CHEST

Comprehensive Care of the Lung Transplant Patient

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Lung transplantation has evolved into a life-saving treatment with improved quality of life for patients with end-stage respiratory failure unresponsive to other medical or surgical interventions. With improving survival rates, the number of lung transplant recipients with preexisting and posttransplant comorbidities that require attention continues to increase. A partnership between transplant and nontransplant care providers is necessary to deliver comprehensive and optimal care for transplant candidates and recipients. The goals of this partnership include timely referral and assistance with transplant evaluation, optimization of comorbidities and preparation for transplantation, management of common posttransplant medical comorbidities, immunization, screening for malignancy, and counseling for a healthy lifestyle to maximize the likelihood of a good outcome. We aim to provide an outline of the main aspects of the care of candidates for and recipients of lung transplants for nontransplant physicians and other care providers. CHEST 2017; 152(1):150-164

KEY WORDS: adherence; chronic medical conditions; coordination of care; drug interactions; immunization; immunocompromised; lung transplantation; obesity; preventive medicine; primary care; pulmonary fibrosis; pulmonary rehabilitation; quality improvement; reproductive health; screening

Lung transplantation (LTx) is a well-established therapy for selected individuals with end-stage pulmonary disease. Since the first successful combined heart and lung transplants in 1981, the field of LTx has advanced in the selection of candidates, operative techniques, critical care management, immunosuppression, and long-term follow-up.[1,2] Although no data exist on the worldwide prevalence of respiratory failure requiring lung transplant, it is estimated at tens of thousands, one-third of whom have fibrotic lung diseases and another one-third of whom have severe COPD. The relative increase in transplants during the past 10 years has been greatest with lung transplants compared with that of other organs. According to the International Society for Heart and Lung Transplantation, more than 51,000 adult lung transplants were performed worldwide through June 2014.[3]

ABBREVIATIONS: ACR = acute cellular rejection; CF = cystic fibrosis; CMV = cytomegalovirus; CNI = calcineurin inhibitor; DM = diabetes mellitus; GER = gastroesophageal reflux; HCV = hepatitis C virus; HR = humoral rejection; LTx = lung transplantation; mTOR = mechanistic target of rapamycin; PCP = primary care physician; TDM = therapeutic drug monitoring

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FUNDING/SUPPORT: A. A. is supported by the National Institutes of Health [grant T32 HL 07605].

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DOI: http://dx.doi.org/10.1016/j.chest.2016.10.001

With improving survival rates, the number of people living with lung transplants has increased and as of 2014 exceeded 11,000 in the United States, representing the highest number of living lung recipients since the first successful lung transplant.[2] Despite this finding, the LTx procedure rate falls significantly short of the number of patients with respiratory failure in need of lung transplants. Among those patients who make it to the waiting list in the United States, an average of 300 patients die annually while waiting for lung transplants.[4] The ever-increasing number of people in need of lung transplants and the progressive improvement in posttransplant survival suggest that an effective partnership between transplant and nontransplant providers will be required for continued progress in quality of life and outcomes. The long-term care of the transplant recipient is focused on the prevention of complications, recognition of emergent medical issues and optimization of immunosuppression, and return to independent daily living. Primary care physicians (PCPs) are uniquely positioned to assess these patients for emerging issues, manage common comorbidities, counsel for healthy lifestyle, and screen for malignancy (Table 1).

TABLE 1] Major Domains for Contribution of Care by Nontransplant Health-care Providers

Pretransplant phase
Identification of candidates for transplant
Timely referral
Optimization of treatment of chronic respiratory failure
Medical treatment
Pulmonary rehabilitation
Adherence
Treatment of preexisting comorbidities
Hypertension
Diabetes mellitus
Dyslipidemia
Osteoporosis and osteopenia
Mood disorders (anxiety, depression)
Avoid sensitization by limiting transfusion of blood products
Health maintenance
Preventive care and age-appropriate cancer screening
Counseling against substance use
Exercise, cardiac, or pulmonary rehabilitation
Weight optimization
Immunization
Posttransplant phase
High index of suspicion for rejection and infection
Avoid drug interactions
Contact transplant center as indicated (Table 6)
Treatment of preexisting and de novo comorbidities (as above)
Health maintenance (as above)
Adherence

Coordination of Care

Although collaboration between specialists and community physicians and care providers leads to improved outcomes[5] and elimination of errors by means of sharing information, there are no established standards for coordination of care before or after receiving lung transplants. Poor communication between providers can impair patient safety, decrease patient satisfaction, and increase the economic burden of health care. The facilities, support staff, and resources at the PCP office make it ideal for delivering preventive care and managing chronic comorbidities effectively.

In lung transplant recipients, the complex interactions of the host, graft, immunosuppressive drugs, and the patient's environment pose challenges. These challenges include nonspecific symptoms and signs of allograft rejection, infection, malignancy, medication toxicities, and drug interactions. The American Society of Transplantation recommends that significant changes in the clinical condition of lung transplant recipients are communicated to the transplant center promptly.[6] Even prior to a patient receiving a lung transplant, changes in functional capacity, worsening oxygenation, hospitalizations, infections, pulmonary embolism, stroke, need for continuous mechanical ventilation, pulmonary hypertension, elevation in serum creatinine levels, or deterioration in arterial blood gasses in lung transplant candidates should all be communicated to the transplant center because they may affect the listing status or transplant candidacy.

