9 Lung transplantation

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Allotransplantation of the human lung was first performed in 1963 by Dr James Hardy at the University of Mississippi. It did not become successful enough to achieve acceptance as a treatment for end-stage lung disease (ESLD) until the mid-1980s to the early 1990s when improved surgical techniques, advances in organ preservation, and the development and clinical implementation of novel immunosuppressive drugs allowed long-term survival of lung allograft recipients. Lung transplantation has evolved considerably over the past two decades and is now a definitive treatment for ESLDs that do not respond to other therapeutic interventions. As lung transplantation has become accepted as a life-prolonging therapy for ESLD and performed at various centers world-wide, many complications have been identified, and methods for monitoring and treating those complications have arisen. Despite considerable progress in preventing and treating complications, only half of recipients survive more than 5 years after receiving a lung transplant. The risks and benefits of lung transplantation must be carefully weighed for each patient. In addition, the timing of the procedure is of critical importance. Thus, a great deal of attention has been focused on appropriate referral criteria and timing for this procedure in order to maximize its benefit. Improvements in surgical technique and immunosuppressive regimens combined with a growing awareness of common complications and the measures to prevent them have extended survival and provided most recipients with an improved quality of life after lung transplantation.

This chapter focuses on the three main aspects of optimizing the outcome of lung transplantation: first, patient selection and appropriate timing and criteria for lung transplantation is reviewed; the focus then turns to the technical aspects of the procedure; finally, attention focuses on perioperative and postoperative complications and strategies to prevent or treat such complications.

Selection of patients for lung transplantation

Indications and contraindications

Indications for lung transplantation include the broad categories of obstructive, restrictive, suppurative, and vascular pulmonary diseases. Older adults undergo transplantation much more frequently for chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) than children and young adults, who undergo lung transplantation predominantly for suppurative lung diseases, of which cystic fibrosis (CF) is the most common.

The task of determining eligibility for lung transplantation should be the responsibility of a multidisciplinary team that evaluates both the physiologic and psychosocial characteristics of individuals referred for transplantation. This team typically consists of physicians (medical and surgical), nurses, pharmacists, mental health specialists, and social workers. Patients and families should be informed of the rigors inherent

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in undergoing lung transplantation. Candidates for lung transplantation must have the ability to deal with these challenges physically, psychologically, and financially.

In 1998, the American Thoracic Society (ATS) and the European Respiratory Society (ERS) developed a consensus statement for the selection of candidates for lung transplantation. This statement, updated in 2006, considers both general and disease-specific factors, which include age, expected survival without lung transplantation, and quality of life. In general, most transplant centers would agree that the upper age limit is 65 years for single lung transplantation (SLT) and 60 years for bilateral lung transplantation (BLT). At the other end of the age spectrum, children are limited by the size of their thorax and the size of available donor lungs.

Of particular importance in deciding whether a patient with ESLD is a candidate for lung transplantation is the status of native lung function. As lung transplantation candidates generally wait an average of 18–24 months before they can be transplanted, the referring physician is charged with the difficult task of predicting 2-year mortality for their patients with ESLD so that the effectiveness of this potentially life-prolonging procedure can be optimized. Table 9.1

Table 9.1 Indications for disease-specific patient referral and transplantation

Recipient indication	Referral	Transplantation
Obstructive lung disease • COPD • Obliterative/ constrictive bronchiolitis	• BODE index >5 (BODE is a composite score based on BMI, FEV_1, dyspnea index, and exercise capacity) • Criteria used before the creation of the BODE index: • Post-bronchodilator FEV_1 < 25% of predicted normal value • $PaCO_2$ > 7.3 kPa (55 mmHg) • Associated pulmonary arterial hypertension/cor pulmonale	Patients with a BODE index of 7–10 or at least one of: • history of hospitalization for exacerbation associated with acute hypercapnia (PCO_2 >50 mmHg) • pulmonary hypertension or cor pulmonale (or both) despite supplemental oxygen therapy • FEV_1 < 20% predicted and either *D*LCO < 20% predicted or homogeneous distribution of emphysema
Pulmonary fibrosis • IPF • Fibrotic NSIP • Sarcoidosis • Other ILD	Histologic or radiologic evidence of UIP irrespective of VC Histologic evidence of fibrotic NSIP Other characteristic with predictive value (IPF): • VC < 60–70% predicted • DL_{CO} < 50–60% predicted • Resting hypoxemia (PaO_2 < 7.3 kPa [55 mmHg]) • Hypercapnia ($PaCO_2$ >6 kPa [45 mmHg]) • Desaturation during 6-MWT to <88% • Secondary pulmonary arterial hypertension • NYHA functional class III/IV for other ILD (sarcoidosis, LAM, PLCH)	IPF or fibrotic NSIP: *D*LCO < 39% predicted (IPF) or <35% (fibrotic NSIP) ≥10% decline in FVC during 6-month follow-up (IPF, NSIP) Decrease in oxyhemoglobin saturation to <88% during 6MWT Honeycomb change on HRCT (fibrosis score >2) Sarcoidosis: NYHA class III/IV and any of: • resting hypoxemia • pulmonary hypertension • right atrial pressure >15 mmHg • LAM or PLCH: severe impairment in lung function and exercise capacity and/or resting hypoxemia

Table 9.1 (*Continued*)

Recipient indication	Referral	Transplantation
Septic obstructive lung disease • Cystic fibrosis • Non-CF bronchiectasis	Post-bronchodilator FEV_1 < 30% (especially young females) Exacerbation of pulmonary disease requiring ICU stay Increasing frequency of exacerbations requiring intravenous antibiotics Refractory and/or recurrent pneumothorax Recurrent hemoptysis not controlled by embolization Other factors with predictive value for CF: • hypercapnia ($PaCO_2$ >6 kPa [45 mmHg]) • rapidly progressive decline in lung function • resting hypoxemia (PaO_2 < 7.3 kPa [55 mmHg])	• Oxygen-dependent respiratory failure • Hypercapnia • Pulmonary hypertension
Pulmonary vascular disease • Primary pulmonary hypertension (PPH) • Chronic thromboembolic disease	• NYHA class III/IV regardless of ongoing therapy • Rapidly progressive disease (e.g. worsening functional capacity despite escalating doses of vasodilator therapy) • Not a surgical candidate if indication is chronic thromboembolic disease	• Persistent NYHA class III/IV on maximal medical therapy • Low (<350 m) or declining 6MWT • Failing therapy with intravenous epoprostenol or equivalent (PPH) • Cardiac index <2 L/min per m^2 • Right atrial pressure > 15 mmHg
Heart and lung disease[a] • Eisenmenger's syndrome • Other cardiopulmonary disease	• NYHA class III/IV despite optimal therapy • Progressive symptoms • Other factors to consider: cor pulmonale, declining cardiac output, presence of cyanosis	• Persistent NYHA class III/IV on maximal medical therapy • Low (<350 m) or declining 6MWT distance

6MWT, 6-minute walk test; BODE, body mass index, airflow obstruction, dyspnea, and exercise capacity index in COPD; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; *D*LCO, diffusion capacity of the lung for carbon monoxide; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; HRCT, high-resolution computed tomography of the thorax; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; LAM, lymphangioleiomyomatosis; NSIP, non-specific interstitial pneumonia; NYHA, New York Heart Association; PLCH, pulmonary Langerhans' cell histiocytosis; PPH, primary pulmonary hypertension; VC, vital capacity; UIP, usual interstitial pneumonia.
[a]Heart–lung transplant usually required.See Orens, et al. *J Heart Lung Transplant* 2006;**25**:745–55.

summarizes referral criteria and ideal timing of transplantation according to specific indications for the procedure. For each indication, guidelines for listing are discussed separately below.

As the primary goal of lung transplantation is to prolong life rather than to permanently cure an ESLD, consideration of how the patient will benefit from lung transplantation must be made. There is ongoing debate about the survival benefit of lung transplantation based on the underlying disease. For the most part, individuals with CF, ILD, and pulmonary hypertension appear to derive a survival benefit from lung transplantation. However, studies evaluating survival benefit for patients with COPD have yielded mixed results. For many patients with an otherwise untreatable form of ESLD, lung transplantation can provide palliation of symptoms and improved quality of life even when long-term survival is not extended. For example, in patients with Eisenmenger's syndrome, a clear survival benefit of lung transplantation has not been identified. However, most patients with this disorder experience improvement in exercise tolerance and are able to improve their daily function after lung transplantation.

The absolute and relative contraindications to lung transplantation vary from center to center (see Key points 9.1). In general, absolute contraindications include severe extrapulmonary disease, use of tobacco or alcohol, impaired functional status, and refractory psychosocial problems. Examples of severe extrapulmonary disease that would preclude lung transplantation are infection with human immunodeficiency virus (HIV), active tuberculosis, hepatitis B, significant left ventricular dysfunction, active malignancy within 5 years, renal insufficiency, hepatic dysfunction, portal hypertension, diabetes mellitus with end-organ damage, and osteoporosis with vertebral compression fractures.

Key points 9.1 Absolute and relative contraindications to lung transplantation[a]

- **Absolute contraindications**
  - Malignancy within 2 years, with the exception of cutaneous squamous and basal cell tumors[b]
  - Untreatable, advanced dysfunction of another major organ system
  - Non-curable chronic extrapulmonary infection
  - Significant chest wall and/or spinal deformity
  - Documented non-adherence or inability to follow through with medical therapy and monitoring
  - Untreatable psychiatric or psychologic condition that will impair compliance with medical therapy
  - No reliable social support system
  - Substance addiction within past 6 months
- **Relative contraindications**
  - Critical or unstable condition
  - Severely limited functional status with poor rehabilitation potential
  - Colonization with highly resistant or highly virulent microorganisms
  - Severe obesity (BMI >30 kg/m^2)
  - Severe or symptomatic osteoporosis
  - Mechanical ventilation
  - Suboptimally treated serious medical condition

[a]See Orens et al. *J Heart Lung Transplant* 2006;**25**:745–55.
[b]In general, a 5-year disease-free interval is prudent.

The need for mechanical ventilation at the time of transplantation is an absolute contraindication for some centers but a relative contraindication at others, depending on the underlying ESLD. Adults with CF should not be excluded from undergoing lung transplantation if they are mechanically ventilated, because mortality rates are not influenced by the need for ventilation at the time of transplantation. In contrast, the need for mechanical ventilation in children with CF is associated with poor short- and long-term outcomes. Many individuals require supplemental oxygen and even non-invasive ventilation in the form of bi-level positive airway pressure (BiPAP) as a "bridge" to transplantation. Currently available data suggest that post-transplant outcomes are improved for recipients with CF who use BiPAP before lung transplantation.

There are some factors that may make lung transplantation more challenging and place the patient at considerable risk for suboptimal outcome. Patients who have had previous chest surgery or pleurodesis (chemical or surgical) may have significant pleural fibrosis and adhesion of the visceral and parietal pleura. This makes explantation of the native lungs

extremely difficult and prone to hemorrhagic complications. Nevertheless, prior surgery or pleurodesis is not considered an absolute contraindication to future lung transplantation. Oral corticosteroids are known to impair wound healing, and many centers consider a daily dose of prednisone >20 mg to be a contraindication, although this is not universal.

