Chapter 7
Primary Care of the Adult Lung Transplant Recipient

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Introduction

Lung transplantation has become an increasingly frequent treatment for patients with a variety of end-stage lung diseases. In 2016, there were over 4600 lung transplants worldwide reported to the registry for the International Society for Heart and Lung Transplantation (ISHLT) with nearly 2600 of those performed in North America [1]. The registry data also shows that the face of the lung transplant recipient has been changing over time. In 1987 the median age of lung transplant recipients was 43 years and in 2017 this had risen to 59 years, with the largest increase in lung transplants performed proportionally occurring in patients older than 65 years. As of 2016, as reported to the ISHLT, idiopathic pulmonary fibrosis (IPF) is the most common indication for lung transplantation in ~30%, followed by chronic obstructive pulmonary disease (COPD) in ~25%, and cystic fibrosis (CF) in ~15%. This propensity for lung transplantation in patients with IPF is increased in the United States as reported to the Scientific Registry of Transplant Recipients (SRTR). Between July 1, 2018, and June 30, 2019, over half of patients undergoing lung transplantation in the United States had a diagnosis of IPF, approximately one-quarter with COPD, and 10% with CF. [2]

Survival after lung transplantation has improved but is still limited as compared to other solid organ transplant recipients. In the most recent era defined as 2009 to June 2016, the median life expectancy for a lung transplant recipient is 6.5 years [1]. This survival is improved from a median of 4.3 years during the era of 1990–1998. For patients who survive the first year after a lung transplant, the median survival improves to 8.6 years in the most recent era for which data is available, 1999–2008. Survival following lung transplantation varies based on underlying lung disease,
ranging from an overall median survival of 5.2 years for patients with IPF to a median survival of 9.5 years for patients with CF. For patients who survive the first year after a lung transplant, the median survival ranges from 7.2 years for patients with IPF to 12.2 years for patients with CF. There are many longer living lung transplant survivors, however. The longest living post-lung transplant and post-heart-lung transplant survivors at the author’s center will be 27 years and 30 years post-transplant in early 2020 respectively.

Chronic lung allograft dysfunction (CLAD) is a significant contributor to morbidity and mortality after lung transplantation, occurring in 40% of patients by 5 years post-transplant [1]. It is the leading cause of death after the first year, being reported as the cause of death in approximately 25–30% of patients. CLAD is one of the primary reason lung transplant recipients require such intensive monitoring for the remainder of their life following lung transplantation.

With increased rates of transplantation and improving survival, it is increasingly likely that the primary care provider will assist in caring for recipients of a lung transplant.

**Lung Transplant Anatomy**

Lung transplantation is performed in the orthotopic position. There are various surgical techniques. The most common approach for a bilateral lung transplant is through bilateral anterior thoracotomies with transverse sternotomy (the “clamshell” incision in the front of the chest), or, if a unilateral transplant, a posterolateral thoracotomy incision. This chapter does not cover heart-lung transplantation or living-related lobar lung transplantation.

**Anastomoses** (Fig. 7.1)

- **Pulmonary artery**: The donor pulmonary artery is anastomosed to the corresponding recipient’s pulmonary artery.
- **Pulmonary veins**: There are different techniques to anastomose the pulmonary veins and may depend on the anatomic variant found during surgery. When two or more distinct pulmonary veins are present, one common method is to join the recipient’s pulmonary veins as a single insertion to the left atrium. This technique allows for a single anastomosis rather than joining each pulmonary vein individually.
- **Bronchial arteries**: The recipient bronchial arteries are ligated and generally not anastomosed.
- **Airway**: The donor and recipient bronchi are anastomosed at the level of the mainstem bronchi.
• Pleura: During bilateral lung transplantation via the clamshell approach, there is disruption of the individual pleural spaces resulting in interpleural communication (i.e., connection between the right and left pleural spaces). This is pertinent in the case of post-transplant pleural complications such as pneumothorax or empyema in which there may be extension to the contralateral pleural space.
• Lymphatics: Normally, lymphatic vessels from the lungs drain into the thoracic duct. After lung transplantation there is no lymphatic vessel anastomosis and therefore disruption of normal lymphatic drainage. There is likely lymphangiogenesis to a certain extent with development of collateral lymphatic drainage within several weeks following the transplant surgery; however, this has not been fully elucidated.

**Immunosuppression in the Lung Transplant Recipient**

Immunosuppression following lung transplantation can be divided into induction and maintenance immunosuppression.

