 0 or 1. A score of zero represents the absence of frailty, a score of 1–2 represents pre-frailty status, score \( \geq 3 \) indications frailty. 28% of lung transplant candidates meet the criteria for frailty by FFP. Higher FFP is associated with increased risk of delisting, mortality before lung transplant, and mortality within 1-year post-transplantation. Cardiopulmonary rehabilitation can be helpful to preserve or even improve functional status in patients with end-stage lung disease [16]. It is our practice to refer patients with medical frailty to cardiopulmonary rehabilitation in addition to nutrition evaluation very early in the evaluation process.

7.4 Telomeropathy

Chromosomal telomeres protect against the loss of genetic information in normal cell division. Mutations in telomerase can lead to the shortening of the telomeres. This further leads to cell cycle arrest with associated bone marrow failure,
malignancy, hepatic failure, and IPF. Pre-transplant telomere shortening is associated with earlier age of presentation and progressive phenotype [17]. Leukocyte telomere length < 10th percentile is seen in 25% of sporadic IPF cases and 37% of familial IPF cases [18]. Patients with short telomere length (coined short telomere syndrome) also have been seen to have worsened lung transplantation outcomes with worse survival, shorter time interval to CLAD, and higher incidence of grade 3 PGD [19]. These patients also have a high incidence of cytopenias, especially given that many medications given in the post-transplant period are associated with further bone marrow toxicity (such as mycophenolate, valganciclovir) [20]. Several studies have also demonstrated increased renal impairment and calcineurin toxicity [21, 22]. The current recommendation is that all patients with possible familial IPF be evaluated for signs of telomeropathy with attention to hematologic abnormalities and liver cirrhosis. Our center tests all IPF patients with a strong family history undergoing transplant work-up for telomere length studies based on significant complications encountered in patients with short telomere syndrome. In patients diagnosed with short telomere syndrome, pre-transplant evaluation with hematology to assess baseline bone marrow function, including bone marrow biopsy, liver function assessment, and cirrhosis evaluation with ultrasound elastography, MRI, or even MRI trans-jugular liver biopsy may be required in some patients. Post-transplant therapy modifications in this group, including strategies to preserve bone marrow function by avoiding cell cycle inhibitor-based immunosuppression may be helpful in ensuring long-term success in this group of patients.

8. Cardiac issues

8.1 Coronary artery disease

Coronary artery disease is common in patients with IPF, being common comorbidity in the age group affected by this disease, inflammation, lipid abnormalities, and the impact of disease-specific therapies. Incidence as high as 65.8% has been described in cohorts with left heart catheterization data pre-transplant [23]. Optimization pre-transplant is recommended by cardiologists and cardiovascular surgeons experienced with the transplant process. Percutaneous interventions, particularly in IPF patients, should be discussed in a multidisciplinary manner depending on the understanding of illness related to the IPF, severity of the coronary lesions, and type of intervention, especially the placement of drug-eluting
stents, which may require prolonged dual antiplatelet regimens for several months and complicate the listing or transplant of the patient. There is increasing literature that patients can safely undergo coronary artery bypass grafting and still undergo lung transplantation with equivalent outcomes, although there may be technical limitations. Most of these patients may be eligible only for a single lung transplant (typically right single lung transplant) secondary to the prior sternotomy status, disruption of the left pleural space, and danger of disrupting the bypass grafts [24].

8.2 Left ventricular diastolic dysfunction

In patients with intact LV systolic function by ejection fraction, it is important to evaluate LV diastolic dysfunction. This is defined by evaluating early mitral inflow velocity (E) to early diastolic mitral annular velocity (e prime). In patients with poor echocardiographic visualization, an elevated pulmonary capillary wedge pressure on right heart catheterization or a directly measured elevated left ventricular end diastolic pressure (LVEDP) can also be suggestive. Diastolic dysfunction greatly increases the risk of primary graft dysfunction in the immediate post-operative period and increases the duration of mechanical ventilation post-transplant [25]. Optimization of volume status is essential in these patients.

8.3 Pulmonary hypertension

Secondary Pulmonary hypertension (PH) is common in patients with end-stage IPF. Pulmonary hypertension is defined as a mean pulmonary artery pressure of more than 20 mmHg (decreased from 25 mmHg in most recent guidelines) [26]. One prior study of IPF patients undergoing transplant evaluation found that 49% demonstrated PH (utilizing 25 mmHg as cutoff). PH is associated with lower FVC and a greater need for supplemental oxygen pre-transplant. However, a prior study of UNOS data in IPF showed no difference in mortality post-transplant [27].