Pretransplant evaluation

As there are contraindications to lung transplantation, a comprehensive pretransplant evaluation is required to identify potential comorbidities that present potentially insurmountable problems in the perioperative and postoperative periods and that may significantly decrease the likelihood of long-term survival. Table 9.2 lists both medical and psychosocial evaluations that are helpful in assessing risk in a lung transplantation candidate. This list, although extensive, is not absolute and may not cover all situations. Subsequent sections will address specific disease states and/or comorbidities that may require additional evaluation.

COPD and α_1-antitrypsin deficiency-associated emphysema

COPD, including the obstructive disease resulting from α_1-antitrypsin deficiency, is the most common

Table 9.2 Evaluation of potential candidates for lung transplantation

- Psychosocial evaluation
  - ? Tobacco use within 6 months
  - ? Illicit drug use, drug-seeking behavior
  - Compliance with medical therapies
  - ? Significant psychiatric illness
  - Adequate social support
- Cardiopulmonary
  - Full pulmonary function tests
  - Standardized exercise test (e.g., 6-minute walk test)
  - Electrocardiogram
  - Stress echocardiogram (plus coronary catheterization as appropriate)
  - High-resolution CT scan of thorax
  - Lipid profile
- Other
  - Peripheral blood cell survey
  - Glucose and hemoglobin A1C
  - 24-hour creatinine clearance
  - Bone mineral density scan
- Infection specific
  - Quarterly respiratory tract cultures (for suppurative lung disease)
  - Gram-negative bacilli
  - Meticillin-resistant *Staphylococcus aureus*
  - Mycobacteria
  - Fungi
  - Serology
  - HIV
  - Hepatitis B and C
  - Varicella
  - Cytomegalovirus
  - Toxoplasmosis
  - Vaccinations
  - PPD skin test
  - Evaluation and treatment of paranasal sinus disease

indication for lung transplantation in adults. As the surgical risks are lower for SLT versus BLT in patients with COPD, SLT is commonly performed for this lung transplantation indication, which helps to expand the donor pool when a single donor can be used for two recipients. Although there may be an advantage to BLT with regard to outcome and lung function, exercise capacity is comparable for SLT versus BLT recipients with COPD.

Certain criteria must be met to list candidates with COPD for lung transplantation, and these include a demonstrated ability to abstain from smoking. Most transplant centers require abstinence from cigarette smoking anywhere from 6 months to 12 months. Physiologic parameter thresholds for lung transplantation in COPD have included forced expiratory volume at 1 s (FEV_1) <25% predicted without reversibility and/or $PaCO_2$ ≥ 7.3 kPa (55 mmHg) with or without elevated pulmonary artery pressures and progressive deterioration. The most recent recommendations from the International Society for Heart and Lung Transplantation (ISHLT), however, advocate use of the BODE index (body mass index, airflow obstruction, dyspnea, and exercise capacity index in COPD) for decision-making (see Table 9.1) The American Thoracic Society and European Respiratory Society (ATS/ERS) have also made the recommendation that priority for lung transplantation be given to patients who require oxygen supplementation and who exhibit progressive deterioration and elevated $PaCO_2$ because mortality is increased for such patients.

Interstitial lung disease

Idiopathic pulmonary fibrosis (IPF) is the most common form of ILD for which lung transplantation is performed. Indications for referral include symptomatic and progressive disease recalcitrant to therapy, significantly impaired lung function with decrease in forced vital capacity (FVC) to <60–70% of the predicted normal value and/or diffusion capacity for carbon monoxide (*D*LCO) <50–60% predicted. As the median survival after diagnosis of IPF is approximately 2–3 years, current ISHLT guidelines recommend referral to a lung transplantation center at the time of diagnosis due to the progressive nature of the disease. Hemoglobin oxygen desaturation during a 6-minute walk test (6MWT) may be helpful in determining the degree of lung function decline. Specifically, desaturation to 88% or less predicts a survival rate of approximately 35% at 4 years.

The progression of other ILDs is quite variable. In the case of non-specific interstitial lung disease (NSIP) and sarcoidosis, progression tends to be less rapid (compared with IPF) and more likely to respond to immunomodulatory medications. However, the fibrotic variant of NSIP, if accompanied by oxyhemoglobin desaturation to ≤88% during a 6MWT, carries a prognosis that is fairly similar to that for IPF. Therefore, recommendations to refer patients with NSIP are based on the aggressiveness of the disease and whether it is characterized by a cellular and/or fibrotic histopathology. Likewise, sarcoidosis may progress to extensive pulmonary fibrosis, and wait-listed patients with severe impairment of lung function have a projected survival that is very similar to that for wait-listed patients with IPF.

In the case of ILD, SLT is more commonly performed than BLT. However, BLT should be considered if there is significant bronchiectasis in the native lungs that would predispose the lungs to a chronic suppurative process.

Bronchiectasis/Cystic fibrosis

BLT is the recommended procedure for severe suppurative lung disease due to bronchiectasis (sometimes the result of advanced CF), which is typically widespread throughout both lungs. Conventional wisdom dictates that, if only one lung is transplanted, residual infection in the native lung can spread to the transplanted lung and cause unacceptable complications in the immunocompromised recipient. The suppurative and fluctuating nature of CF lung disease presents a significant and often vexing challenge to physicians in determining the appropriate and optimal time for referral as well as preparing the patient for referral to a lung transplantation center.

The presence of multidrug-resistant *Pseudomonas aeruginosa* is not a contraindication for transplantation, but persistent carriage of pan-resistant *P. aeruginosa* is considered to be a contraindication at some centers. However, several studies have shown no difference in post-lung transplantation survival for patients infected with pan-resistant *P. aeruginosa* and those with antibiotic-sensitive strains. Additionally in vitro sensitivities of *P. aeruginosa* may not accurately reflect in vivo sensitivity and should be interpreted with caution because some individuals have been

shown to improve clinically despite the use of anti-pseudomonal antibiotics that would not be considered effective according to in vitro susceptibility testing. In some cases, the use of aerosolized colistin has been reported to cause a re-emergence of sensitive *P. aeruginosa* in CF patients awaiting lung transplantation.

Chronic infection with *Burkholderia cepacia* in patients with CF is viewed by some centers to be a contraindication to lung transplantation. One retrospective study of patients with cystic fibrosis showed that 6-month mortality was significantly increased only in cases where genomovar III strains of *B. cepacia* caused the chronic infection. These data suggest that determining the specific *B. cepacia* genomovar may be useful in weighing the risk of lung transplantation for patients who harbor *B. cepacia* in their respiratory secretions before transplantation.

Aspergillus fumigatus is commonly isolated from respiratory secretions of patients with CF. Surprisingly, this fungus is rarely a serious pathogen in the post-transplant patient with CF. When aspergillosis occurs in lung transplant recipients with CF, it is usually in the form of tracheobronchial aspergillosis in the allograft bronchi adjacent to the anastomoses (the injured epithelium at the anastomosis is susceptible to aspergillus infection as it heals after reperfusion).

Severe malnutrition with very low body mass index (BMI), which frequently occurs in patients with CF and ESLD, may place the patient in a risk category that is too high to safely perform lung transplantation. Supplemental nutrition via enterostomy tube may be required before transplantation to improve a low BMI. Another consideration in patients with CF is the presence of significant hepatobiliary disease. As survival into adulthood progressively increases, advanced liver disease is becoming more prevalent and may pose a problem after otherwise successful lung transplantation. Although combined lung and liver transplantation can be considered, relatively few centers are willing to perform a combined lung–liver transplantation during the same operation.

The timing of referral for patients with advanced CF lung disease presents a significant challenge to referring physicians. The recommended physiologic parameters that predict respiratory failure within 2 years and, thus, the basis for referral include post-bronchodilator $FEV_1 < 30\%$ predicted, $PaO_2 < 7.3$ kPa (55 mmHg), and $PaCO_2 > 6$ kPa (45 mmHg). Other criteria or complex scoring systems that utilize multiple parameters have not shown significantly better predictive value. Determining the optimal time for referral and transplantation for children is particularly difficult. Although FEV_1, PaO_2, and $PaCO_2$ continue to be important factors in deciding when to refer the child with CF for lung transplantation, most centers continue to evaluate on a case-by-case basis. Pneumothorax and hemoptysis are associated with a significant increase in 2-year mortality, even when FEV_1 is not severely impaired, and their occurrence may indicate a need to consider early referral. In addition, a rapid and sustained decline in lung function, especially when occurring in young females, may indicate a need to refer for lung transplantation. Lastly, frequent, recurrent exacerbations that require hospitalizations and/or antibiotic treatment also may herald a rapid decline in lung function and impending need for lung transplantation referral.

Pulmonary hypertension

Patients with primary pulmonary hypertension who meet criteria for New York Heart Association (NHYA) class III or IV, and who have progressive disease despite medical therapy, meet the criteria for lung transplantation. Right heart catheterization measurements that show mean pulmonary artery pressure >55 mmHg, mean right atrial pressure >15 mmHg, and cardiac index <2.0 L/min per m^2 support the decision to refer for lung transplantation. An important decision when evaluating patients with pulmonary hypertension for lung transplantation is whether SLT or BLT should be performed. Although a well-functioning single lung should have adequate capacitance to prevent right heart strain or failure, published data do not provide clear guidelines, and the decision to perform SLT versus BLT should be made on a case-by-case basis. Heart and lung transplantation is necessary when left ventricular function is irreversibly compromised.

Patients with Eisenmenger's complex may tolerate mean pulmonary artery pressures >55 mmHg and mean right atrial pressures >15 mmHg, making their risk of mortality and clinical course more difficult to predict. For these patients, heart–lung transplantation appears to confer a better outcome in regard to mortality.

With the advent of new medications (e.g., bosentan, prostaglandin infusion, and sildenafil) to treat

pulmonary hypertension, patients are able to live longer without the need for lung transplantation. In contrast to other indications for lung transplantation, the need for donor lungs for this indication has decreased with the advent of medical therapies that successfully lower pulmonary arterial pressures and improve cardiac output.

UNOS allocation (old and new systems)

The United Network for Organ Sharing (UNOS) recently made a significant change to the allocation system for lung donation in the USA, and implemented the new system in 2005. Before this change, recipient rank on the lung transplantation wait-list was based on waiting time, blood group compatibility, and size matching. In contrast to policies for heart and liver transplantation, severity of disease was not a factor in the old system, with the exception of patients with IPF, who were automatically credited 90 days of accrued wait-list time due to the relatively severe and progressive nature of their disease.

The new UNOS allocation system does take into account severity of disease and assigns each potential recipient a lung allocation score based on medical information. The medical parameters taken into account by the new lung allocation system (LAS) are listed in Table 9.3. Specific types of ESLD are prioritized according to the inherent degree of severity and expected progression of the disease. However, the LAS scoring system applies only to individuals aged >12 years. For those aged <12 years, waiting time is still the most significant factor in determining lung allocation priority.