**Induction**

Induction immunosuppression is used in the immediate perioperative and postoperative periods. It is intended to deplete circulating T cells with the purpose of reducing acute cellular rejection (ACR) immediately following lung transplantation, particularly until maintenance immunosuppression has reached full effect.

The use of induction immunosuppression appears to be increasing with time with 76% of lung transplant recipients receiving induction immunosuppressive
agents in 2016. The most commonly used agent is an interleukin-2 receptor (IL-2R) antagonist such as basiliximab, reported to be used in ~65% of all lung transplant recipients [1]. Other induction immunosuppression regimens include polyclonal or monoclonal T-cell antibody treatments, such as anti-thymocyte globulin (ATG) or muromonab-CD3 (OKT3) [1].

**Maintenance**

Maintenance immunosuppression is used for the remainder of the patient’s life after lung transplantation. Significant improvements in immunosuppressive agents have been made since the beginnings of solid organ transplantation; however, the optimal post-transplant maintenance immunosuppression regimen in lung transplant recipients remains unclear. In data reported from 2016, at 1 year post-lung transplant, the vast majority of lung transplant recipients received the calcineurin inhibitor tacrolimus (93%), mycophenolate mofetil or mycophenolic acid (83%), and prednisone [1]. In contrast, at 1 year post-transplant, only 5% of lung transplant recipients received the calcineurin inhibitor cyclosporine, 7% received a mammalian target of rapamycin (mTOR) inhibitor such as sirolimus or everolimus, and 9% received azathioprine. In the 2018 ISHLT annual registry report, unadjusted data showed statistically significant lower rates of ACR within the first year post-transplant in patients who receive maintenance immunosuppression therapy with tacrolimus plus mycophenolate mofetil or mycophenolic acid [1]. There was no difference found between tacrolimus plus azathioprine and cyclosporine plus mycophenolate mofetil or mycophenolic acid, but there was a statistically significantly increased risk for ACR in patients receiving cyclosporine plus azathioprine [1].

Regardless of the maintenance immunosuppression regimen used, optimization of the prescribed regimen should be assured by adherence, avoidance of interacting medications or foods, and close monitoring of drug trough levels when available. Medication nonadherence is a complicating factor in lung transplant recipients as with all patients. One single-center study found an average individual medication timing adherence (± 30 minutes from prescribed timing) of 98.1%, although the range was 31.2–100% [4]. Overall, medication adherence, defined as having an individual timing-adherence score of ≥80%, was seen in 92.3% of recipients. However, over 14% of patients missed one or more 24 hour period of medication, with over 40% in the non-adherent group (an individual timing-adherence score of ≤80%) missing one or more 24 hour period of medication. Instruction and emphasis on the importance of taking immunosuppressant medication regularly and at the prescribed time are important factors to assure adequate immunosuppression levels. Primary care providers can assist by evaluating adherence at each outpatient visit.

In general, many lung transplant recipients will remain on at least a three-drug immunosuppression regimen for the remainder of their life post-transplant unless there are side effects or complications requiring a reduction in immunosuppression. In patients with CLAD, it is common to see patients prescribed four maintenance immunosuppressive agents.
See Chap. 3 for more discussion of immunosuppressive medications and side effects.

**Post-Transplant Surveillance and Monitoring for Complications**

Recipients of a lung transplant require intensive, life-long monitoring for the assessment, evaluation, and management of both allograft and non-allograft transplant-related complications. While every lung transplant center has an individualized follow-up plan/schedule, most centers request that patients undergo formal spirometry at least several times a year and be seen by the lung transplant team at least 1–2 times a year. In addition, lung transplant centers will require laboratory testing generally every 1–3 months to measure immunosuppressive drug levels and monitor for transplant-related complications such as chronic kidney disease (CKD), diabetes mellitus (DM), cytopenias, and other issues as needed. In addition, post-lung transplant monitoring may include home spirometry measurements as well as periodic surveillance bronchoscopy as discussed below.

**Monitoring/Spirometry**

As a decline in forced expiratory volume in 1 second (FEV$_1$) is often the first sign of acute rejection and/or CLAD, close monitoring of spirometry is essential for early identification [5]. Lung transplant recipients are encouraged to utilize home spirometers to monitor lung function parameters such as the FEV$_1$ and the forced expiratory capacity (FVC). Monitoring of daily home spirometry has been shown to improve detection of a sustained decline for 3 days or more of FEV$_1$ by $\geq 20\%$ from the lung transplant recipient’s baseline best FEV$_1$ by an average of 276 days earlier than without daily home monitoring [6]. Despite this significantly earlier detection, no studies have demonstrated a benefit in survival with home spirometry monitoring, although several studies have shown a non-statistically significant positive trend for freedom from bronchiolitis obliterans syndrome (BOS) and reduced rates of re-transplantation [7].