9. Gastro-esophageal issues

Gastro-esophageal issues have long been associated with lung disease. There is a strong association between gastroesophageal reflux disease as a major independent risk factor with IPF. In a 2005 study 78 consecutive patients referred for lung transplantation found 63% of patients had GERD symptoms, 72% had a hypotensive lower esophageal sphincter, 44% had prolonged gastric emptying, and 38% at abnormal pH testing [28]. These issues are not limited to patients with symptoms, and testing is recommended in all patients being evaluated for transplant. Post-transplant gastro-esophageal reflux, including intra-esophageal reflux from esophageal dysmotility and potential for micro-aspiration or frank oropharyngeal aspiration, is a major factor in poor outcomes post-transplant with early allograft dysfunction, development of donor-specific antibodies and chronic lung allograft dysfunction (CLAD) [29]. Post-transplant gastro-esophageal issues are associated with worsened outcomes. Patients with GERD post-transplant has been shown to have diminished recovery of FEV1 [30]. Aspiration is closely associated with both chronic and acute rejection, with an increased rate of bronchiolitis obliterans syndrome [31]. Patients with significant reflux should be considered for anti-reflux surgery. Pre-transplant surgery (where tolerated) is associated with trend toward fewer IPF exacerbations [32]. In patients unable to undergo pre-transplant anti-reflux surgery, early post-transplant surgery is associated with preserved lung function in addition to decreased bronchiolitis obliterans and a signal toward improved mortality [33, 34].
10. Pre-transplant work-up

Once a patient is referred for consideration of lung transplantation, further evaluation is undertaken to uncover risk factors and/or contraindications for transplantation.

11. Cardiovascular evaluation

An echocardiogram is obtained with a bubble study to identify structural heart issues, including ventricular dysfunction, valvulopathy, and cardiac/pulmonary shunts. Right heart catheterization is performed, evaluating for pulmonary hypertension, and filling pressures, and cardiac output. Left heart catheterization is performed to evaluate for coronary arterial disease. A baseline ECG is obtained. A peripheral arterial disease evaluation includes carotid ultrasound and ankle-brachial index.

12. Gastro-intestinal evaluation

Given the association of gastro-esophageal reflux with IPF and its association with poor transplant outcomes, a gastro-esophageal workup is pursued even in the asymptomatic patient with IPF. We typically order a modified barium swallow to assess oral pharyngeal function and aspiration risk, a barium esophagram to assess dysmotility, intra-esophageal reflux, hiatal hernias, or esophageal strictures, and a gastric emptying study to assess gastric motility. Further testing based on this initial screen includes formal esophageal manometry and pH probe monitoring. We do not recommend surgical intervention prior to the transplant in these IPF patients. However, protocol-based reassessment of these tests is done 3 months post-transplant for potential early surgical intervention, including fundoplication and hiatal hernia repair.

13. Malignancy evaluation

Age-appropriate cancer screening is ensured, including prostate, breast, cervical, and colorectal. If eligible, lung cancer screening with a low dose CT chest is performed. Patients are counseled regarding skin lesions and referred to dermatology if concerning. Apart from malignant melanoma, other skin cancers are not considered a contraindication to proceeding with lung transplantation. However, depending on the sun exposure, a patient may have had during their lifetime and the burden of pre-existing cancers, this can cause major post-transplant morbidity. Transplant immunosuppression clearly predisposes to increased incidence of new and recurrent skin cancers, rapid rate of growth or doubling time, and higher than expected rate of metastasis compared to the general population [35]. There is also increasing evidence that the use of voricoazole as anti-fungal prophylaxis may be independently associated with skin cancers in the predisposed population [36].

14. Criteria/timing for listing

A decision to list a patient for lung transplantation is a multi-disciplinary effort that should only be undertaken after careful workup and counseling the patient
extensively on the risks and benefits. A multi-disciplinary committee should make this decision with input from both transplant pulmonology, transplant surgery, consultants, social work, physical therapy, and nutrition.

15. Impact of anti-fibrotic therapy on listing

Anti-fibrotic therapy has improved the outcomes for patients with IPF, with initial studies showing a decreased decline in FVC and more recent meta-analyses demonstrating improved mortality [3]. Patients should be starting on these therapies immediately, and they may delay the need for transplantation. Early in their use, there were concerns regarding the impact of anti-fibrotic on wound healing. However, observational studies have demonstrated no impaired wound or anastomotic healing [37, 38]. While the efficacy of anti-fibrotic agents in late IPF with FVC < 30% is not clear, there is no contraindication to continue these drugs through to the transplant if the patient is already on the same. Anti-fibrotic combination therapies with different mechanisms of action for IPF are undergoing clinical trials. There is no current literature evidence outside of anecdotal case reports to justify the use of anti-fibrotic agents routinely after the lung transplant, even in single lung transplant recipients with a native IPF lung. A clinical trial is currently investigating the continuation of Nintedanib following single lung transplantation in IPF (NCT 03562416).