Once the potential recipient is determined to be a candidate for lung transplantation, they are registered into the UNet secure internet-based system for organ allocation and data collection, and the data are used to compile a score ranging from 0 to100, with higher scores corresponding to higher priority. This score, along with the ABO blood group compatibility, size matching, and the patient's distance from the hospital, will determine the order of patient eligibility when an offer for a donor lung is received by the lung transplantation center where the patient is listed. In the case of a tie score, time spent on the list is used to break the tie. Information must be updated every 6 months, but data may be updated at any time to reflect changes in the patient's status. If lung transplantation center physicians believe that certain patients have exceptional circumstances and their LAS does not accurately reflect the patient's situation and urgency for transplantation, they may petition the Lung Review Board to determine if an adjustment can be made.

In the case of pediatric lung allocation, lung size needs to be taken into account and recipient priority is based on donor age. Those under the age of 12 continue to have their recipient priority determined

Table 9.3 Lung allocation scoring (LAS) system in the USA

LAS score determinants
• Specific disease indication for lung transplant
• Forced vital capacity (percent predicted)
• Pulmonary arterial systolic pressure
• Supplemental oxygen requirement (L/min)
• Age
• Height and weight
• Functional status (I, II, III)
• 6MWT distance
• Ventilator use
• Pulmonary capillary wedge pressure
• Serum creatinine
• PCO_2
Calculation of the LAS score
• Waiting list survival probability during next year is calculated
• Calculate wait-list urgency
• Calculate post-transplant survival probability during first post-transplantation year
• Calculate post-transplant survival measure
• Calculate raw allocation score
• Raw allocation score is then normalized (0–100; organ offers go to candidate with highest score within specific blood group and thoracic dimension category)

by the time spent on the waiting list. Key points 9.2 also reflects how children receive priority over adult patients for donor lungs.

Key points 9.2 Pediatric transplantation: matching and prioritization

• Donor age (years)	<12	12–17	18+
• First priority recipient	Age <12	Age 12–17	Age ≥12
• Second priority recipient	Age 12–17	Age <12	Age <12
• Third priority recipient	Age 18+	Age 18+	

Policies for listing and delisting in other countries do not use a LAS scoring system as is done in the USA. The Eurotransplant organization, a supranational consortium of numerous European countries, still uses time on the wait-list combined with donor–recipient suitability to match recipients with donor organs. However, patients who display imminent need for invasive mechanical ventilation or other evidence of rapid decompensation can be granted a high urgency status and be given the highest transplant priority.

Before the change in the US allocation system, time spent on the waiting list ranged from a median of 18 months to 24 months and the number of wait-listed lung transplant candidates continued to rise as the donor pool remained static. The goal of the new system is to decrease the number of patients dying while awaiting lung transplantation by allocating lungs to those individuals most in need. The new LAS system takes into account the anticipated benefit linked to the underlying cause of ESLD, as well as the anticipated mortality without a transplant. However, the ability to predict mortality from ESLD continues to be limited due to marked variability across different patient cohorts and disease processes. Early results indicate that the new allocation system has shifted recipient diagnoses toward pulmonary fibrosis while reducing the overall mortality rate for those on lung transplantation wait-lists. One concern is that this shift will tend to select patients who will have a decreased post-transplant survival due to the severity of their illness at the time of transplantation.

Technical considerations

The donor

Careful selection of an organ donor and optimized donor management are crucial determinants of post-lung transplant outcome. Unfortunately, the rate of donor procurement for lungs remains <20% (17% in the USA and 12% in Europe) and represents the major limiting factor for the number of lung transplantations performed. Potential donors vary considerably in terms of clinical stability and organ function, and significant decline in pulmonary function all too frequently occurs during the critical management period when donors are managed in an intensive care setting. The lungs are particularly prone to injury, and maintaining optimal lung function in a potential donor requires tactics that are counterproductive to maintaining optimal function of other organs (e.g., providing high perfusion pressures to maintain adequate intravascular volume for procurement of optimally functioning kidneys). High central venous pressures may cause the lungs to develop hydrostatic edema, loss of compliance, and impaired gas exchange. The period of time from the inciting illness, such as a traumatic brain injury, to the point when brain death is declared poses significant risk for pulmonary complications that include aspiration, barotrauma, ventilator-associated pneumonia, diffuse lung injury, and non-cardiogenic pulmonary edema.

Brain death adversely affects cardiovascular function, and donor management includes measures to achieve optimal hemodynamics by maintaining normovolemia, blood pressure, and cardiac output to sustain adequate perfusion pressure and blood flow, and thereby preserve organ function while trying to limit vasoactive drug requirements. Supportive interventions required to stabilize and maintain optimal organ function in the donor may include infusion of fluids and red blood cells for hypovolemia and anemia, sodium bicarbonate for acidosis, hypotonic solutions for hypernatremia, insulin infusions for hyperglycemia, and vasoactive drug support for hypotension, (see Chapter 3).

Traditional ("standard") criteria that were initially used to define ideal donors included donor age <55 years, minimal tobacco exposure, normal chest radiograph, $PaO_2:FiO_2$ ratio >300 during ventilation with 5 cmH_2O of positive end-expiratory pressure (PEEP) and FiO_2 100%, and the absence of aspiration, purulent secretions, or trauma (Table 9.4). However, adherence to these ideal criteria would exclude most potential donors, and adequate objective evidence to support their value has not been forthcoming. Therefore, most centers have judiciously relaxed these requirements to expand the donor pool. Atelectasis and excessive fluid resuscitation are correctable causes of hypoxemia, and aggressive management protocols that include ventilator manipulation to promote lung expansion, early bronchoscopy and aggressive secretion clearance, antibiotic administration, and judicious fluid management have allowed donors who were initially considered unsuitable by traditional criteria to become lung donors.

Table 9. 4 Criteria for acceptability of donor lungs

Traditional criteria
• Age <50 years
• Minimal tobacco exposure
• Normal chest radiograph
• PaO_2 > 39.9 kPa (300 mmHg) on 5 cmH_2O PEEP with FiO_2 = 100%
• No evidence of aspiration
Liberalized criteria (marginal/extended donor)
• Age up to 65
• Smoking up to 20 pack-years
• Severe chest trauma
• Mechanical ventilation >4 days
• Positive Gram stain on tracheobronchial washing and/or BAL
Interventions to improve donor lung function
• Frequent suctioning to remove secretions
• Ventilatory manipulation to promote lung expansion and reverse atelectasis (e.g. alveolar recruitment with inspiratory pressures at 25 cmH_2O and PEEP 15 cmH_20 for 2 h)
• Reverse fluid overload (diuresis and fluid restriction)
Absolute criteria required when donor lungs with extended criteria utilized
• PaO_2/FiO_2 > 300
• No persistent radiographic infiltrates
• No copious purulent secretions
• No bronchoscopic evidence of aspiration

BAL, bronchoalveolar lavage; PEEP, positive end-expiratory pressure.

Indeed, most centers have relaxed a number of the "standard" criteria (e.g., age up to 65 years, smoking history >20 years, $PaO_2/FiO_2 < 300$), and the acceptance of extended donor criteria coupled with improvements in donor management has contributed to an increase in lung transplantation procedures over the past decade. Outcomes using allografts with extended donor criteria have not been shown to be significantly different from outcomes when lungs were used from candidates who met ideal donor criteria. For certain disease states, however, use of lungs with extended donor criteria may lead to poor outcome. SLT for pulmonary hypertension and IPF with secondary hypertension presents situations in which the native lung would be unable to support a marginal donor lung. In addition, donor conditions that exclude use of a donor lung include uncontrolled sepsis, positive HIV status, viral hepatitis or encephalitis, active tuberculosis, Guillain–Barré syndrome, illicit drug use, malignancy, and significant chronic lung disease. Regardless of HIV antibody testing, potential donors with significant risk factors for HIV infection should be excluded from donation unless the risk to the recipient of not performing the transplantation is perceived to be greater than the risk of transmitting HIV infection and disease to the recipient. These risk factors include men who have had sex with another man within 5 years, use of non-medical drugs via injection within the preceding 5 years, engaging in sex for money or drugs within 5 years, inmates of a correctional institution, and people having contact with an HIV-infected individual within 12 months (sexual, shared needles, open wound contact, or mucous membrane contact).

In addition to the use of lungs with extended donor criteria, some centers have expanded the donor pool further by considering potential donors who do not

meet criteria for brain death but have catastrophic, irreversible illness. Viable lungs can be procured and utilized after life support has been withdrawn and cardiac arrest has occurred in this setting, and the use of lungs from donation after cardiac death (DCD) donors represents one strategy to increase the donor pool. Another technique that can increase the donor pool in lung transplantation is the living lobar lung transplantation. Introduced in 1993, living lobar lung transplantation uses two donors who each provide one lobe (usually the lower lobe) to supply the recipient with adequate lung tissue for the transplant. The most common use of this technique is for patients with CF (usually children) with two parents serving as donors. A recent report of a 10-year experience with living lobar donation indicated that survival was similar to that of recipients transplanted with deceased donor grafts, except in cases of re-transplantation or when the recipient was intubated and mechanically ventilated.

The graft

Careful explantation of the lungs, which is done together with explantation of the heart, is crucial to achieving optimal post-transplant physiologic function. Careful attention to all aspects of excising the lung from the donor and preserving it ex vivo are crucial for preventing primary graft dysfunction (PGD), which accounts for a substantial number of all deaths in lung transplant recipients.

Just before cross-clamping the major vessels to free the lungs from the donor, the explant is typically flushed with epoprostadil followed by flushing with cold preservation fluid, and the explanted lungs are maintained at 4–10°C (on ice) until reimplantation is performed. Retrograde flushing (pulmonary vein to pulmonary artery) with preservation fluid can be done before implantation to try to free any clots that have embolized to the lung before explantation. When retrograde flush is performed through the pulmonary veins *in situ* while the lungs are still ventilated (following antegrade flush), lung preservation may be enhanced with better distribution of flush solution throughout the vasculature and less impairment of surfactant function. Retrograde flush may also be performed in vivo when the lung has been partially implanted (before construction of vascular anastomoses) in the recipient. Once *in situ* perfusion of the donor lungs has been cut off, minimization of ischemic time is of key importance in preventing graft injury. Older donor age and prolonged ischemic time have been shown to correlate with decreased 1-year survival, and early graft function is significantly affected by prolonged ischemic times with a threshold estimated at 330 min, although ischemic time may be extended to 8 h for young donors.

Optimal ex vivo preservation of the donor lung and minimization of ischemic time are critical to postimplantation allograft function. Poor initial graft function can have considerable adverse effects upon postimplantation recovery and prolong the need for invasive mechanical ventilation, thereby predisposing recipients to nosocomial infections and other complications of prolonged intensive care unit (ICU) stays. Furthermore, poor initial graft function may increase the risk of developing subsequent allograft rejection. The ideal preservation solution should prevent intracellular acidosis, calcium accumulation, and edema while suppressing the generation of oxyradicals and promoting the regeneration of intracellular energy metabolism. Although intracellular preservation solutions (e.g., Euro-Collins, University of Wisconsin [UW] Solution) have been used by many centers, experimental and clinical evidence now support the use of extracellular solutions, in particular the low-potassium dextran–glucose agent, Perfadex, as an optimal preservation fluid. Antegrade flush of the lungs is typically performed in concert with inflation of the lungs with an adequate tidal volume (10 mL/kg) and maintenance of airway pressures in the range of 20–25 cmH_2O before cross-clamping. Equilibration airway pressures should, however, be limited to 10–15 cmH_2O to avoid barotrauma during storage and air transport, and flushing pressures should be limited to 10–15 mmHg.