**Monitoring/Surveillance Bronchoscopy**

Despite being commonly performed, there is little data to support the utilization of surveillance screening for ACR via bronchoscopy and transbronchial biopsy (TBBX) [8]. The intention of surveillance monitoring by TBBX is to attempt to identify subclinical ACR before the onset of symptoms or graft dysfunction and to intervene therapeutically with the belief that early and prompt treatment of ACR is
beneficial for improving outcomes and decreasing the risk of CLAD in lung transplant recipients. However, there is no definitive evidence that earlier identification of these abnormalities in an asymptomatic patient with preserved lung function alters the treatment course or overall outcome in lung transplant recipients. Bronchoscopy can result in many complications including, but not limited to, pneumothorax, bleeding, and complications of sedation; therefore, further studies are needed to determine if there is a benefit in performing surveillance bronchoscopy with TBBX in lung transplant recipients and if the benefit outweighs the procedural risks.

Post-Lung Transplant Pulmonary Complications

General Issues

There are a myriad of pulmonary issues that may arise after a lung transplant, and while many times these issues are benign, subtle findings may herald a much more concerning complication or trigger lung function decline. As such, the lung transplant team should be notified to help direct evaluation and management for any lung transplant recipient who presents with respiratory symptoms or signs including, but not limited to, decline in spirometry, decline in oxygenation by pulse oximetry, dyspnea, cough, decreased exercise tolerance, respiratory viral symptoms, or new/worsened edema. Empiric corticosteroids and/or antibiotics for respiratory symptoms should be avoided unless directed by the lung transplant team as they may greatly impact the ability to diagnose lung transplant complications, particularly acute rejection, if a patient develops significant worsening of symptoms. In addition, many post-lung transplant recipients are colonized with bacteria that will not respond to the typical empiric antibiotics given for conditions such as community-acquired pneumonia or may already be prescribed azithromycin as an anti-inflammatory agent in the setting of CLAD. Finally, due to the disrupted lymphatic drainage after lung transplantation, lung transplant recipients are highly susceptible to pulmonary edema with the administration of large-volume intravenous (IV) fluids. IV fluids should not be administered to a lung transplant recipient outside of the acute setting such as sepsis or other severe, life-threatening hypotension or blood loss, without a discussion with the lung transplant team (see Table 7.1).

Patients who present with new respiratory symptoms or a decline in spirometry despite the presence or absence of symptoms should undergo formal evaluation for diagnosis. Possible etiologies include, but are not limited to, acute cellular or antibody-mediated rejection, infection, anastomotic and/or airway stenoses, or the onset of CLAD. Testing by the lung transplant team will generally include formal spirometry, computed tomography (CT) scan of the chest with inspiratory and expiratory images, testing for donor-specific antibodies (DSA) as part of the diagnosis of antibody-mediated rejection, as well as bronchoscopy to evaluate for anastomotic
and/or airway stenoses and to obtain specimens via bronchoalveolar lavage (BAL) and transbronchial biopsies (TBBX). Additional evaluation and testing may be warranted depending on the clinical presentation.

**Acute Rejection**

Acute cellular rejection (ACR) and antibody-mediated (humoral) rejection (AMR) are two forms of acute rejection seen following lung transplantation.

- **Symptoms:** Most lung transplant recipients with ACR or AMR present with minimal to no symptoms and are generally identified due to a decline in home or formal spirometry. If symptoms are present, they most commonly include dyspnea and/or cough. At times, lung transplant recipients may present with more acute respiratory failure ranging from mild hypoxia to acute respiratory distress syndrome (ARDS). Importantly, there is no clear distinction in symptoms that differentiate between acute rejection and other post-lung transplant complications such as infection.
• Exam findings: Physical exam findings in acute rejection are generally absent or nonspecific. Patients presenting with advanced or fulminant acute rejection may show mild to severe hypoxia on O₂ saturation monitoring, evidence of increased work of breathing, and nonspecific findings on pulmonary examination.

• Evaluation: Evaluation for acute rejection should be directed by the transplant team and may include formal spirometry, chest radiographic imaging, testing for donor specific antibodies, and bronchoscopy. Because infection may present similarly, broad infectious testing will often be performed in the setting of a decline in spirometry or new respiratory symptoms, including an extended-spectrum respiratory viral panel, respiratory cultures, and other testing. It is important to note that respiratory infection may trigger acute rejection, further limiting the ability to clinically differentiate post-lung transplant complications without additional testing. An evaluation may occur in the inpatient or the outpatient setting, depending on the severity of the patient’s presentation as well as the ability to expeditiously obtain the necessary testing.