Pretransplant Phase

Candidate selection begins with a referral from the nontransplant pulmonologist or PCP. The referring physician often has an established relationship with the patient and can provide historical background data and salient details of adherence and social support. The timing of patient referral is of the utmost importance and permits thorough evaluation, identification and optimization of comorbidities, improvement in

TABLE 2] Disease-Specific Guidelines for Referral and Listing for Lung Transplant

Pulmonary Disease	Timing of Referral	Timing of Listing
COPD	Progressive disease despite maximal therapy (including medication, supplemental oxygen, and pulmonary rehabilitation) Patient is ineligible for endoscopic or surgical LVRS. (Patients with COPD may be referred simultaneously for lung transplant and LVRS evaluation.) BODE index of 5 or 6 $PaCO_2 > 50$ mm Hg (or 6.6 kPa) ± $PaO_2 < 60$ mm Hg (or 8 kPa) $FEV_1 < 25\%$ predicted	BODE index ≥ 7 **or** at least one of the following: • $FEV_1 < 20\%$ predicted • ≥ 3 severe exacerbations during the preceding year • At least one severe exacerbation with acute hypercapnic respiratory failure • Moderate to severe pulmonary hypertension
ILD	Histopathologic or radiographic evaluation demonstrates: • Usual interstitial pneumonitis, **or** • Fibrosing nonspecific interstitial pneumonitis Lung function impairment: • FVC < 80% predicted • DLCO < 40% predicted Dyspnea or functional limitation resulting from lung disease Requirement for supplemental oxygen. For inflammatory ILD, lack of improvement in dyspnea, oxygen requirement, and/or lung function after trial of clinically indicated medical therapy	FVC decline during 6-month follow-up is ≥ 10% DLCO decline during 6-month follow-up is ≥ 15% 6-min walk test: • desaturation < 88%, or • distance < 250 m, or • distance declines by > 50 m across 6 months Pulmonary hypertension on • catheterization of the right side of the heart, **or** • two-dimensional echocardiography Hospitalization because of: • respiratory decline, **or** • pneumothorax, **or** • acute exacerbation
Cystic fibrosis	Patient infected with nontuberculous mycobacterial or *Burkholderia cepacia* complex with or without diabetes mellitus who demonstrates: • $FEV_1 < 30\%$, **or** • Rapidly declining FEV_1 despite optimal therapy in a patient with advanced disease (especially female) 6-min walk test < 400 m Pulmonary hypertension develops in the absence of hypoxic exacerbation, and systolic pulmonary arterial pressure • 35 mm Hg (at echocardiography), **or** • 25 mm Hg (at catheterization of the right side of the heart) Clinical decline and increasing frequency of exacerbations and at least one of the following: • An episode of acute respiratory failure requiring noninvasive ventilation • Increasing antibiotic resistance and poor clinical recovery from exacerbations • Worsening nutritional status despite supplementation • Pneumothorax • Life-threatening hemoptysis despite bronchial embolization	Chronic respiratory failure with: • Hypoxia, $PaO_2 < 60$ mm Hg (or 8 kPa) with or without • Hypercapnia, $PaCO_2 > 50$ mm Hg (or 6.6 kPa) Long-term therapy with noninvasive ventilation Pulmonary hypertension Frequent hospitalization Rapid decline in lung function World Health Organization Functional Class IV
Pulmonary vascular diseases	NYHA class III or IV while escalating therapy Rapidly progressing disease (in the absence of concerns about weight or rehabilitation) Use of parenteral targeted pulmonary arterial hypertension therapy	Persistent NYHA class III or IV after ≥ 3 months of combination therapy including prostanoids Cardiac index < 2 L/min/m^2 Mean right atrial pressure > 15 mm Hg

(Continued)

TABLE 2] *(Continued)*

Pulmonary Disease	Timing of Referral	Timing of Listing
	Known or suspected pulmonary venoocclusive disease or pulmonary capillary hemangiomatosis	6-min walk test < 350 m Development of • significant hemoptysis, **or** • pericardial effusion, **or** • signs of progressive failure of the right side of the heart (renal insufficiency, increasing bilirubin, brain natriuretic peptide, or recurrent ascites)

BODE = BMI, airway obstruction, dyspnea, exercise capacity[8]; DLCO = diffusing capacity of lung for carbon monoxide; ILD = interstitial lung disease; LVRS = lung volume reduction surgery; NYHA = New York Heart Association. Adapted from Weill et al.[7]

nutritional and functional status, and preparation of the patient and family for the life-altering event of LTx.[7] Identification and referral of potential transplant candidates for screening should occur early enough to survive the prolonged waiting list period and not too late to preclude listing. In adults, a lung transplant is indicated in a broad spectrum of end-stage pulmonary diseases (Table 2).[8,9] COPD, idiopathic pulmonary fibrosis, and cystic fibrosis (CF) account for most lung transplants performed worldwide.[10] Disease-specific candidate selection for a lung transplant usually follows the updated international guidelines (Table 2).[7-9]