Other therapies may be administered to optimize the donor lung. Prostaglandins, which counteract ischemia-induced vasoconstriction, and corticosteroids, which prevent intense inflammatory responses, are used to prevent reperfusion injury. Newer interventions that seek to prevent or mitigate primary graft dysfunction (PGD) include the use of inhaled nitric oxide (NO), surfactant replacement, continuous infusion of prostaglandin E_1 into the recipient during early stages of reperfusion, preimplantation donor leukocyte depletion, administration of oxyradical scavengers, donor leukocyte infusion, and administer-

ing other anti-inflammatory therapies (inhibition of platelet-activating factor, chemokine receptor inhibition, complement antagonists). Although promising, these latter interventions have yet to be adopted in clinical lung transplantation protocols that attempt to improve early graft function and prevent PGD.

The match

Donor–recipient matching is primarily based on donor lung size, which must approximate the predicted lung size of the recipient, and ABO blood group match. With the exception of living donor lung transplantation, HLA matching is not feasible. Matching for cytomegalovirus (CMV) status is desirable but not mandatory with currently used antiviral prophylaxis.

Size matching is done by measuring dimensions on a standard chest radiograph or computed tomography (CT) of the thorax. Total lung capacity (TLC) of recipients with pulmonary fibrosis usually approximates that of the donor lung post-transplantation when SLT is performed. However, the donor lung may be restricted and TLC may be lower than expected due to increased compliance of the residual native lung when SLT is performed for COPD. TLC should approximate the recipient's predicted value after BLT. For children, size matching varies from institution to institution and even within institutions. Matching recipient and donor within 10 cm or 10% of the body length are two examples of estimations used for size matching in children. If there is a mismatch in the sizing where the donor lung is too large for the recipient thoracic cage, the donor lung can be down-sized via plication or lobectomy.

Case

A suitable donor was identified for a 56-year-old man with idiopathic pulmonary fibrosis. However, CT of the thorax revealed that the donor lung was 12 cm longer than the lung of the recipient. Lobectomy was performed to achieve adequate size matching and single lung transplantation was performed successfully.

The implantation procedure

A well-coordinated effort that minimizes ischemia time and allows the surgical team to create technically perfect vascular and bronchial anastomoses is extremely important in maximizing the likelihood of postoperative success. Inhaled NO and cardiac bypass should be available for every procedure. Intraoperative cardiopulmonary bypass (CPB) or extracorporeal membrane oxygenation (ECMO) may be needed to support the recipient during surgery and should be used as needed to support recipient gas exchange during the procedure. CPB, when performed intraoperatively in higher-risk patients, allows controlled initial reperfusion of the graft(s) while using lower inspired oxygen tensions, thus helping to limit reperfusion injury. In addition to surgical expertise, experienced anesthesiologists play a key role in surgical management. Decisions about the use of double-lumen intubation techniques, ventilation strategies, the need for cardiac bypass, the role of vasoactive medications such as NO, and hemodynamic support, must be addressed jointly by surgeons and anesthesiologists during removal of native lungs and implantation of donor organs.

Single lung transplantation

SLT can be performed for all recipient indications with the exception of suppurative lung diseases (CF and non-CF bronchiectasis). In the case of IPF and pulmonary hypertension, the graft should have optimal appearance and function because the native lung will have little to contribute to respiratory function. Also, although some centers find SLT acceptable for patients with pulmonary hypertension, there may be specific circumstances for which a BLT would be more advantageous. In cases of pulmonary hypertension with left ventricular dysfunction, heart–lung transplantation is indicated.

Ventilation–perfusion (V/Q) scanning in the potential recipient plays an important role in determining which lung should be transplanted. It can demonstrate areas of poor ventilation and perfusion and can estimate the relative contribution of each lung to respiratory function. The native lung with poorest function should be chosen for replacement.

Surgical pneumonectomy is typically performed through a posterolateral incision for SLT recipients. However, posterolateral thoracotomy for the left lung and anterolateral thoracotomy for the right lung will optimally expose the hilar structures. The procedure can be performed without the need for CPB if the non-transplanted native lung has residual function that is

adequate to support the individual during the procedure. The non-transplanted lung is selectively ventilated as the contralateral lung is deflated and removed. If significant hypoxemia occurs due to shunting through the deflated lung, the pulmonary artery is clamped to promote better *V*/*Q* matching. If refractory hypoxemia or other manifestations of inadequate residual lung function occur, CPB should be used.

Once the recipient native lung has been explanted, the donor lung is positioned and anastomoses are made between donor and recipient bronchus, donor and recipient pulmonary artery, and donor pulmonary veins to recipient left atrium. Precautions must be taken not to disrupt the phrenic and vagus nerves and, in the case of left SLT, the recurrent laryngeal nerve. Bronchial anastomoses are often performed by telescoping the donor and recipient bronchi because end-to-end anastomoses tend to require a tissue patch and are more prone to healing complications. As the bronchial circulation provides blood flow to the airways, anastomosis of the donor and recipient bronchial arteries may theoretically prevent airway mucosal ischemia and anastomotic complications. However, outcomes when the bronchial arteries are anastomosed are not significantly different from outcomes without bronchial artery anastomosis, and perfusion of the bronchi via retrograde flow through the bronchial artery from the pulmonary circulation appears to be adequate to promote healing and to maintain viability of the bronchial mucosa.

Bilateral lung transplantation

Originally performed as an en bloc procedure (double lung transplantation) whereby both lungs were transplanted at once via a single airway anastomosis at the trachea, BLT is now most often performed by bilateral sequential transplantation of the lungs via an anterior clam-shell incision. The advantage to sequential transplantation is that the patient may not need to undergo CPB, and the bilateral bronchial anastomoses are more stable than a single tracheal anastomosis. In addition, the transverse thoracosternotomy incision used in the sequential technique allows for better exposure of the pleura when compared with the median sternotomy incision used in the en bloc double lung transplant procedure. The contralateral lung is selectively ventilated during the transplantation, and CPB can be utilized in the event of refractory hypoxemia or when transplantation is being performed for pulmonary hypertension. Hypoxemia or hemodynamic instability may occur during cross-clamping of the first pulmonary artery, after perfusion of the first transplanted lung, or after clamping of the second pulmonary artery.

Living lobar transplantation

As previously stated, the living lobar lung transplantation represents a technique established to expedite transplantation and relieve some of the stress on the UNOS donor pool. The donors must be larger than the recipient to allow adequate matching of the donor lobe to the dimensions of the recipient thoracic cage. Inadequate donor graft size may result in pleural complications and the development of bullae. Blood group matching must be performed, but donor–recipient HLA mismatches appear to have no significant influence on survival. The operation is performed similarly to SLT or sequential BLT. Donor morbidity generally consists of a prolonged need for thoracotomy tubes or a need for additional thoracotomy tubes, and donor mortality is quite low. Recipient survival has been reported to be comparable to cadaveric lung transplant survival at 1, 3 and 5 years post-transplantation.

The postoperative period

The perioperative period

Initial postoperative management is directed by the hemodynamic status of the patient and initiation of appropriate immunosuppressive and prophylactic therapies. Upon completion of the surgical procedure, intensive supportive care should start, including hemodynamic monitoring, close attention to allograft function, use of vasoactive medications as needed to maintain appropriate perfusion, assessment of renal function, appropriate prophylaxis for peptic ulcer disease and deep vein thrombosis, and strict glucose control and nutritional supplementation. Hemodynamic support during the early postoperative period should focus on avoiding pulmonary edema while maintaining adequate perfusion pressure. Pulmonary capillary occlusion pressure should be kept as low as possible while maintaining adequate urine output and systemic blood pressure. Vasoactive agents, fluid restriction, and diuretics should be used as needed to achieve this goal.

The goals of mechanical ventilation include avoiding any additional damage to the reperfused allograft and using low tidal volume ventilation strategies as needed to avoid barotrauma. Inspired oxygen should be weaned as rapidly as possible to avoid tissue injury due to hyperoxia. The ultimate goal is to liberate the patient from mechanical ventilation as soon as possible and thereby avoid complications related to prolonged ventilatory support. In the case of SLT for COPD, PEEP and high airway pressures should be minimized to avoid overdistension of the native lung. In extenuating circumstances such as severe early graft failure, individual lung ventilation may be needed to provide appropriate airway pressures for each lung and avoid ventilator-induced lung injury. Most recipients are weaned from mechanical ventilation within 48–72 h. In the case of lung transplantation for pulmonary hypertension, the patients may need to be sedated for a slightly longer period of time to prevent the occurrence of hemodynamic compromise due to the relative instability of the pulmonary vascular bed combined with a heart that has been chronically conditioned to high pulmonary artery pressures.

Protocols should be in place to begin immunosuppressive therapies and prophylactic antimicrobial agents to prevent rejection and post-lung transplant infectious complications. Immunosuppressive regimens are discussed below. Monitoring for hyperacute rejection (a rare occurrence) and acute rejection (AR) is extremely important and is discussed below.

Complications in the perioperative period

Perioperative lung transplantation complications include, but are not limited to, pulmonary edema, immediate graft failure, acute bacterial infection, bleeding, diaphragmatic paresis or paralysis, anastomotic stenosis or dehiscence, renal failure, and stroke (Table 9.5). Size matching is a key issue in transferring lungs from one thoracic cavity to another, and problems may arise from size discrepancy. Undersized lungs may over-inflate, leading to possible graft dysfunction, and pleural effusions may form. Lungs that are too large for the recipient are prone to the development of atelectasis and pneumonia, and oversized lungs may compromise hemodynamic parameters. Although size matching is important, surgical lung volume reduction can be done to allow a better fit for oversized lungs and has no apparent ill-effects on graft survival or mortality.

Pulmonary edema is almost always present in the immediate postoperative period. Although usually mild, severe pulmonary edema may occur as a consequence of multiple complications that include fluid overload, reperfusion injury, massive transfusions, and acute renal failure. Disruption of lymphatic vessels or vascular anastomoses also may cause pulmonary edema.

Reperfusion lung injury (Figure 9.1) caused by damage of endothelial–alveolar interfaces is a major contributor to early respiratory failure and mortality in patients receiving lung transplantation and is now termed PGD and graded on the basis of severity of gas exchange impairment (see Key points 9.3). PGD occurs in 13–25% of lung transplant recipients and typically has an overwhelmingly negative effect on recovery, causing prolonged hospitalization and increased mortality. One group has suggested that an even higher incidence of primary graft failure (50%) can be detected using criteria of radiographic infiltrate in the first 3 days after transplantation with $PaO_2:FiO_2$ ratios <300. A higher incidence of ICU mortality occurs in those with PGD versus those without (29% vs 10.9%, respectively). Four variables predict higher mortality in the setting of PGD: age, degree of impaired gas exchange, graft ischemia time, and severe early hemodynamic failure.