• Treatment: The management of ACR and AMR is complex and may be individualized based on the unique situation of each patient but is guided by early diagnosis and prompt treatment that includes augmentation of immunosuppression among a variety of additional medical strategies. Treatment of ACR and AMR is important not only because of the risk of acute graft loss during the rejection episode but also because acute rejection is associated with the subsequent development of CLAD.

Airway Complications

Airway-related complications after lung transplantation have been reported to range from 2% to 18% and are felt to be related to donor bronchial ischemia [9]. Airway dehiscence occurs at the surgical anastomotic sites while airway stenosis and/or malacia can occur at the surgical anastomotic sites as well as the more distal airways. The airway-related complications often present with a decline in spirometry with or without dyspnea or evidence of unilateral large airway noise on physical exam. As with the evaluation of any decline of spirometry or new respiratory symptoms in a lung transplant recipient, evaluation for the concern of airway-related complications should be dictated by the transplant team. Management may include monitoring, balloon dilation, stent placement, ablative therapies, or surgical intervention. While many airway complications occur early post-lung transplant, a proportion of patients may have persistent issues that require management for years.

Infections

Respiratory viruses, both symptomatic and asymptomatic, have been found to possibly play a role in the development of ACR [10]. In addition, respiratory viral infections when present concurrently with ACR may cause more severe lung dysfunction
and a slower short-term recovery [11]. Perhaps more importantly, however, respiratory viruses have been associated with the subsequent development of CLAD [9, 12]. Fisher et al. found an adjusted hazard ratio of 1.9 (1.1–3.5, \( p = 0.03 \)) for CLAD following the diagnosis of an upper or lower respiratory tract viral infection. The association of the development of CLAD following a respiratory viral infection was stronger the earlier after the respiratory viral infection but persisted for 12 months following the diagnosis (HR 4.8 (1.9–11.6), \( P < 0.01 \); 3.4 (1.5–7.5), \( P < 0.01 \); and 2.4 (1.2–5.0), \( P = 0.02 \) in multivariate analysis for 3, 6, and 12 months following respiratory viral infection, respectively). As such, even mild respiratory viral infections in lung transplant recipients should prompt review by the lung transplant team with close monitoring for the development of worsening symptoms or decline in lung function. An extended-spectrum respiratory viral panel by nasal swab can be helpful even in the setting of mild upper respiratory infection in order to potentially identify the causative virus, provide treatment if warranted, and depending on the causative viral infection determine the need for closer follow-up to monitor for post-respiratory viral complications (i.e., acute rejection, development of CLAD, etc.). If additional evaluation or treatment is being considered due to clinical symptoms or findings, it is reasonable to contact the transplant team for guidance as to the most appropriate evaluation and/or treatment based on the individual patient’s clinical transplant history.

Transplant centers vary widely with respect to antiviral prophylaxis for cytomegalovirus (CMV) but are generally driven by the donor and recipient serostatus, tolerance of the medication, and the recipient’s post-transplant CMV history. CMV seronegative recipients (R) of a CMV seropositive donor (D) organ (CMV D+/R–) are at the highest risk of CMV reactivation. However, any lung transplant recipient may experience CMV reactivation regardless of donor or recipient serostatus with the exception of CMV seronegative recipients of a seronegative donor organ (CMV D−/R−) who are at risk of developing primary CMV infection. Valganciclovir is generally the agent used for CMV prophylaxis with the duration dependent on the specific transplant center protocol, which can range from 3 months to indefinite prophylaxis. Acyclovir may be used for early postoperative HSV or VZV prophylaxis in CMV D−/R− lung transplants or later post-transplant in any recipient with recurrent HSV or VZV reactivation.

Overall, it is important to recognize the increased risk for any pulmonary or non-pulmonary infection in a lung transplant recipient. Given the range of infectious complications and the complexity of managing infections in the setting of immunosuppression, it is reasonable to contact the transplant team to alert them to any infection in a lung transplant recipient, so they may provide insight into atypical infectious etiologies as well as preferred treatment and treatment duration. The transplant team may also elect to adjust immunosuppression in the setting of active or recurrent infections. While lung transplant recipients may present with “typical” infections as in the general population, they may also present with what appears to be a “typical” infection but, in fact, is something much more serious (for example, gram-negative or fungal cellulitis). Delayed or inadequate treatment of an infection can have dire consequences, thus early involvement of the transplant team may be beneficial to assist the primary care provider managing an infection in a lung transplant recipient (see also Chap. 8).
The COVID-19/SARS-CoV-2 pandemic that began in 2020 may pose particular risk to lung transplant recipients. At the time of this book’s publication, data regarding this infection’s presentation and outcomes in lung transplant recipients continues to evolve. Evaluation and management should be directed by the transplant pulmonologist and take into consideration local epidemiology and public health guidelines. Lung transplant recipients are in a high risk category and should avoid potential exposures to SARS-CoV-2.