16. Single vs. double lung transplant

The modern growth in lung transplant volume has been largely that of a double lung transplant. In general, double lung transplantation is preferred over single lung with superior long-term outcomes (7.8 years versus 4.8 years) [1]. However, short-term outcomes may favor offering single lung transplantation in elderly and frail patients, as there is typically less ischemic time to the allograft, a shorter ICU stay, hospitalization, and less overall perioperative morbidity [39]. In patients who are candidates for both single and double lung transplants, the current recommendation is to list for both, as there is decreased waiting list mortality, increased transplantation rate, and no difference in 1- or 5-year mortality [40, 41].

17. Management of acute exacerbations of IPF (AE-IPF) in transplant candidates

AE-IPF (colloquially referred to as flares) are frequently observed in patients with IPF and can result in rapidly progressive respiratory failure and death within days. AE-IPF is categorized by increasing hypoxia and dyspnea with bilateral ground-glass opacities and negative infectious evaluation [2]. The in-hospital mortality is above 50–85% for these episodes. Standard empiric therapy for AE-IPF includes corticosteroids, empiric antimicrobials, and supplemental oxygen. However, no therapeutic modality has demonstrated effectiveness in randomized controlled trials. These exacerbations’ exact pathophysiology and mechanisms have yet to be fully elucidated. However, infections, post-operative, drug toxicity, and aspiration have been identified as triggers. More recently, autoantibodies have been identified as a possible trigger of IPF flares. A randomized controlled clinical trial for consisting of plasmapheresis, rituximab, and intra-venous immunoglobulin (IVIG) to reduce auto-antibody burden is currently ongoing [42]. Notably, treatment outcomes are much worse in patients who require mechanical
ventilation, with studies reporting 87–96% mortality [43]. The American Thoracic Society guidelines recommend having a value-based goal of care discussion prior to instituting mechanical ventilation [44]. Notably, mechanical ventilation is a significant barrier to lung transplantation as it predisposes patients to immobility, over-sedation, deconditioning, and ventilator induced lung injury (VILI) [45]. In patients who are listed (preferably) or undergoing evaluation for lung transplantation, the use of veno-venous extracorporeal membrane oxygenation (VV-ECMO) is an attractive therapeutic modality for patients with refractory hypoxemia to avoid mechanical ventilation as a bridge to lung transplantation. Our center has a large amount of experience with ambulatory ECMO to help improve patient conditioning while an acceptable donor organ is found.

18. Mechanical ventilation in the pre-transplant period

Mechanical ventilation is a relative contraindication to transplant. It is associated with several deleterious effects, including sedation and immobility, leading to rapid deconditioning and ventilatory induced lung injury. Additionally, given the high incidence of pulmonary hypertension in this population, the induction period can be associated with high morbidity and even mortality. For these reasons, our center avoids mechanical ventilation where possible in lung transplantation candidates with IPF in an acute flare with high oxygen needs that would typically need mechanical ventilatory support. Instead, we prefer to use a strategy of elective veno-venous ECMO cannulation and maintenance once oxygen needs exceed a FiO2 of 80% on a high flow nasal cannula or non-invasive ventilatory support. This enables us to provide adequate oxygenation and ventilation to the patient while allowing ambulation to avoid deconditioning, nutrition via oral means and lets the patient maintain communication.

19. ECMO as a bridge to transplant

Despite early cohorts showing poor outcomes, ambulatory ECMO has emerged as an attractive option to bridge candidates with poor native lung function to transplant. A recent cohort study demonstrated 59% survival to transplant in those bridged with ECMO and excellent long-term outcomes in those surviving to discharge with 88% 1 year and 83% 3 year survival [46]. Ambulation is one of the greatest benefits of ECMO in the pre-transplant period. The improved oxygenation and physiologic reserve provided by ECMO allow these patients to ambulate to a greater extent. In fact, the above cohort found that ambulation was the only independent predictor of survival to transplantation. A dual lumen right internal jugular cannula is often preferred over femoral cannulation strategies for ease of ambulation. Bi- femoral venous cannulation is not a contraindication to ambulation, and we routinely ambulate patients with femoral cannulas in our center with specific practical safety measures to avoid accidental decannulation or adverse events.