Key points 9.3 Classification of primary graft dysfunction

PGD grade	Infiltrates on chest radiography	PaO2/FiO2 ratio
0	None	≥300
1	Present	≥300
2	Present	200–300
3	Present	<200

Bronchial anastomoses may develop ischemia, dehiscence, ulcerations, malacia, or stenosis. Implantation of grafts with smaller airways, particularly lung transplantation performed on children, are more prone to develop significant airway

Table 9.5 Post-transplant complications

Allograft rejection
- hyperacute (humoral)
- acute cellular
- lymphocytic bronchitis/bronchiolitis
- chronic rejection (bronchiolitis obliterans)

Primary graft dysfunction
Bronchial anastomosis complications (dehiscence, malacia, stenosis)
Infection
- bacterial (pneumonia, bacterial tracheobronchitis, empyema)
- fungal infection (e.g. *Aspergillus, Candida* spp., tracheobronchial aspergillosis)
- viral (e.g. CMV, RSV, influenza)
- mycobacterial
- *Pneumocystis* spp.

- Coagulation/thrombotic events
- hemorrhage
- hypercoagulability
- thrombosis of venous anastomoses
- venous thromboembolism
- axillary vein thrombosis
- heparin-induced thrombocytopenia with thrombosis
- Multisystem failure

Neurological complications (usually drug induced)
- central nervous system dysfunction
- tremor

Pleural effusion
Phrenic nerve injury
Vocal fold paralysis
Renal dysfunction/insufficiency
Native lung complications (single lung transplantation)
- hyper-inflation (emphysema)
- infection
- pneumothorax

Cardiovascular
- systemic hypertension
- cardiac rhythm disturbances
- hyperlipidemia

Hemolytic–uremic syndrome
Diabetes mellitus
- new onset
- worsened control of established disease

Gastrointestinal complications
- impaired motility (diarrhea, bezoar)
- colonic (diverticulitis, perforation, colitis)
- hepatobiliary dysfunction

Musculoskeletal complications
- Impaired bone metabolism:
  - osteoporosis
  - compression fractures
  - avascular necrosis
- Myopathy

Myelosuppression
Malignancies/lymphoproliferative disease (PTLD, primary lung cancer, other)
Menstrual irregularities

CMV, cytomegalovirus; PTLD, post-transplantation lymphoproliferative disease; RSV, respiratory syncytial virus.

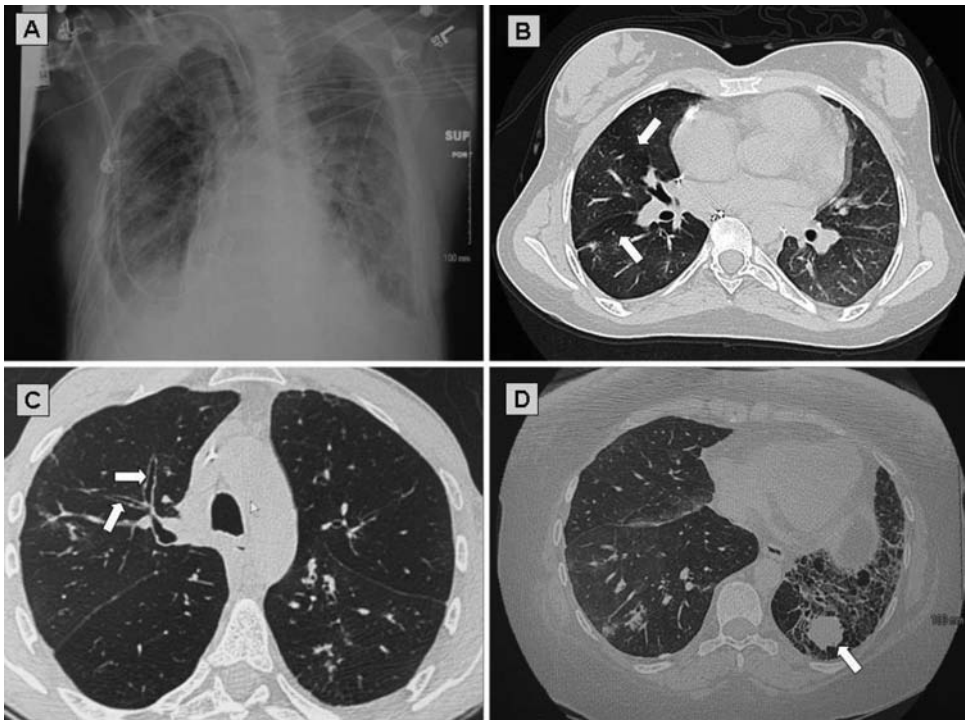

Figure 9.1 Thoracic imaging of lung transplant recipients. (a) Anteroposterior chest radiograph of a recipient with grade 3 primary graft dysfunction (PGD). (b) High-resolution CT (HRCT) scan showing air trapping in a bilateral lung transplant recipient with bronchiolitis obliterans syndrome. (c) HRCT scan showing allograft bronchiectasis (arrows). (d) HRCT scan showing a new small cell carcinoma in the fibrotic native lung of a single lung transplant recipient with idiopathic pulmonary fibrosis.

complications. Preoperative steroid use, CPB, reperfusion injury, acute rejection, airway infection, and administration of postoperative cytolytic drugs have all been linked to anastomotic dysfunction. Anastomotic complications arising in the first year after lung transplantation may be increased in recipients who are tall or in those receiving organs from donors who had prolonged mechanical ventilation. Aspergillus infection of tracheobronchial anastomoses may occur, especially in CF patients. Risk factors for anastomotic complications in children include prolonged mechanical ventilation and infection with *B. cepacia* or fungus.

Infection is a constant concern in the perioperative period and can arise from aspiration, surgical sites, or nosocomial infections. Pediatric recipients appear to have a higher incidence of pneumonia than adults. Infection in the perioperative period is largely caused by bacterial organisms, although viral and fungal infections should not be overlooked. Broad-spectrum antibiotics should be given until organisms can be identified, and it is important to consider infections that may have existed in the donor before transplantation. Infectious complications are discussed in more detail under "Postoperative period".

Phrenic nerve injury or diaphragmatic dysfunction can occur due to the transplant procedure. Diaphragmatic dysfunction can have significant effects on weaning from the ventilator and, thus, tends to prolong hospitalization. Fortunately, this complication does not seem to have a significant impact on long-term outcome.

Pulmonary embolism can be a devastating complication that may occur during the perioperative period,

especially during the first postoperative month, with an incidence that ranges up to 30%. As with all postoperative patients, lung transplant recipients are at high risk for developing deep venous thrombosis (DVT) and subsequent pulmonary emboli (PEs). In addition, clot can form at sites of vascular anastomoses. As a result of the potentially devastating effects of DVT/PE, patients should receive adequate DVT prophylaxis. In some situations, it may be prudent to place an inferior vena cava filter to prevent fatal PEs.

Hyperacute, antibody-mediated rejection may occur in the immediate postoperative period, although very few cases have been reported. Hyperacute rejection is characterized by the development of diffuse infiltrates within a few hours of lung transplantation. These recipients test positively for panel-reactive antibodies and retrospective tissue cross-match studies. Clinical features of this aggressive clinical syndrome include sudden, rapid increases in airway pressure, copious amounts of blood-tinged fluid emanating from the airways, a precipitous decline in $PaO_2:FiO_2$, and coagulopathy. Treatment includes escalation of immunosuppressive therapy combined with plasmapheresis to attenuate the production and the presence of pre-formed antibodies.

The postoperative period

Patients who survive the perioperative period and leave the hospital usually experience a significant improvement in lung function over the next few months. It is imperative that the patient and the healthcare team work to ensure the vitality of the transplanted lung to achieve and maintain this improvement in lung function over time. Although there is no consensus for various aspects of postoperative surveillance, lung transplantation programs are more likely to succeed if frequent and reasonably intense surveillance is employed to prevent or recognize complications. The rigorous post-transplant surveillance program and the complex medical regimen that lung transplant recipients must adhere to as outpatients underscores one reason why patients must be carefully screened before listing for lung transplantation. Nevertheless, even with rigorous surveillance protocols in place, multiple complications may occur.

As the recipient recovers from the transplant procedure and management shifts to long-term ambulatory care, complications associated with long-term immunosuppressive agents emerge as major issues. The combinations of immunosuppressive drugs required to prevent graft rejection pose a risk of side effects and toxicities that include renal dysfunction, central nervous system complications, osteoporosis, hyperlipidemia, and increased risk of malignancy. Other potential complications include pulmonary disorders that can affect the transplanted lung, such as acute rejection, allograft infection, recurrence of disease in the transplanted lung (e.g., pulmonary Langerhans' cell histiocytosis, lymphangioleiomyomatosis, sarcoidosis), problems with the native lung that may affect allograft function in recipients of SLT (e.g., hyperinflation of an emphysematous native lung, infection, pneumothorax), post-transplant lymphoproliferative disorder (PTLD), and bronchiolitis obliterans (BO).

Immunosuppression

The goal of immunosuppressive therapy is to promote immune tolerance of the lung allograft. Despite seemingly adequate immunosuppressive regimens, a high proportion of lung transplant recipients will develop acute rejection, which tends to occur more frequently in lung transplantation than in other solid organ transplantations. Immunosuppression of the lung transplant recipient must be intense and sustained to suppress the numerous factors that promote and drive allograft rejection. Immune system components that mediate a rejection cascade include innate immunity, adaptive immunity, humoral immunity, and autoimmune responses. As a result of the complexity and overlap in these components of the immune system, there is no simple physiologic "switch" that can be shut off to control rejection. The post-transplant immunosuppressive regimen usually consists of a calcineurin inhibitor (CNI), a purine synthesis inhibitor, and a corticosteroid. In addition, almost 45% of lung transplantation centers report that they utilize induction therapy with either anti-thymocyte globulins (ATGs), monoclonal anti-CD3 antibody (OKT3), or anti-interleukin (IL)-2-receptor antibodies. The rationale for use of induction antibody therapy in lung transplantation includes the high risk of acute rejection and the beneficial effect of providing time to achieve therapeutic levels of maintenance agents. Recent data from the International Society for Heart and Lung Transplantation (ISHLT) database show a small but statistically significant survival advantage associated

with the use of induction antibodies in the early postoperative period. Unfortunately, adequately powered, prospective, randomized controlled trials are lacking to support or refute the use of any specific induction/maintenance immunosuppressive regimen to optimize long-term allograft survival after lung transplantation.

Adequate maintenance immunosuppressive therapy, which is started immediately postoperatively, is of key importance in preventing AR. Currently, the CNIs (cyclosporine and tacrolimus) provide the "backbone" for maintenance regimens administered to lung transplant recipients. Although tacrolimus may have greater efficacy for refractory AR, and switching from cyclosporine to tacrolimus has been reported to stabilize or slow declining allograft function due to "chronic rejection," it remains unclear whether tacrolimus is truly better than cyclosporine in preventing AR. The purine synthesis inhibitors, azathioprine or mycophenolate (mycophenolate mofetil or mycophenolate sodium) are generally used in combination with a CNI. Although smaller studies have suggested that mycophenolate may have superior efficacy over azathioprine in preventing AR, results from larger prospective, randomized, multicenter trials have not demonstrated any convincing difference between the two agents in suppressing AR. Finally, prednisone is the corticosteroid of choice in most centers and is helpful for preventing as well as treating AR. As a result of its adverse effects, especially on blood sugar control and bone mineral density, some centers significantly decrease or discontinue prednisone dosing over the first year after lung transplantation. Large doses of intravenously administered methylprednisolone followed by a gradual taper of oral prednisone are typically used to treat episodes of AR.