Recent malignancy, active hepatitis B virus or hepatitis C virus (HCV) infection, severe psychiatric illness, continued tobacco and other substance use, inability to demonstrate a reliable and active social support structure, and recurrent medical noncompliance with clinical care still constitute absolute contraindications to receiving a lung transplant (Table 3). If deemed suitable candidates, patients older than 65 years may undergo a lung transplant without any significant increase in short-term mortality,[9] though, as expected, longer-term survival is less than that in younger patients.[11,12]

In contrast to that in uninfected patients, outcomes in lung transplant recipients with chronic (HCV) infections are less well established. Although a previous retrospective single-center study described no difference in survival between lung transplant recipients who were HCV positive and those who were HCV negative,[13] a recent study in 17,762 lung transplant recipients showed a moderate decrease in survival of those with chronic HCV.[14] Newer therapeutic agents such as sofosbuvir and velpatasvir may be effective in reducing the increased mortality in lung transplant recipients with chronic HCV.[15,16] As the management and transplant outcomes of patients with HIV infection continue to improve, patients with HIV may be considered for receiving a lung transplant on an individual basis. The passage of the HIV Organ Policy Equity Act into law permits transplanting lungs from HIV-infected donors to HIV-infected recipients.[17]

Esophageal dysmotility and gastroesophageal reflux (GER) are common in patients with end-stage pulmonary disease[18-22] and may increase across time after lung transplant.[23] GER has also been associated with early allograft injury,[24] which independently predicts bronchiolitis obliterans syndrome and survival after lung transplant.[25,26] Thus, preoperative initiation of antireflux interventions in candidates for lung transplant who have GER may improve pretransplant lung function,[27] transplant-free survival,[28] and outcomes after lung transplant.[29]

Optimizing Medical Comorbidities

End-stage lung disease is often associated with sleep-disordered breathing,[30] microaspiration from GER,[31] pulmonary hypertension,[32] deconditioning,[33] coronary artery disease,[34] and venous thromboembolic disease,[35] with anxiety[36,37] and depression[36,37] often exacerbated by the uncertainty that characterizes the lung transplant process.[38] Efforts targeted at these comorbidities to optimize the patient and prepare for surgery may reduce the risk of complications and improve outcomes.

Pulmonary Rehabilitation

End-stage pulmonary diseases are frequently associated with sedentariness, deconditioning, and skeletal muscle dysfunction[39] that may be improved by pulmonary rehabilitation. Pulmonary rehabilitation enhances exercise capacity and maintains oxygen uptake in candidates for lung transplant.[40-42] Identifying and targeting patients who are at risk and frail before lung transplant may reduce perioperative complications and

TABLE 3] Absolute and Relative Contraindications to Lung Transplant

Absolute contraindications
Recent history of malignancy
Significant dysfunction of another major organ system (such as the heart, liver, kidney, or brain) refractory to therapy, unless combined organ transplants can be performed
Atherosclerotic disease that remains uncorrected, with suspected or confirmed end-organ ischemia or dysfunction and/or coronary artery disease, not amenable to revascularization
Acute medical instability, such as acute sepsis, myocardial infarction, and liver failure
Uncorrectable bleeding disorder
Chronic infection with highly virulent and/or multidrug-resistant pathogens that are poorly controlled before transplant
Active Mycobacterium tuberculosis infection
Significant chest wall or spinal deformity likely to result in severe restriction after transplant
Class II or III obesity (BMI $\geq$ 35 kg/m^2)
Noncompliance with medical therapy or history of recurrent or extended periods of noncompliance with medical therapy likely to increase risk of noncompliance after transplant
Psychiatric or psychologic conditions that may impede the ability to cooperate with the medical and health-care team and/or adhere with complex medical therapy
Lack of adequate or reliable social support
Severe limitation of functional status and poor potential for rehabilitation
Relative contraindications
Age > 65 years and low physiologic reserve and/or other relative contraindications
Class I obesity (BMI $\geq$ 30 but < 35 kg/m^2), particularly when truncal or central
Malnutrition, when progressive or severe
Osteoporosis, when severe or symptomatic
Prior extensive chest surgery with lung resection
Mechanical ventilation and/or extracorporeal life support
Colonization or infection with highly resistant or highly virulent pathogens
HIV infection (select centers)
Infection with *Burkholderia cenocepacia*, *Burkholderia gladioli*, and multidrug-resistant *Mycobacterium abscessus*

Adapted from Weill et al.[7]

mitigate disability after lung transplant.[43] Furthermore, participants with greater exercise capacity before lung transplant have more favorable early outcomes, with shorter hospitalization after transplant.[42]