20. Immunosuppression

In the immediate peri-transplant therapy, induction immunosuppression is achieved with high dose corticosteroids and traditionally thymoglobulin; however, basiliximab, an IL-2r monoclonal antibody, is being utilized with increased
frequency. Following the transplant, standard immunosuppression is continued with calcineurin inhibitor (typically tacrolimus), a cell-cycle antagonist (typically mycophenolate mofetil or mycophenolic acid), and low dose prednisone.

21. Post-transplant infections and prophylaxis

Bacterial infections are common peri-transplant, and our practice is to cover prophylactically for 48–72 hours with vancomycin and cefepime. This addressed both gram positives (especially methicillin resistant staph aureus) and more resistant gram negatives (most prototypically pseudomonas).

Pneumocystis is a life-long concern post-transplant. Trimethoprim-sulfamethoxazole (TMP/SMX) is the preferred prophylaxis, given that it also has activity against Strep pneumoniae, staphylococcus, Enterobacteriaceae, Listeria, and Nocardia. Other agents, including dapsone and atovaquone can be utilized in the event TMP/SMX is not tolerated.

Cytomegalovirus (CMV) infection can be devastating following lung transplantation, and prophylaxis has been demonstrated to improve outcomes. Valganciclovir is the preferred option, however IV ganciclovir can be utilized if the patient does not have enteral access or is not absorbing medications. Donor-recipient CMV status informs the duration of treatment. In donor positive-recipient negative (D+/R-), the highest risk group, 12 months of prophylaxis is recommended. In D+/R+ and D−/R+ a minimum of 6 months of prophylaxis is recommended [47]. Prophylaxis is re-initiated if the patient undergoes additional immunosuppression and CMV viral PCR titers are followed regularly. Routine prophylaxis is not recommended in D−/R- subgroup; however, blood products administered to this group must be CMV negative.

Fungal infections are also common post-lung transplantation. This may be of particular importance in patients with IPF undergoing a single lung transplant as their native lungs may harbor or be colonized with fungal organisms. Some patients may develop aspergilloma cavities or progress to invasive fungal disease with the enhanced immunosuppression with invasive pulmonary aspergillosis and ulcerative tracheobronchitis being the most feared variants. The two most common approaches to prophylaxis are systemic azole therapy to cover aspergillus, and some centers will use nebulized liposomal amphotericin B to prevent aspergillus colonization at the anastomotic site.

22. Monitoring protocol post-transplantation

Most transplant centers have post-transplant protocols that address post-transplant follow-up in terms of clinic visits, post-transplant diagnostics, and laboratory tests. IPF patients undergoing transplants will typically follow the same protocol similar to other patients. Patients typically are encouraged to monitor and log their vitals, spirometry, blood glucose, activity levels, nutritional intake, participation in cardiopulmonary rehab and to call the transplant center for any medical problems. Frequent clinic visits in the first one to 3 months after transplant helps ensure frequent clinical assessment for medical or social and financial issues, compliance, establishing rapport and confidence with the transplant team.

23. Outcomes

Return of pulmonary function is dependent on graft characteristics, recipient thoracic cage, and post-operative complications. A value of 80% of predictive value
can be achieved 3 months postoperatively in both FVC and FEV₁, and patients may reach 100% by 6–12 months. Lung function typically stabilizes more rapidly in single lung transplants; at 3 months, some patients achieve FVC and FEV₁ over 80% predicted [48]. Since 2010, 1 year and 5-year survival have been 85% and 59%, respectively, with some variation with regards to pre-transplant risk factors and post-transplant complications. Younger patients with lesser comorbidities tend to have better survival overall [1, 49].

Furthermore, a lung transplant has been shown to improve health-related quality of life in a clinically meaningful way. Most of this change occurs in the first 6–7 months post-transplant. This is despite the systemic effects of immunosuppression and the development of often serious co-morbid conditions [50].

24. Conclusion

Overall, a lung transplant is a therapeutic option for patients with advanced IPF that continue to progress despite being on medical therapies. It has the potential to increase their survival and provide a quality of life. It is important to refer these patients with typical or probable UIP early to a lung transplant center due to the risk of rapid progression of disease or deterioration from AE-IPF. Acute decompensation can potentially make a transplant evaluation difficult to complete due to clinical instability. Transplant centers will typically list only patients with evidence of clinical deterioration and can help co-manage patients that may be stable on medical therapies. Access to resources at transplant centers may impact patients beyond the immediate medical needs, including referral or evaluations for cardiopulmonary rehab, nutrition, or weight loss, other medically indicated consultations, and clinical trials, and help introduce patients to other social forums like patient support groups.

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