Strategies to avoid toxicity (e.g., monitoring CNI levels in peripheral blood) yet maintain adequate immunosuppression and avoid opportunistic infection must be followed. Trough levels (C_0) of cyclosporine and tacrolimus have traditionally been used for monitoring CNIs. However, in the case of cyclosporine, some centers use C_2 levels that may better reflect area-under-the-curve (AUC) pharmacokinetics. Although C_2 monitoring has been linked to enhanced clinical benefit in heart, liver, and kidney transplant recipients, data that support improved outcomes in association with its use in lung transplantation remain limited.

Data from the 2007 report of the ISHLT indicate that lung transplantation centers prefer tacrolimus over cyclosporine and mycophenolate over azathioprine. Target of rapamycin (TOR) inhibitors (sirolimus and everolimus) have been touted as CNI-sparing agents. However, sirolimus therapy has been sporadically linked to adverse pulmonary reactions and must be monitored carefully. Moreover, new use of these agents has been associated with impaired wound healing and, in lung transplant recipients, with dehiscence of the tracheal anastomosis. Novel approaches to preventing or treating AR include the administration of inhaled cyclosporine. One single-center, randomized, placebo-controlled trial of inhaled cyclosporine demonstrated improvement in overall allograft survival and chronic rejection-free survival, although a significant effect on preventing AR was not demonstrated.

AR can be treated with high-dose intravenous corticosteroids and, when applicable, conversion from cyclosporine to tacrolimus. If this is unsuccessful, cytolytic therapy with ATG or OKT3 may be used. If further treatment is needed, high-dose intravenous immunoglobulin (IVIG) provides another option. Chronic rejection should be treated by switching from cyclosporine to tacrolimus for at least 3–6 months, and high-dose corticosteroids and ATG can also tried if refractory. Finally, other modalities such as total lung irradiation, photopheresis, or chronic use of azithromycin may be helpful in stabilizing lung function in recipients with progressive loss of lung function due to chronic rejection.

Complications in the postoperative period

The major complications that occur beyond the perioperative period are predominantly linked to rejection and infection. Successful transplant programs must have systems in place to identify and treat these complications early and effectively, and various measures should be taken to minimize complications and optimize post-transplant outcomes (Table 9.6).

Acute rejection Malaise, cough, fever, and/or leukocytosis, decrease in FEV_1, changes on chest radiograph, and gastrointestinal complaints should signal the possibility of AR. It is graded histologically based on a commonly accepted scale that was most recently revised in 2005 (Table 9.7). Perivascular mononuclear infiltrates with or without lymphocytic

Table 9.6 Measures to optimize post-transplant outcomes

Experienced and multidisciplinary transplant team in place (thoracic surgeons, pulmonologists, consultants, coordinators/nursing, pharmacists, nutritionists, health psychologists, social workers)

Adequate yearly transplant volume to keep team skills at a high level

Careful selection of transplant candidates

Optimized pretransplant management

- Adequate pharmacologic therapies
- Avoidance of debilitation/deconditioning (optimal nutrition, pulmonary rehabilitation)

Donor management

- Careful selection
- Optimal supportive care

Use of strategies to avoid/minimize ex vivo allograft preservation injury

Aggressive postoperative ICU management

- Avoid ventilator-induced injury
- Consider early extracorporeal membrane oxygenation for severe, refractory graft dysfunction
- Judicious fluid restriction
- Closely monitor graft function

Prophylactic/pre-emptive therapies

- Adequate immune suppression
- Cytomegalovirus
- *Aspergillus* spp.
- *Pneumocystis* spp.

Surveillance

- Lung allograft
  - spirometry
  - radiologic imaging
  - bronchoscopy (BAL and transbronchial biopsy)
- Immunosuppressant monitoring
  - CNI peripheral blood levels
  - bone marrow function
- Intermittent assessment of non-pulmonary issues
  - renal function
  - gastrointestinal function (GER, etc.)
  - cardiac function
  - lipid profile
  - systemic blood pressure
  - nutrition
  - bone metabolism
  - glucose metabolism
  - malignancy risk

BAL, bronchoalveolar lavage; CNI, calcineurin inhibitor; GER, gastroesophageal reflux; ICU, intensive care unit.

Table 9.7 Grading of acute rejection and bronchiolitis obliterans syndrome

Disorder	Grade	Findings/Severity	Comments
Acute rejection (perivascular and interstitial inflammation)	A0 A1 A2 A3 A4	None Minimal Mild Moderate Severe	Adequate specimen requires five or more pieces of alveolated parenchyma Routine H&E processing at three levels required Special stains for microorganisms (GMS, AFB) required Connective tissue stain (e.g. elastic) recommended
Lymphocytic bronchiolitis (airway inflammation)	B0 B1 B2 BX	None Low grade High grade Ungradable	Lymphocytic bronchitis/bronchiolitis (LBB) is also a form of acute rejection
Bronchiolitis obliterans syndrome	BOS 0 BOS 1 BOS 2 BOS 3	$FEV_1 \geq 80\%$ of baseline[a] FEV_1 66–80% of baseline FEV_1 51–65% of baseline $FEV_1 \leq 50\%$ of baseline	Other causes of lung function decline must be excluded: • acute rejection • infection • native lung problems (single lung transplant recipients) • excessive recipient weight gain • anastomotic dysfunction • respiratory muscle dysfunction • technical problems

[a]Baseline defined as the average of the two best FEV_1 determinations post-lung transplantation.
AFB, acid-fast bacilli; GMS, Gomori methenamine silver; H&E, hematoxylin and eosin.

bronchitis/brochiolitis in the absence of infection is the histologic hallmark of AR (Figure 9.2). Acute cellular rejection is by far the most common rejection response. Hyperacute rejection is rare. However, another form of AR, characterized by alveolar septal capillary injury that lacks the lymphocyte infiltration characterizing cellular AR, has been reported to be associated with anti-endothelial antibodies specific for non-major histocompatibility (MHC) antigens.

The grading for AR ranges from A0 to A4. Grade A2 or greater is generally considered to be clinically significant and requiring intervention. Grade A1 (minimal) is commonly seen on surveillance transbronchial lung biopsy (TBLB) and is of unclear significance. Although grade A1 rejection has generally been considered to be clinically insignificant, it has been associated with increased risk for developing BO. However, no clear benefit has been demonstrated with intensifying immunosuppression for recipients with A1 rejection detected via surveillance bronchoscopy (SB). AR of grade A2 or higher requires intensified immunosuppression because it is usually accompanied by worsening lung function and oxygenation. One of the main reasons why surveillance TBLB is performed is because some patients may have grade A2 or even A3 AR that is clinically occult without a perceptible decline in lung function or gas exchange. A follow-up TBLB should be performed after the intensification of immunosuppression and corticosteroid burst to verify that the rejection episode has been adequately treated and suppressed.

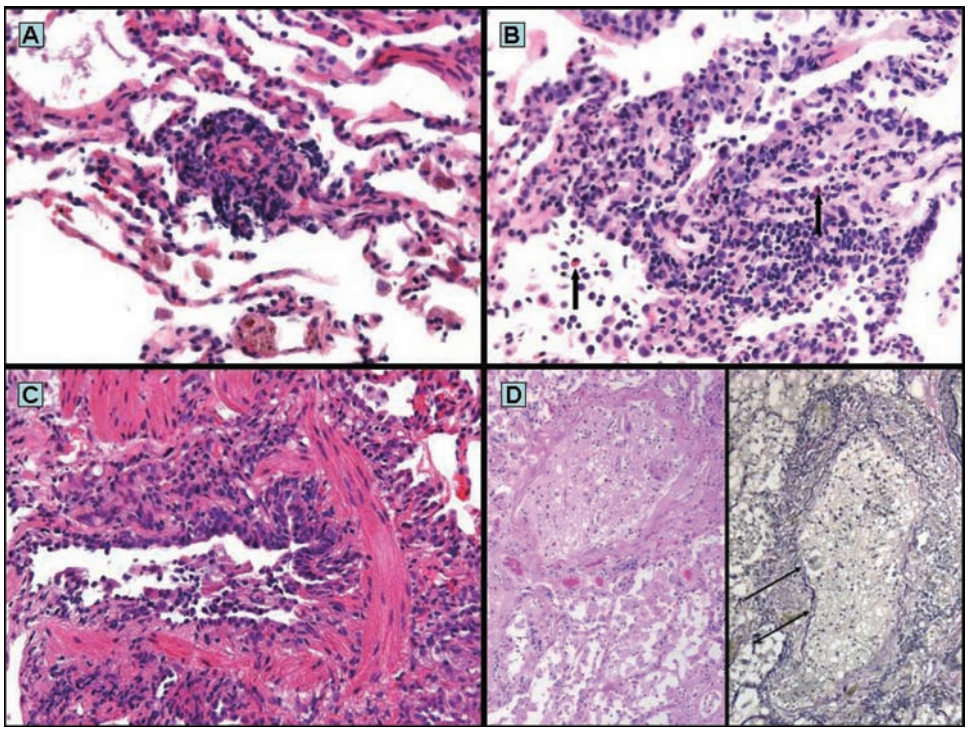

Figure 9.2 Histopathology of acute and chronic rejection. (Images provided courtesy of Henry Tazelaar, MD.) (a) International Society for Heart and Lung Transplantation (ISHLT) grade A2 acute rejection with one dense perivascular mononuclear infiltrate and no interstitial extension. (b) ISHLT grade A3 acute rejection; note the presence of eosinophils (arrows). (c) ISHLT grade B1 with mild bronchiolar lymphocytic infiltrate. (d) Chronic airway rejection (obliterative bronchiolitis), with complete airway scarring. The right panel shows an adjacent section stained with an elastic stain, highlighting the internal elastic lamina (arrows).

Case

A 23-year-old woman developed fever and leukocytosis 9 weeks after bilateral lung transplantation for cystic fibrosis. THE FEV_1 was 15% lower than a baseline value obtained 1 month earlier. Transbronchial lung biopsy revealed grade A2 acute rejection and no evidence of infection. She was treated with high doses of intravenous methylprednisolone. Cyclosporine was switched to tacrolimus. Fever and leukocytosis resolved. Repeat transbronchial biopsy 1 month later showed no evidence of acute rejection.

Infection Infection can occur at any time after lung transplantation. The incidence of bacterial pneumonia is approximately 16% in the first month after lung transplantation. Prolonged mechanical ventilation predisposes individuals to ventilator-associated bacterial pneumonia, and impaired cough reflexes and mucociliary clearance combined with immunosuppression sustain this risk after extubation. Undetected infection may be present in the lung allograft before donor explantation. Ischemic mucosa in the perianastomotic areas and impaired lymphatic drainage contribute to the risk of bacterial pneumonia. Fever, radiographic infiltrate, and culture-positive lower airway secretions can be diagnostic of pneumonia in the transplanted patient, but bronchoscopy with bronchoalveolar lavage (BAL) may be needed to make the diagnosis.