Weight and Nutritional Status

The pretransplant weight and nutritional status of patients with end-stage lung disease may significantly impact postoperative outcomes. The lung transplant evaluation process includes a thorough assessment of the nutritional history, anthropometric data, and biochemical markers of nutrition. Pretransplant nutritional status varies with the underlying lung disease and may lead to patients being underweight, overweight, or obese. BMI is commonly used to classify patients as underweight (BMI < 18.5), overweight (BMI = 25-29.9), or obese (BMI $\geq$ 30).[44,45] Obesity is further divided into class I (BMI = 30-34), class II (BMI = 35-39), and class III (BMI $\geq$ 40).[44,45] Postoperative immunosuppressive therapy exacerbates the preexisting risk of infection particularly in those with positive markers of malnutrition.[46] Approximately 12% of patients undergoing lung transplant have a low BMI[44] and may have decreased survival after lung transplant.[44,47] Similarly, data from the United Network for Organ Sharing show that patients who are obese constitute more than 11% of US lung transplant recipients.[48] Given that 69% of US adults are overweight or obese, this percentage is likely to increase.

As observed in candidates for lung transplant with low BMI, being overweight or obese was previously associated with increased mortality risk.[44,49] However, a large study suggests that survival in the first year after transplant may not be decreased in patients with a BMI 25.0 to 34.9 kg/m^2.[45] Current guidelines include class II obesity as an absolute and class I obesity as a relative contraindication for lung transplant[7] (Table 3). Although leptin levels may supersede BMI as a measure of adiposity and better predict 1-year mortality after lung transplant, BMI remains a readily available tool in guiding management.[45] PCPs are encouraged to optimize the nutritional status of transplant candidates with appropriate corticosteroid withdrawal and avoidance, nutritional counseling, dietary modification, and exercise and lifestyle changes by following guidelines where available.[50,51] In select lung transplant cases, bariatric surgery may be helpful for weight loss and reduction of comorbidities.[52,53]

Optimizing Adherence

The treatment regimen of a patient who has received a transplant consists of lifelong medication therapy; regular evaluation for therapeutic drug monitoring (TDM); surveillance for rejection, infection, or other complications; mitigating risk factors for cardiovascular

disease and cancer; and avoidance of substance dependence.[54] This process can be overwhelming and may result in nonadherence. Initiating measures preoperatively to address identified risk factors adequately could positively impact posttransplant outcomes.[55,56]

Referring pulmonologists and PCPs who have a long-term relationship with their patients are uniquely qualified to identify patients who may benefit from adherence-enhancing interventions and addressing issues with social support. A team approach to interventions including cognitive therapy and behavioral counseling may be effective in improving long-term medication adherence.[57,58] When possible, therapy with immunosuppressive regimens that have a reduced dose frequency may be used to improve medication adherence and patient satisfaction.[59]

Restricted Transfusion of Blood Products

As in the general population, patients may develop acute lung injury from transfusion of blood products.[60] Repeated transfusion of blood products[61] increases the risk of developing donor-specific anti-human leukocyte antigen antibodies in the sera of transplant recipients (humoral sensitization), raising the potential for acute rejection and mortality.[61,62] To prevent transfusion-associated graft-vs-host disease in patients who are immunocompromised who are treated with lymphocyte-depleting monoclonal antibodies, a rare condition, irradiation of whole blood and blood components is currently recommended.[63,64] In the posttransplant phase, patients who are cytomegalovirus (CMV) seronegative who are receiving seronegative organs should receive CMV-safe blood products (leukoreduced or from donors who are CMV seronegative). Overall, the benefit of transfusion of any blood product needs to outweigh the risk, and alternatives to the use of blood products should be encouraged.

Immunization

Every effort should be made to ensure the transplant candidates, close contacts, and health-care workers have completed the recommended vaccinations prior to transplant.[65] The vaccination status of potential transplant candidates is reviewed at the first clinic visit and a strategy decided on.[65-67] Any patient receiving high-dose corticosteroids or immunosuppressive medications should avoid live attenuated vaccines, including influenza virus (inactivated influenza vaccine is safe), rotavirus, varicella zoster, measles, mumps, and rubella.[65] The US Centers for Disease Control and Prevention website provides direct access to vaccination recommendations at http://www.cdc.gov/vaccines.

Cotreatment of Patients After Transplant

The important factors to consider in care after lung transplant include the altered immune system, the denervated lung graft, and a high potential for drug-drug interactions.

Routine Posttransplant Care

Hypertension: The 5-year prevalence of hypertension in adults after lung transplant approaches 62%,[68,69] surpassing that of the general US population.[70] The 2014 evidence-based guideline for the management of high BP in adults by the Eighth Joint National Committee[71] recommends treatment of patients with hypertension who are 60 years or older to a target BP $<$ 150/90 mm Hg. Those aged 30 to 59 years should have a diastolic BP $<$ 90 mm Hg, and patients younger than 30 years should have their BP reduced to $<$ 140/90 mm Hg. The target BP for patients with coexistent diabetes mellitus (DM) or chronic renal impairment is similar to that of patients with hypertension who are younger than 60 years.[71]

Although calcineurin inhibitors (CNIs) have been implicated in the development of hypertension and renal failure after lung transplant, renal impairment should not be routinely attributed to CNIs.[72] When choosing an antihypertensive agent, the physician should consider comorbid conditions and drug interactions. Calcium channel blockers may counteract CNI-mediated hypertension. Unlike diltiazem, amlodipine lacks significant interaction with CNIs and hence could be a safe first choice followed by angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. In the presence of proteinuria or DM, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are preferred.[73] After lung transplant, diuretics mitigate volume overload, and beta-blockers are deemed safe.