**Gastroesophageal Reflux Disease**

Gastroesophageal reflux disease (GERD) irrespective of symptoms or acid content appears to have the potential for a significant impact on post-lung transplant graft function likely due to the predisposition to aspiration of gastroesophageal reflux contents and the subsequent injury that occurs. Several studies in lung transplant recipients have found that GERD diagnosed by 24-hour pH study or 24-hour pH-impedance study is associated with an earlier onset of ACR, higher rate of ACR, and multiple episodes of ACR [13, 14]. In addition, one study found that anti-reflux surgery performed either pre-transplant or within the first 6 months following lung transplantation resulted in a decreased risk of ACR in the first year [15].

Several studies have shown that the occurrence of GERD increases after lung transplantation and may increase with time following transplant surgery [16–18]. Although no studies have found a causative link between GERD and CLAD, several studies have evaluated the impact of post-transplant fundoplication surgery and the development or progression of CLAD. Lung transplant recipients who undergo early post-transplant fundoplication for documented GERD have been found to have a better FEV$_1$ at 1-year post-transplant, higher peak FEV$_1$, and longer survival [19, 20]. Evaluation and management of GERD are therefore critical in lung transplant recipients that present with graft dysfunction particularly if no immunologic etiology is found.

Many lung transplant centers will prescribe life-long proton-pump inhibitors (PPIs) for all lung transplant recipients regardless of a diagnosis of GERD or GERD symptoms given the concern that even episodic acidic reflux with microaspiration may result in lung allograft injury. The primary care provider should contact the transplant team if there is concern for side effects relating to the use of PPIs so that there may be a discussion about the risk-benefit ratio in the setting of lung transplantation.

**Chronic Lung Allograft Dysfunction (CLAD)**

CLAD is the leading cause of death after the first year following lung transplantation, being reported as the primary cause of death in approximately 25–30% of lung transplant recipients [1]. CLAD is a clinical diagnosis based purely on a sustained decline of $\geq$20% in FEV$_1$ from a lung transplant recipient’s baseline best FEV$_1$.
without another clinical explanation [19]. Frequently, lung transplant recipients are diagnosed with CLAD solely by a sustained decline in spirometry and remain asymptomatic with no functional limitations. CLAD is divided into two phenotypes: obstructive CLAD, previously termed bronchiolitis obliterans syndrome (BOS), and restrictive CLAD, also referred to as restrictive allograft syndrome (RAS). CLAD may be progressive either due to an ongoing process resulting in continuing allograft injury or due to a series of independent injuries. Over time, lung transplant recipients may develop end-stage obstructive or restrictive lung disease with manifestations of dyspnea with exertion, chronic hypoxia requiring supplemental oxygen, and a decline in functional status.

If a lung transplant recipient manifests a sustained decline of $\geq 10\%$ in FEV$_1$, from their baseline best FEV$_1$, the lung transplant team will determine the appropriate evaluation and management. As CLAD is a clinical diagnosis, bronchoscopy with transbronchial biopsies is primarily helpful to exclude ACR, infection, and/or airway stenosis as the cause of decreased spirometry. Chest CT may show air-trapping or areas of fibrosis; however, these findings are supportive of the diagnosis of CLAD, not diagnostic in isolation.

Unfortunately, there are no true treatments for CLAD; thus the effort is focused on preserving the remaining lung function and treating contributing factors and pulmonary complications (i.e., rejection, infection, etc.) as soon as possible. Azithromycin may be used for its anti-inflammatory properties as a means to mitigate ongoing lung function decline due to inflammation but not to reverse allograft injury that has already occurred.

Primary Care of the Lung Transplant Recipient

**General Issues**

Following transplantation, medical management of the lung transplant recipient is vital for maintaining the health of the allograft and to promote an overall successful outcome after a lung transplant surgery. A large number of non-pulmonary complications that may arise following lung transplantation are related to immunosuppressant effects and/or toxicities. Non-pulmonary complications include, but are not limited to, renal dysfunction, hematologic abnormalities, gastrointestinal complications, neurologic sequelae, oncologic manifestations, and metabolic derangements. While monitoring lung allograft function following transplantation is critical to overall survival, monitoring for the subsequent non-pulmonary complications is also important to avoid increased morbidity and mortality in lung transplant recipients.