Gram-negative organisms, especially *P. aeruginosa*, are the predominant organisms followed by *Staphylococcus aureus*, which may be meticillin

resistant. Empyema occasionally complicates lung transplantation and may be difficult to distinguish from postoperative pleural effusions which frequently occur as a consequence of disrupted lymphatic drainage. Although pneumonia usually occurs in the transplanted lung in single lung transplant recipients, pneumonia can occasionally occur in the residual native lung. Antimicrobial prophylaxis and aggressive treatment of infection in the early postoperative period can decrease the incidence or progression of lung infection and, ultimately, improve early graft function. In the case of recipients transplanted for suppurative lung disease (CF or non-CF bronchiectasis), pathogens isolated from pre-lung transplantation sputum cultures or pathogens typically isolated from these individuals are usually the causative pathogens when post-lung transplantation bacterial pneumonia occurs. In addition, the paranasal sinuses continue to harbor organisms that can infect the lower respiratory tract after lung transplantation. As a result of this possibility, paranasal sinus disease should be optimally managed in the pre- and perioperative period. Some centers perform endoscopic sinus surgery to enhance sinus drainage, although there are no convincing data that such intervention has a significant impact on post-lung transplantation outcome.

CMV can cause serious infection that can be life threatening, and patients are at greatest risk during the first 3 months post-transplantation. Although most patients have been exposed before transplantation, recipients with negative CMV serology at the time of transplantation are particularly at risk, especially if they receive a graft from a CMV-positive donor. Other risk factors for CMV disease include blood transfusions, immunosuppressive induction regimens that deplete lymphocytes, co-infection with human herpesviruses 6 or 7, and bronchiolitis obliterans syndrome (BOS).

Infection with CMV may manifest as a pulmonary syndrome, with increased shortness of breath and decreased graft function mimicking AR. In addition, CMV may involve other organ systems and cause extrapulmonary disease including pancytopenia, gastrointestinal dysfunction, or dermatologic reactions. As pulmonary CMV infection may be difficult to distinguish from AR (and both may be present simultaneously), bronchoscopy with TBLB is usually required to make a definitive diagnosis. The advent of rapid shell-vial culture techniques and polymerase chain reaction (PCR) methodologies has greatly enhanced the ability to rapidly detect CMV in BAL fluid, but CMV infection must be distinguished from CMV disease, which is characterized by a cytopathologic process in the lung allograft. The demonstration of inclusion bodies in cytomegalic cells on TBLB specimens is diagnostic of CMV pneumonitis. However, obtaining diagnostic TBLB may be difficult, and a presumptive diagnosis of CMV disease can be made on the basis of clinical features and positive culture or PCR results.

There is no consensus as to the timing, duration, or optimal dose of prophylactic agents for CMV. Some centers employ universal prophylaxis with either ganciclovir or valganciclovir, whereas others utilize pre-emptive treatment that is based on screening and early identification of CMV infection. Disadvantages of universal prophylaxis include cost, toxicity, and the possible emergence of resistant organisms, while disadvantages of the pre-emptive method are the cost of screening and the possibility of failure to identify individuals with CMV infection before they develop a serious form of CMV disease. Nevertheless, significant CMV infection during the early post-lung transplantation period is now rare, and most centers continue prophylactic therapy for the first year after lung transplantation. Although the appearance of drug-resistant CMV is a concern and has been estimated to range in frequency from 3% to 16% in solid organ transplant recipients, such approaches appear to have significantly decreased the morbidity and mortality of CMV infection in lung transplant recipients. When CMV pneumonitis or CMV affecting other organ systems occurs, treatment with ganciclovir or valganciclovir is usually effective. In addition, CMV-specific or polyvalent immune globulin may be used to augment the treatment regimen in recipients with CMV disease.

Most opportunistic fungal infections are caused by *Candida* and *Aspergillus* spp. Pneumonia caused by *Candida* spp. is rare, but surgical site infection and dissemination can occur. Aspergillosis is a common post-transplantation opportunistic infection that can cause pulmonary and/or extrapulmonary disease, and invasive disease occurs in approximately 5% of recipients. *Aspergillus* spp. can cause infection at the anastomotic site and may cause dehiscence in the early post-transplant time period. In addition, aspergillosis can affect the lung parenchyma and cause angioinva-

sive disease with cavitating lesions, and sometimes involves other organ systems. Prophylactic regimens, especially when used for patients with known pretransplant colonization, may decrease the risk of post-transplant aspergillosis. A confident diagnosis of aspergillosis is made by obtaining biopsy specimens that show tissue invasion. However, *Aspergillus* spp. growing in culture, combined with the appropriate clinical picture, may be sufficient to make a presumptive diagnosis and commence therapy.

Aspergillus spp. can produce devastating, life-threatening illness if not identified rapidly and treated appropriately. When aspergillosis is suspected, immediate evaluation of the patient for the extent of organ system involvement, combined with the administration of intense, multiagent, appropriate antifungal therapy, is required. Treatment has traditionally consisted of intravenous amphotericin B, but newer approaches include the administration of voriconazole and caspofungin, depending on the site and severity of disease. Many programs administer antifungal agents (e.g., inhaled, nebulized amphotericin B, oral itraconazole, oral voriconazole) for prophylaxis, especially to patients known to be colonized with *Aspergillus* spp. pretransplantation.

Many other infectious complications can occur in the lung transplant recipient. Possible viral infections include herpes simplex virus, adenovirus, respiratory syncytial virus (RSV), influenza, and parainfluenza. Other fungal infections include *Cryptococcus* and *Coccidioides* spp. Mycobacterial infections with both *Mycobacterium tuberculosis* and non-tuberculous mycobacteria may also occur. Finally, other agents such as *Pneumocystis jiroveci* can cause life-threatening illness in the intensely immunosuppressed lung transplant recipient. Trimethoprim–sulfamethoxazole (or other agent if true allergy exists) is used routinely as prophylaxis for *Pneumocystis* spp.

Case

A 55-year-old man with a history of end-stage lung disease from COPD developed fever and exertional dyspnea 8 months after a single lung transplantation. Chest radiograph revealed new bilateral interstitial infiltrates. Hybrid capture DNA for CMV was previously negative, but CMV prophylaxis had been discontinued 6 months post-transplantation. Transbronchial biopsy revealed inclusion bodies consistent with CMV. The patient completed a 4-week course of therapy (intravenous ganciclovir for 1 week, oral valganciclovir for 3 weeks) and the syndrome resolved.

Bronchiolitis obliterans The development of BO, which is widely perceived to occur as a consequence of chronic rejection, continues to be the major factor that limits long-term survival and quality of life after lung transplantation. Despite improvements in immunosuppression and other elements of patient management, BO still occurs in more than half of all lung transplant recipients who survive to 5 years after lung transplantation. As BO is difficult to diagnose by radiologic imaging or transbronchial biopsy, the surrogate marker of FEV_1 (see Table 9.7) is used to detect and grade BO, which is then termed BO syndrome. However, when this diagnosis is made, other potentially reversible causes of a decline in lung function (e.g., AR, infection, native lung problems for single lung transplant recipients, excessive recipient weight gain that impairs lung function) must be ruled out as causes of chronic allograft dysfunction. BOS rarely occurs in the first 6 months post-lung transplantation, and median time to diagnosis is 16–20 months. Some patients may not display symptoms at all and may be identified only by screening lung function tests.

Risk factors that have been linked to the development of BOS include episodes of AR, HLA mismatching, and an autoimmune reaction to the lung matrix component, collagen V. However, alloimmune-independent factors such as inhaled irritants, airway ischemia, viral infections (e.g., CMV and respiratory viruses including influenza virus, RSV, parainfluenza virus, adenovirus, and rhinovirus), gastroesophageal reflux (GER), and donor factors (underlying asthma, smoking, and head injury as the cause of death) may also cause or contribute to the pathogenesis of BOS. Recipients who have three or more episodes of acute rejection in the first 6–12 months have a three- to fourfold increased risk of developing BO. However, some recipients do not develop BO despite multiple episodes of AR, and recipients who have never had AR may develop BO. In the pediatric lung transplant population, GER appears to be quite prevalent, and most pediatric lung transplant centers are very aggressive about identifying and treating GER. Finally, one must consider non-adherence to the medical regimen when evaluating rejection in the lung transplant recipient.

Although the pathogenesis of BO is not completely understood, both animal and human data suggest that there is an initial injury to airway epithelium that leads to a significant recruitment of inflammatory cells. Prominent among these inflammatory cells are neutrophils which accumulate in airspace secretions and may orchestrate the activation of the immune system. Proinflammatory cytokines and chemokines mediate and potentiate this inflammatory response, eventually leading to progressive airway damage, fibrosis, and airway smooth muscle proliferation with bronchiolar scarring and obliteration – all culminating in irreversible airflow obstruction. However, it should be emphasized that BO is a heterogeneous disorder with causes and immune/inflammatory responses that may vary from one lung transplant recipient to another.

One of the first clues to the presence of BO is a decrease in small airway function (forced expiratory flow at 25–75% – $FEF_{25–75\%}$), which may precede symptoms of cough, mucus production and dyspnea. Transbronchial lung biopsy has a disappointingly low sensitivity (17%) for detecting BO, necessitating adoption of the FEV_1 as a surrogate marker for BOS, with a sustained decline in FEV_1 to <80% of the best value post-transplantation indicating the onset of BOS. Revision in the BOS staging system in 2002 included a decline in $FEF_{25–75\%}$ to <75% of the best post-lung transplantation value as indicating the probable onset of BOS, because this parameter may identify airway obliteration earlier in the disease process. As AR (especially if it occurs early, is high grade, and recurrent) is thought to be a major risk for developing BOS, most lung transplantation centers use frequent monitoring to identify and treat AR early and hopefully prevent the development of BOS. Existing data support the use of intensive induction immunosuppression post-lung transplantation, combined with aggressive treatment of AR detected via frequent surveillance bronchoscopy (SB), with TBLB as a way of decreasing the risk of developing chronic rejection precipitated by episodes of AR. In addition, as GER is highly prevalent in patients with advanced lung disease and has been linked to chronic allograft dysfunction and BOS, some investigators have taken a more aggressive approach to its management. Fundoplication performed early after lung transplantation has been reported to be associated with both improved lung function and survival in comparison to control groups and appears to have relatively little morbidity. Laparoscopic fundoplication can also be performed safely on patients with ESLD before lung transplantation.