Diabetes Mellitus: Lung transplant recipients with DM have an increased risk of 5- and 10-year mortality after transplant.[74] Some studies estimate that the incidence of posttransplant DM exceeds 30%[75,76] and that the prevalence of DM is $>$ 60% in patients with CF.[76,77] Preexisting DM in lung transplant recipients can worsen because of use of steroids and CNIs.

Guidelines[78] state that posttransplant DM can be diagnosed when (1) repeated measurements of fasting glucose exceed 126 mg/dL; (2) random measurements of glucose exceed 200 mg/dL with symptoms; (3) 2-hour glucose measurement after an oral glucose tolerance test exceeds 200 mg/dL; or (4) glycosylated hemoglobin is > 6.5%, except for the first year after lung transplant when transfusion of packed red blood cells can alter the glycosylated hemoglobin results. These guidelines recommend fasting plasma glucose monitoring weekly during the first month and then every 3 months for 1 year and annually after that.

In the management of posttransplant DM, the choice of therapy should be tailored to the patient. Metformin is contraindicated in most transplant patients with impaired renal or hepatic function[79] because patients with an unstable glomerular filtration rate may be at increased risk of lactic acidosis. Gastrointestinal adverse effects and altered peak immunosuppressant levels with the use of glucagon-like peptide-1 agonists such as liraglutide and exenatide are concerning. Extreme caution should be exercised with the use of sodium-glucose cotransporter-2 inhibitors because of their association with greater risk of infection and diabetic ketoacidosis in transplant recipients.[80] In suboptimal glycemic control, a more aggressive approach such as the use of an insulin pump may be beneficial.[80] Dietary and lifestyle modifications such as exercise and weight optimization and annual screening are performed as in the general population.

Dyslipidemia: Hyperlipidemia is prevalent and predicts rapid decline in renal function, greater incidence of major cardiovascular events, and worsened mortality in lung transplant recipients.[81,82] Drug therapy is initiated in patients with a history of heart disease, stroke, and low-density lipoprotein cholesterol levels > 190 mg/dL; patients with DM aged 40 to 75 years with a low-density lipoprotein cholesterol level of 70 to 189 mg/dL; and patients with a global 10-year risk of cardiovascular disease that exceeds 7.5%. Current guidelines in patients with transplants suggest statins as first-line therapy for hypercholesterolemia.[83] However, caution and clinical judgment must be used when a combination of statins and/or fibrates with CNIs is used due to the increased risk of rhabdomyolysis and nephrotoxicity.[84,85]

Bone Health: In lung transplant candidates, the prevalence of osteoporosis and combined osteopenia and osteoporosis exceed 37% and 69%, respectively.[86,87] Hence, vitamin D levels and bone mineral density are routinely included in the evaluation of lung transplant candidates. Avoidance of tobacco and alcohol and regular weight-bearing exercise help preserve bone density. After lung transplant, all patients should receive the recommended daily allowance for calcium (1,000-1,500 mg/d) and vitamin D (400-800 IU/d). Studies in lung transplant recipients suggest that bisphosphonate may be the most effective choice in the prevention of increased bone resorption and rapid bone loss early after transplant,[88,89] and recombinant human parathyroid hormone (teriparatide) remains useful in the treatment of glucocorticoid-induced osteoporosis.[90,91] After initial bone mineral density assessment, follow-up testing can range from 2 to 3 years for those with osteopenia and normal bone mineral density and annually for those with osteoporosis.

Psychologic Issues, Return to Work, Recreation, and Life: Transplant recipients become increasingly self-reliant and independent as they progress further into the years after lung transplant; however, when persistent, depressive symptoms and lower neurocognitive performance are associated with decreased survival.[92,93] Selective serotonin reuptake inhibitors are well tolerated and effective therapies for depression, posttraumatic stress disorder and panic disorder. Among these medications, the risk of drug-drug interactions appears to be least in patients receiving citalopram and escitalopram.[94] In difficult cases, referral for therapeutic intervention by psychiatrists with a special interest in LTx may be required.

Soon after transplant, patients often look and feel like they had before transplant, and many wish to resume their pretransplant healthy lifestyle.[95] Posttransplant employment rates vary substantially and could exceed 40%.[95] The only restrictions would be to avoid activities that could potentially increase the risk of infections. To our knowledge, there are no studies specifically addressing limitations in return to driving and operating a vehicle in patients with lung transplants.