Given the range of non-pulmonary complications following lung transplantation, any new medical diagnoses should be discussed with the lung transplant team to assure that no changes in the post-lung transplant medication regimen are warranted. In addition, new medications prescribed for non-pulmonary medical issues should also be discussed with the lung transplant team to assure that no potential interactions exist between the new medication and the immunosuppressive medications in particular. For example, diltiazem and the azoles, such as fluconazole, have
significant interactions with the calcineurin inhibitors, tacrolimus and cyclosporine, resulting in decreased metabolism of these medications. The doses of the calcineurin inhibitors will need to be reduced in the setting of administration of diltiazem or the azoles in order to prevent toxic levels resulting in renal failure or severe neurologic issues (see Chap. 3).

General age-related health maintenance and screening for lung transplant recipients should not be different from the general population outside of the known issues

Table 7.2  Clinical pearls for the primary care provider—evaluation of the lung transplant recipient at outpatient clinic visits (see text for details, also see Chap. 2 for discussion of general history-taking)

| Initial visit: |
| Review pre-transplant and initial post-transplant course: |
| Indication for transplant |
| Single vs bilateral lung transplant |
| EBV and CMV serostatus |
| Type of induction immunosuppression |
| Complications (surgical complications, infection, rejection) |

| Symptoms, exam, medications, laboratory studies, metabolic complications, and general preventive health similar to follow-up visits |

| Follow-up visits: |
| Symptoms: |
| Inquire about dyspnea, cough, symptoms of infection, malignancy, or medication side effects |

| Habits: |
| Ask about tobacco, marijuana, and other use |

| Exam: |
| Should have expected surgical scars from incision, drains, etc. |
| Complete exam for abnormal respiratory findings |

| Medications: |
| Review immunosuppressive medication regimen, adherence, side effects |
| Review infectious prophylaxis |
| Review other possible medications intended to treat or prevent post-transplant complications (PPIs, azithromycin, magnesium supplementation, calcium/vitamin D supplementation, statin, among others) |

| Laboratory and other studies: |
| Adherence to surveillance schedule set forth by the transplant team |

| Surveillance for graft function |
| Home spirometry |
| Formal spirometry |
| Bronchoscopy (if done) |

| Metabolic complications: |
| Assess and treat, in conjunction with the transplant team, if present, including hypomagnesemia, gout, osteopenia or osteoporosis, diabetes, hypertension, chronic kidney disease |

| General preventive health: |
| Review immunizations, skin exams including history of skin cancer, other routine screening |
relating to the side effects and complications of post-lung transplant medications (see Chap. 12). Patients are strongly recommended to stay up to date; however, their immunosuppressed state may worsen or complicate management of routine age-related medical diagnoses.

At the initial visit, the patient’s history should be reviewed (Table 7.2).

- The pre-transplant course should be reviewed. In some cases, patients have had a prolonged course on the waiting list and may have suffered from complications, hospitalizations, and frailty.
- The indication for transplantation should be clearly identified.
  - In some cases, the disease may continue to affect other organ systems—for example, a patient with cystic fibrosis may have a well-functioning bilateral lung transplant without complications but still have pancreatic disease, sinusitis, and episodes of distal intestinal obstruction syndrome (DIOS). The primary care provider may be actively involved in managing these other conditions.
- Single lung transplant recipients may continue to have disease and complications in the native lung. For example, a patient with a single lung transplant for COPD is still at risk for cancer and pneumothorax in the native lung.
- The initial transplant postoperative course should be reviewed for complications, rejection episodes, and opportunistic infections.

At all visits (initial and follow-up), the primary care provider should review the following (Table 7.2):