Reproductive Health: Pregnant lung transplant recipients are at increased risk of acute rejection and progressive graft dysfunction, so spirometry should be monitored and changes investigated. Approximately 40% to 50% of pregnancies among lung transplant recipients result in a live birth.[96,97] The incidence of birth defects appears similar to that in the general population but is increased for pregnancies in patients

using mycophenolate and mechanistic target of rapamycin (mTOR) inhibitors.[97]

Although pregnancy is not discouraged in patients with lung transplants, the process is best meticulously planned.[98] Genetic counseling is crucial for patients with hereditary diseases, including heritable pulmonary hypertension, CF, familial pulmonary fibrosis, and alpha-1 antitrypsin deficiency. Although the timing is an area of debate, most centers recommend waiting for 1 to 2 years after lung transplant before conception.[96,99] Patients need to be counseled regarding the relatively limited long-term survival of lung transplant recipients and the impact of pregnancy on long-term outcomes further confounding the ability to participate in raising the child. Extrapolation from heart transplant data suggests that paternity by lung transplant recipients may be safe.[100]

Cancer Screening and Preparation for Surgical Procedures: Malignancy is a major cause of late deaths in lung transplant survivors, with prevalence increasing across time to 20% 10 years after lung transplant.[101] Lung cancer risk is increased sixfold in lung transplant recipients.[102] In addition to the usual risk factors effective in the general population, such as exposure to tobacco, alcohol use, age, and genetic predisposition, immunosuppression-induced reduction of cancer immunosurveillance and a higher risk of oncogenic viral infections increase the incidence of malignancy.[103,104] Dermatologic malignancies, especially squamous cell and basal cell carcinoma, are the most frequent malignancies in organ transplant recipients[105]; therefore, skin cancer surveillance with dermatologic examinations every 6 or 12 months is recommended.[106,107] mTOR inhibitors, sirolimus, and everolimus have antineoplastic properties and are associated with significantly reduced risk of developing posttransplant malignancy.[108] Lung transplant recipients also have an increased incidence of the relatively rare tumors, such as posttransplant lymphoproliferative disorders, Kaposi sarcoma, and various sarcomas.[109] The beneficial effect of aggressive management and treatment for earlier-stage disease underscores the need for regular screening (Table 1).

Lung transplant recipients can safely undergo surgery when their clinical care is optimized. Sirolimus and everolimus may impair wound healing, so the risks and benefits of preoperative cessation and replacement with another agent should be discussed. Lung transplant recipients receiving corticosteroid therapy may require perioperative stress-dose steroids.

Drug Interactions

The primary immunosuppressive therapies commonly used in various combinations for maintenance in patients with lung transplants include corticosteroids, CNIs, antimetabolite cell cycle blockers, and mTOR inhibitors.[110] CNIs and mTOR inhibitors are metabolized through the cytochrome P450 3A4 system and have significant interactions with many commonly used medications (Table 4).[111] Modest alterations in medication doses may lead to therapeutic failure or severe adverse drug reactions because of their narrow therapeutic indexes. Such consequences may be irreversible and could result in graft loss, disability, or death. TDM is routinely performed for mTOR inhibitors and CNIs to minimize these risks.

Although TDM is not commonly used for mycophenolate or azathioprine, a number of drug interactions are particularly important: Bile acid sequestrants, antacids,

TABLE 4] Significant Drug Interactions for Cytochrome P450 3A4 System

Inducers (Risk of Rejection)	Inhibitors (Risk of Toxicity)
Barbiturates	Amiodarone
Carbamazepine	Azole antifungals
Glucocorticoids	Fluconazole
HIV antivirals	Itraconazole
Efavirenz	Ketoconazole
Nevirapine	Posaconazole
Nafcillin	
Phenobarbital	Calcium channel blockers
Phenytoin	Diltiazem
Pioglitazone	Nicardipine
Rifabutin	Verapamil
Rifampin	Cimetidine
Troglitazone	Ciprofloxacin
St. John wort	Glucocorticoids
	HIV antivirals
	Indinavir
	Nelfinavir
	Ritonavir
	Saquinavir
	Macrolides
	Clarithromycin
	Erythromycin
	Telithromycin
	Grapefruit juice

Adapted with permission from the Indiana University School of Medicine Department of Medicine Clinical Pharmacology.[111]

proton pump inhibitors, and rifampin decrease serum concentrations of mycophenolate, whereas acyclovir and valacyclovir increase the levels. Severe bone marrow suppression and cytopenias may occur when azathioprine is used concurrently with allopurinol, captopril, or other angiotensin-converting enzyme inhibitors.[112,113] The transplant center should thus be informed about all medication changes to enable closer monitoring of therapeutic levels until a steady-state level is achieved. Changes in immunosuppressant medications should be made only by the transplant center.

Caution With Generic Substitution of Immunosuppressant Medications: Exposing the lung transplant recipient to different generic formulations of a particular immunosuppressant medication could result in adverse outcomes because of the potential variation in their pharmacokinetic effects and drug-drug interactions.[114,115] The International Society for Heart and Lung Transplantation recommends that[114] (1) patients inform their care coordinators of any potential generic drug substitution of their immunosuppressant medications, (2) generic immunosuppressants should be used with a high degree of caution, and (3) surveillance strategies and frequent TDM should be implemented until stable immunosuppression is achieved.