- Symptoms: Patients should be asked about symptoms of allograft dysfunction, including dyspnea or cough. Symptoms of infection and malignancy should also be addressed, as well as potential side effects of immunosuppressant or infection prophylaxis medications.
- Adherence: As noted above, nonadherence is common and should be discussed. Knowing the common side effects will help the PCP direct questions, as side effects are a potential factor in nonadherence (see Chap. 3).
- Habits: Smoking relapse can occur in patients after lung transplantation. Primary care providers should actively inquire about smoking and treat aggressively if needed. Other inhaled substances are also strongly discouraged, including vaping marijuana. The transplant team should be made aware if a patient is smoking or inhaling any substance so that they may be able to counsel the patient appropriately from a lung transplant perspective.
- Exam: In addition to any other physical examination as indicated, lung transplant recipients should be assessed for abnormal respiratory findings, including oxygenation. Examination should show expected surgical scars and a well-functioning lung allograft should be clear to auscultation. The extremities should be assessed for edema and cyanosis. Lung transplant recipients should be monitored for excessive weight gain and, if present, managed aggressively.
- Laboratory and surveillance: The lung transplant recipient will have frequent, life-long laboratory monitoring as dictated by the transplant team. It is helpful to review the transplant team’s documentation and reinforce the surveillance sched-
ule with the patient, especially if the patient is past due for routine surveillance. The patient should be encouraged to perform life-long home spirometry and the data should be reviewed for changes. If a decrease in home spirometry is present, the transplant team should be alerted regardless of the presence or absence of respiratory symptoms. Abnormal lab tests may require follow-up by the PCP (e.g., hyperglycemia).

• Manage complications: It is important to continue to screen for medical complications and treat them as they arise. Patients with good allograft function might see their lung transplant team twice yearly, but their PCP more often to manage diabetes, hypertension, and other conditions. (Complications are discussed in more detail below and also more generally in Chaps. 10 and 11).

• Preventive health: Primary care providers should continue to conduct routine age-appropriate health screening and immunizations. Note that live virus immunizations are contraindicated due to immunosuppression, and the recombinant shingles vaccine is currently not recommended, pending further evaluation in the transplant population. Vaccine recommendations change frequently and the PCP should review current guidelines and, if in doubt, contact the transplant center (See Chap. 12).

Renal, Cardiovascular, and Metabolic Complications Post-Lung Transplant

While these complications are discussed elsewhere in this book, it is important to recognize the frequency with which non-pulmonary renal, cardiovascular, and metabolic complications occur following lung transplantation. Patients with pre-transplant risk factors for these non-pulmonary issues, such as patients with cystic fibrosis, may have significant worsening of these conditions following lung transplantation and the administration of immunosuppressive medications. Careful monitoring is necessary to prevent long-term sequelae and morbidity due to these complications.

Renal disease is a common and an increasingly recognized complication following lung transplantation. According to data collected by the ISHLT, at 1 year following renal transplantation, nearly 6% of recipients meet the criteria for severe renal dysfunction (creatinine >2.5 mg/dL) and nearly 1.3% require dialysis. By 5-years post-transplant, over 16% of recipients meet the criteria for severe renal dysfunction with an additional 3% requiring dialysis and 0.6% having undergone renal transplantation [1]. If a lung transplant recipient develops proteinuria or a rising creatinine, in addition to the standard workup for acute or chronic kidney disease, the transplant team should be notified. In some cases, the patient’s immunosuppression regimen may be reassessed and/or modified. If the renal disease is progressive, a nephrologist familiar with the care of transplant recipients should be involved.
Several cardiovascular and metabolic alterations can occur following lung transplantation, most commonly due to side effects related to the immunosuppressive medications. Hypertension, hypercholesterolemia, diabetes mellitus, and osteoporosis are all potential complications in lung transplant recipients. Several studies have evaluated the prevalence of these cardiovascular and metabolic alterations. Hypertension has been found to be present in 45% of lung transplant recipients at 1-year post-transplant, 65% by 3-year post-transplant, and 67% by 5-year post-transplant [21]. Similarly, hypercholesterolemia is present in 16% of lung transplant recipients at 1-year post-transplant, 33% by 3-year post-transplant, and 48% by 5-year post-transplant [22]. The estimated prevalence of diabetes mellitus following lung transplantation has varied among studies with 6–23% by 1-year post-transplant and 7–39% by 3-year post-transplant [21, 23, 24]. The prevalence of metabolic syndrome is also increased with 24% of lung transplant recipients meeting the criteria by 1-year post-transplant.

Loss of bone mineral density also is a common complication following lung transplantation, although many patients have preexisting bone mineral density alterations prior to transplant. Wang et al. found that 36% of lung transplant candidates had osteopenia based on bone mineral density testing and 31% had osteoporosis [25]. This increased prevalence is likely due to the common use of corticosteroids in advanced lung disease management, a known risk factor for loss of bone mineral density. Significant bone loss is common following lung transplantation, again primarily to the use of corticosteroids as a mainstay of the transplant immunosuppressive regimen. As such, prevention of bone loss with post-transplant administration of calcium and vitamin D, as well as appropriate monitoring for bone loss and treatment when needed, is essential to reduce the risk of fracture.

For further discussion not specific to lung transplant recipients, see Chap. 11.