Common Complications and Emergencies

Allograft Rejection: Despite advances in immunosuppression, the life expectancy of lung transplant recipients remains limited by the occurrence of organ rejection. During the first weeks after transplant, rejection can be classified as (1) acute cellular rejection (ACR), which is T-cell mediated; (2) acute humoral rejection (HR), which is B-cell mediated; and (3) chronic rejection.

ACR is prevalent in the first year after transplant and may affect 50% to 90% of patients. Because patients may be asymptomatic, surveillance, which includes the use of spirometry, is commonly used. FEV_1 and vital capacity may be decreased in $\geq$ 60% of rejection episodes.[116] Any decline that exceeds 10% in home spirometric monitoring should be confirmed with formal spirometry. ACR may manifest with nonspecific symptoms, including hypoxemia, fever, malaise, dyspnea, cough, and fatigue, with or without radiographic airspace opacities.[117] Clinical and radiographic evaluation, pulmonary function tests, bronchoscopic examination, lavage, and transbronchial biopsies are important in the differential diagnosis. At histologic evaluation, the severity of ACR is graded on a scale of 0 (absent) to 4 (severe).[118] Treatment with high-dose steroids or T-cell-depleting antibodies is often necessary because recurrent or severe episodes of acute rejection increase the risk for allograft dysfunction.

HR is increasingly recognized in LTx. Although the exact underlying mechanisms are poorly understood, HR is thought to result from complement activation and graft dysfunction due to preexisting or de novo donor-specific antibodies, present in up to 15% of lung transplant recipients.[119-121] The clinical manifestation of acute HR is similar to that of ACR, and pathologic demonstration of vascular endothelial inflammation and immunologic evidence of complement deposition should heighten suspicion for acute HR.[118] B-cell depleting therapies such as intravenous immunoglobulin and rituximab with or without plasmapheresis have demonstrated usefulness in clearing donor-specific antibodies.[122-124]

After the first year, the risk of acute rejection substantially decreases but is never eliminated. When declining lung function persists for at least 3 weeks without the FEV_1 and/or FVC returning to $>$ 90% of the postoperative best values, chronic lung allograft dysfunction is suspected. This dysfunction commonly manifests as a physiologic obstruction and is caused by obliterative bronchiolitis, which is characterized by a fibroproliferative airway response from alloimmune and nonalloimmune factors (bronchiolitis obliterans syndrome).[125,126] Less commonly, chronic lung allograft dysfunction may manifest as a restrictive pattern (FVC $<$ 80% of posttransplant baseline FVC) with predominantly upper zone subpleural infiltrates (restrictive allograft syndrome).[127,128] Chronic rejection in either the restrictive or obstructive form remains the leading cause of death during the first year after lung transplant and affects up to one-half of all those surviving beyond 5 years.

Infectious Complications: Lung transplant recipients are at constant risk of infection, which remains one of the most important causes of postoperative morbidity and mortality. Multiple factors contribute to the dramatic reduction in airway defense mechanisms. These include surgical denervation, loss of mucosal barrier, lack of bronchial artery vascularization, disrupted lymphatic channels, blunted cough reflex, and impaired mucociliary clearance. Additionally, immunosuppressive therapy and continuous environmental exposure to irritants and microorganisms heighten this risk. Infections

can be acquired endogenously, from donors, or from the environment. Lung transplant recipients are thus counseled on strategies for safe living and ways to minimize the risk of infection (Table 5).[129]

Early and specific diagnosis must be accompanied by rapid and aggressive clinical treatment to optimize infection outcomes in patients with transplants. In the first 6 months after lung transplant, viruses such as CMV, Epstein-Barr virus, human herpesvirus 6 cause clinical disease; and in combination with higher immunosuppressant levels can lead to opportunistic infections such as *Listeria monocytogenes*, *Aspergillus fumigatus*, and *Pneumocystis jirovecii* even without an intense exposure. Despite universal prophylaxis, CMV infection will occur in up to one-third of lung transplant recipients within the first postoperative year. Prophylaxis with oral valganciclovir decreases risk of CMV infection and disease severity.[130,131] Quantification of circulating or alveolar lavage CMV viral load by using nucleic acid amplification testing techniques or pp65 assays does not always correlate with tissue invasion, and definitive diagnosis requires demonstration of characteristic inclusion bodies or antigens in the lung tissue or alveolar lavage cells.[131] Patients with symptomatic infection (CMV syndrome) frequently present with malaise, fever, leukopenia, nonproductive cough, and hypoxemia. CMV infection may also involve other organ systems such as tissue-invasive disease in the central nervous system, liver, and gastrointestinal tract. A 2- to 3-week course of induction with ganciclovir or valganciclovir, followed by maintenance with valganciclovir, is typically used for therapy.[131] Ganciclovir resistance should be suspected with clinical treatment failure or breakthrough viremia.[131] Alternate therapies such as cidofovir or foscarnet should be explored after confirmation of mutations that confer resistance to ganciclovir.