Malignancy

Malignancy following lung transplantation is common and increases with time after transplant. According to the ISHLT, over 11% of deaths between years 1 and 5 post-lung transplant and over 17% after 5-years post-lung transplant are attributable to malignancy. In addition, post-transplant lymphoproliferative disorder (PTLD) is responsible for 2% of deaths following the first 30 days after transplant [1].

Skin cancer accounts for the majority of malignancy following lung transplantation, with squamous cell carcinoma (SCC) predominating over basal cell carcinoma (BCC) [26]. Lung and heart transplant recipients are more likely to develop skin cancer than other solid organ transplant recipients, likely due to the increased overall intensity of immunosuppression required. Immunosuppression alone is not the only post-transplant medication contributing to the development of skin cancer, however. Exposure to voriconazole, an anti-fungal medication used frequently after lung transplantation, has also been found to significantly impact the occurrence of skin cancer. A retrospective study of over 300 lung transplant recipients found a...
2.6-fold increased risk for SCC in patients who had any exposure to voriconazole with a cumulative effect showing a 5.6% increase in risk for every 60-day exposure [27].

Post-transplant lymphoproliferative disorder (PTLD) is a broad category that contains several distinct processes and is characterized by the proliferation of immune cells in the setting of post-transplant immunosuppression. A review of the United Network of Sharing database, a database of solid organ transplants performed in the United States, found the incidence of PTLD in lung transplant recipients to be 3.7% [28]. Other studies have reported higher incidences with ranges of 6.2–9.4% [29]. PTLD is more common in lung transplant recipients, occurring twice as frequently as in other solid organ transplant recipients [28]. EBV serostatus is the most important risk factor for the development of PTLD, with an EBV seropositive donor organ transplanted into an EBV seronegative recipient having the highest risk. Lung transplant recipients in this category have a 20-fold increased risk of developing PTLD than lung transplant recipients who are seropositive prior to transplantation [28]. As PTLD may present at any time post-transplant and in a variety of locations (i.e., pulmonary, GI, CNS, bone marrow, etc.), patients may possibly present to primary care providers with symptoms of malignancy. Therefore, primary care providers must be aware of this condition and have a high degree of suspicion in order to diagnose it accurately in a timely fashion.

Colon cancer has been found to be generally increased in patients with CF. In a recent review of the US Cystic Fibrosis Foundation Registry during the years 1990 to 2009, the standardized incidence ratio (SIR), defined as the number of observed cases of colon cancer divided by the number of expected cases of colon cancer, was 6.2 in all patients with CF. [30] In patients with CF who underwent organ transplantation, the SIR for colon cancer was 30.1. Screening recommendations for colon cancer in lung transplant recipients with CF have been published with recommendations for both pre- and post-transplant screening initiation and intervals [31].

Short telomere syndromes have been associated with the development of IPF and other interstitial pneumonias and have been shown to be a critical factor driving myelodysplastic syndrome (MDS) and leukemia. Patients with telomeropathies who undergo lung transplantation should be monitored closely for the development of myelodysplasia and other associated hematologic disorders. [32, 33] Consideration should be taken for lung transplant recipients with short telomere syndromes to be proactively followed by hematologist-oncologists who are familiar with the evaluation and management of hematologic disorders associated with telomeropathies.

Lung cancer also appears to occur more frequently following lung transplantation. Several studies have shown an increased risk of lung cancer, particularly in the native lung in COPD and IPF recipients of a single lung transplant [34–36]. These patients have been found to have prevalence of native lung cancer ranging from 1.5% to 8.9% [35]. Although there are no current guidelines for screening for lung cancer in lung transplant recipients, consideration should be given to using current lung screening guidelines in patients who may be at high risk such as recipients of single lung transplants due to COPD and IPF. Screening and evaluation for lung
Cancer in lung transplant recipients should be a joint effort between the lung transplant team and the primary care provider.  
(See also Chap. 10).

Conclusions

Lung transplantation has become an increasingly frequent treatment for patients with a variety of end-stage lung diseases. Survival after lung transplantation has improved over time but is still limited as compared to other solid organ transplant recipients. There are a myriad of pulmonary issues that may arise after a lung transplant as well as a large number of non-pulmonary complications frequently related to immunosuppressant effects and/or toxicities. Non-pulmonary complications include, but are not limited to, renal dysfunction, hematologic abnormalities, gastrointestinal complications, neurologic sequelae, oncologic manifestations, and metabolic derangements. For these reasons, following a lung transplant recipients require intensive, life-long monitoring for the assessment, evaluation, and management of both allograft and non-allograft transplant-related complications.

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