TABLE 5] Summary of Recommendations for Safe Living

Wash hands frequently and thoroughly, particularly before touching mucous membranes
Avoid close contact with persons with respiratory illnesses
Avoid crowded areas, particularly during peak season of viral infections and augmented immunosuppression
Avoid, if possible, other occupational risks, including working in animal care settings, construction, gardening, landscaping, and farming
Avoid construction sites or home remodeling projects
Avoid plant and soil aerosols (such as mulching), pigeon and other bird droppings, chicken coops, and caves
Wear a mask if exposure to high-risk areas is unavoidable
Do not use unscreened or untreated well water
Avoid swimming in water contaminated with human or animal waste
Do not consume unpasteurized dairy, fruit, or vegetable juice or cider
Do not consume raw seed sprouts, raw or undercooked eggs, meat, poultry, or seafood
Do not consume uncooked pâté, meat spreads, cold-cuts, and smoked seafood
Avoid cross-contamination when preparing food (eg, keep cooked and raw foods separate and use cleaned or separate cutting boards)
Wash fruits and vegetables thoroughly before consumption (even if labeled prewashed)
Weigh the benefits of pet ownership with potential risks for transmission of infection
Avoid working with animals during maximal immunosuppression
Avoid cleaning birdcages, bird feeders, and litter boxes, and handling animal feces

Adapted from Avery et al.[129]

Bacteria such as *Pseudomonas aeruginosa* and *Staphylococcus aureus* are among the fatal causes of infection in the early period after lung transplant.[132] Pneumocystis pneumonia, which is up to five times more prevalent after lung than other organ transplants, may be diminished with the routine use of prophylactic agents such as trimethoprim-sulfamethoxazole.[133]

Fungal infections are more common in recipients of lung transplants than of most other solid organs[134,135] and are predominantly due to candida (extrapulmonary infection) or Aspergillus,[134,135] and less commonly *Cryptococcus neoformans* and the endemic fungi. Although extrapulmonary candida infections have been declining, Aspergillus remains a predominant cause of pulmonary fungal infection in lung transplant recipients. Although consensus on the choice of antifungal agents, route of administration, and duration of prophylaxis has not been established, oral azoles and inhaled amphotericin are useful agents in the prophylaxis of airway aspergillosis.[136] Conversely, invasive pulmonary aspergillosis characterized by isolated or multiple radiographic nodules with or without cavitation (halo sign) is more severe and frequently occurs within 1 year after lung transplant.[137] Serum and bronchoalveolar lavage galactomannan have a high specificity for the organism, but poor sensitivity for diagnosis,[138] and the role of nucleic acid amplification testing is evolving. Therefore, tissue sampling is often required for definitive

TABLE 6] Indications for Nontransplant Physician to Contact the Transplant Center

General
1. Hospitalization
2. Change in medication (addition or deletion)
3. Hypotension or unexplained drop in systolic BP of 20 from baseline
4. Increase in resting heart rate > 10 over baseline
5. Fever ≥ 101°F or any unexplained fever ≥ 100.5°F for ≥ 48 hours
6. Weight gain of 2 or more pounds in 1 week
7. Unexplained weight loss of 5 or more pounds
8. Elective surgery
Cardiopulmonary
1. Increased shortness of breath
2. Pneumonia
3. Any respiratory infection in a lung transplant patient
4. Decline of > 10% FEV_1 in lung transplant patients
5. Syncope
6. Chest pain other than musculoskeletal
7. Myocardial infarction, arrhythmia, change in ejection fraction
Gastrointestinal
1. Abdominal pain other than constipation or gas
2. Nausea, vomiting, or diarrhea
3. Major abdominal disease
Neurologic
1. Cerebral vascular event
2. Seizure
3. Mental status changes
Others
1. New-onset renal failure
2. Malignancy
3. Intolerance of oral medications
4. Noncompliance

Adapted with permission from the American Society of Transplantation.[6]

diagnosis. First-line treatment for invasive aspergillosis remains voriconazole with TDM. Alternatives include posaconazole, isavuconazol, and liposomal amphotericin B.[139,140] Although echinocandins are effective in yeast infections and may demonstrate acceptable pharmacokinetics, they have not been studied as first-line treatment for invasive aspergillosis in solid organ transplant recipients.[141] Nontransplant physicians are encouraged to contact the transplant center at the earliest suspicion of infection because of the broad spectrum of potential pathogens and the nonspecificity of signs and symptoms in patients with lung transplants (Table 6).

Conclusions

An increasing population is experiencing the benefits of LTx as an effective treatment for advanced chronic respiratory failure. However, a larger proportion of patients remain in need of lung transplant. Effective collaboration between transplant and nontransplant physicians is required to meet this demand and sustain progressive improvement in survival and quality-of-life outcomes. We have outlined the salient parts of this partnership and hope this stimulates further discussion among all parties involved to ensure that the care of this vulnerable transplant population is seamlessly integrated.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following: M. E. S. has received institutional funding for idiopathic pulmonary fibrosis research from Bristol-Myers Squibb, Genentech, Gilead Sciences, and MedImmune, and she serves on a data monitoring committee for Boehringer Ingelheim and participated in an advisory committee for Genentech. R. B. received institutional funding for research from Gilead Sciences, Medtronic, Reata Pharmaceuticals, and United Therapeutics Corporation. None declared (A. A., E. G., R. G.).

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

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