BO has a devastating effect on long-term survival with only 30–40% of recipients with BOS surviving 5 years after its onset, and management of BOS is difficult and usually ineffective. Treatment of BOS must take into consideration the delicate balance of immunosuppression and risk of opportunistic infection. Although increasing immunosuppressive therapy would be beneficial to control the immune/inflammatory response, it also places the patient at increased risk of infection. Nevertheless, both infection and inflammation must be aggressively treated in an attempt to prevent the progression of BOS. Patients with BOS after transplantation may have increased sputum production, grow *P. aeruginosa* on sputum culture, and show signs of bronchiectasis and end-expiratory air trapping on chest CT. Chronic azithromycin administration has been associated with stabilization or improvement in lung function in some recipients. Use of HMG-CoA (hydroxymethylglutaryl coenzyme A) reductase inhibitors ("statins") also has been associated with a decreased risk of developing BOS. Total lymphoid irradiation (TLI), initiated early in the course of chronic rejection that is refractory to conventional medical management, has been associated with an attenuation of the rate of decline in lung function, and extracorporeal photopheresis may also help stabilize declining graft function in recipients with early BOS. Newer approaches that can prevent or effectively treat BOS are desperately needed. Re-transplantation may be considered, but survival statistics for re-transplantation are significantly worse than that for recipients of primary lung transplantation. Candidates for re-transplantation due to progressive, refractory BOS must be evaluated with intense scrutiny.

Other complications

Gastrointestinal A number of gastrointestinal complications can occur at any time after lung transplantation and affect approximately 50% of lung transplant recipients. GER is highly prevalent in patients with advanced lung disease and has been linked to declines in lung function and the development of BO. Reflux can occur for a variety of reasons

that include postoperative changes to the lower esophageal sphincter and diaphragmatic crura, dysmotility associated with diabetes mellitus, and changes in body habitus (e.g., from corticosteroid-associated weight gain). Non-acid GER occurs in many patients and must be detected via impedance/pH monitoring. Ideally, all candidates and recipients should be screened (pH and impedance measurements) for GER and receive appropriate medical or surgical therapies as needed to prevent significant reflux. Recipients with CF are particularly predisposed to gastrointestinal complications due to disease-related intestinal tract dysfunction. Patients with CF can develop bezoars that often form in the early post-transplant period and that can inhibit absorption of orally administered drugs. Recipients with CF are also at risk for distal intestinal obstruction, biliary tract complications (cholecystitis, significant biliary stasis, ascending cholangitis), and intestinal neoplasm (especially colon cancer).

Renal dysfunction Recipients are at a major risk for developing renal dysfunction after lung transplantation, and renal function should be checked frequently in the first post-transplant months and then at regular intervals thereafter. Blood levels of CNIs need to be monitored closely and doses adjusted to ensure an adequate (but not excessive) level that will give the desired degree of immunosuppression. Other electrolytes that can affect renal function (e.g., magnesium) or rise to dangerous levels (e.g., potassium) also need to be frequently monitored. When serum creatinine rises irreversibly >1.5 g/dL (or estimated glomerular filtration rate [GF]R <50 mL/min), or if significant proteinuria is detected on urinalysis, referral to a nephrologist who is familiar with transplant issues should be considered.

Cardiovascular Common cardiovascular complications include systemic hypertension, rhythm disturbances (e.g., atrial fibrillation), and hyperlipidemia. Systemic hypertension has been linked to corticosteroids, CNI administration, and weight gain. Hyperlipidemia is also linked to immunosuppressive agents, and the administration of statins for hyperlipidemia has been linked to improved survival and decreased risk of developing BO. Systemic hypertension and hyperlipidemia will eventually develop in most lung transplant recipients, and systemic blood pressure and peripheral blood lipid profiles should be monitored frequently to facilitate the detection and treatment of these complications.

Bone metabolism There is a very high prevalence of osteopenia and osteoporosis in patients with advanced lung disease, and lung transplantation can accelerate bone loss. All recipients should have bone mineral density checked frequently (e.g., 6–12 months post-transplantation and then yearly) via bone mineral density scanning and receive appropriate therapies if *T*-scores indicate the presence of osteopenia.

Glucose intolerance Corticosteroids and other transplant medications often disrupt glucose metabolism. Patients with CF are particularly at risk and have a relatively high pretransplant prevalence of diabetes mellitus that increases significantly post-transplantation. Frequent monitoring should be performed to assess glycemic control and to detect new onset of glucose intolerance.

Malignancy The profound immunosuppression required for lung transplant recipients places them at increased risk for developing dermatologic malignancies and PTLD. The latter occurs in approximately 5% of lung transplant recipients, and nearly all cases of PTLD are associated with the Epstein–Barr virus (EBV). Recipients who are EBV seronegative seem to be at highest risk for developing PTLD in the postoperative period. Peripheral blood semi-quantitative EBV PCR may identify recipients at increased risk for PTLD and may warrant cautious reduction of immunosuppression and continued prophylactic antiviral agents to prevent CMV as a cofactor in the pathogenesis of PTLD. Treatment consists of decreasing the level of immunosuppression to attempt to restore immunity against EBV. Other modalities, such as rituximab, have been used with some success. Overall, the mortality rate attributed to PTLD for recipients who develop this complication after lung transplantation is 37–50%.

Primary lung neoplasms may arise in the native lung of single lung transplant recipients, and other neoplasms such as bladder and colon cancer have been reported. Patients and their care providers need to maintain vigilance for any skin changes that may herald the development of a cutaneous malignancy, and internal malignancy must be considered when

unexplained symptoms or signs arise in the post-transplant setting. Cancer screening, including routine skin examinations, mammography, cervical cancer screening and colonoscopy, must be maintained in the post-transplant setting.

Long-term surveillance

The goal of a surveillance program is to identify any acute or evolving issue that is related to an infectious process, acute rejection, or other potential complications, and to intervene before graft function is irreversibly affected or other complications occur. A typical surveillance program should include monitoring of allograft function, evaluation for infectious complications, intermittent laboratory testing and drug monitoring, monitoring of other organ system function (renal, cardiovascular function, and gastrointestinal function), intermittent assessment of bone and glucose metabolism, and attention to risk for malignancy. Most centers require frequent performance of home spirometry to detect declining FEV_1 values once the recipient has been discharged from the hospital, and patients should be educated to recognize changing symptoms including increased shortness of breath, fever, chills, or decline in exertional capacity.

Lung transplant recipients require close and frequent evaluation in the postoperative period to detect allograft dysfunction, particularly rejection and infection. As a result of their high prevalence in lung transplant recipients, there are a number of significant complications (hyperlipidemia, diabetes mellitus, osteoporosis, renal insufficiency, GER, and systemic hypertension) for which screening should be performed. Most of these complications are linked to the intense immunosuppressive regimens initiated at the time of lung transplantation, and frequent monitoring of immunosuppression, especially blood levels of cyclosporine and tacrolimus, should be performed to guide treatment and avoid toxicities.

Heart rate, blood pressure, temperature, and spirometry should be measured on a regular basis to detect complications. Most lung transplantation centers provide their patients with home spirometers and monitor lung function on a daily or even twice-daily basis. Fever and significant decline in lung function (decrease in FEV_1 >10% over 48 h) require immediate evaluation, and bronchoscopy with transbronchial biopsy is usually performed to establish an accurate diagnosis of rejection and/or infection. For recipients with CF, extrapulmonary problems such as CF-related diabetes mellitus, CF liver disease, various other gastrointestinal complications, and paranasal sinus disease must be managed intensively. Frequent clinic visits at a CF center allow the patient to be evaluated for nutritional status, pulmonary status, and identification of early complications including medical and psychosocial problems.

Bronchoscopy with TBLB and BAL is an important tool for the detection of rejection and infection and is performed when clinically indicated. Examination of BAL fluid is particularly helpful in identifying bacterial, viral, and fungal infections, whereas TBLB is especially useful for identifying AR and/or CMV pneumonia. Quantitative bacterial cultures and stains, cultures for fungi and mycobacteria, and viral studies are typically obtained on BAL fluid, and transbronchial biopsies are obtained to evaluate allograft tissue for evidence of rejection and/or infection. The sensitivity and specificity of TBLB in identifying AR are approximately 72% and 90–100%, respectively. Sensitivity and specificity for the detection of CMV pneumonitis are approximately 91% and 70%, respectively. Follow-up bronchoscopy with TBLB is typically performed 4 weeks after the detection and treatment of significant acute rejection to ensure that enhanced immunosuppression has effectively eliminated the process.

Scheduled SB can detect occult infection or AR in patients who appear to be stable and lack radiographic or physiologic manifestations of rejection. However, the routine use of SB is controversial, and SB is routinely performed in only two-thirds of lung transplantation centers in the USA. For those institutions that perform SB, schedules differ from center to center and are usually determined by the lung transplantation center's previous experience. Nevertheless, SB is an important tool that allows inspection of airways and anastomoses, and retrieval of diagnostic specimens via TBLB and BAL for the detection of occult rejection and/or infection. Occult infection and AR are often detected when SB is performed, especially during the first 6 months post-transplantation, and the benefit of detecting and treating AR are thought to be improved survival and decreased risk of developing BO. A significant limitation of SB is the very limited ability to diagnose chronic rejection because of the limited ability to

sample tissue that demonstrates histologic changes consistent with BO.

Thoracic CT scanning can be a useful tool to evaluate the lung allograft. By using end-expiratory, thin-section CT scanning (high-resolution CT [HRCT]) in the postoperative period, changes consistent with BOS may be detected relatively early (see Figure 9.1). When using air trapping as a marker for detecting BOS, studies have shown a sensitivity ranging from 74% to 91% and a specificity ranging from 67% to 94%. Although HRCT with inspiratory and expiratory views may be useful in detecting and assessing the severity of BOS in recipients who are suspected of having developed it, HRCT is not recommended as a routine surveillance test. It can, however, detect changes in addition to air trapping (e.g., small nodules, bronchiectasis) in the lung allograft as well as complications in the native lung of single lung transplant recipients (e.g., opportunistic infection or malignancy) that cannot be detected on routine chest radiographic imaging (see Figure 9.1).

Outcomes

The 5-year survival rate (Kaplan–Meier) is approximately 50% for both adults and children and remains significantly lower than survival for other solid organ transplantations. A steep, early decline in survival that levels off at 1–3 months post-lung transplantation reflects the impact of early events such as surgical complications, PGD, and thromboembolism. BO and infection appear to have the greatest impact on long-term survival, and constant exposure to ambient air as well as aspiration of upper airway and/or refluxed gastroesophageal secretions are likely the major contributors to graft failure and death. As a result of its significant prevalence and tendency to relentlessly progress, BO claims the lives of most individuals who survive the early postoperative period.

Fortunately, most lung transplant recipients experience significant improvements in lung function, exercise tolerance and quality of life (QoL). Average values for vital capacity increase from 43% predicted pre-lung transplantation to 65% and 69% predicted at 3 months and 1 year, respectively, for patients receiving a SLT for IPF. The greatest improvement in lung function usually occurs in the first 3 months after lung transplantation and slowly reaches a plateau at about 1 year, barring any significant complications that affect lung function. For patients receiving SLT for COPD, FEV_1 increases from 20% pre-lung transplantation to 45–60% 1 year after transplantation. Patients with COPD who receive a BLT can expect normal or near-normal lung function 1 year postoperatively. Patients with CF who receive BLT display an increase in FEV_1 from a mean of 20% predicted before lung transplantation to 70–80% predicted at 1 year post-lung transplantation. Finally, normalization of pulmonary pressures, right ventricular function, and cardiac output is expected for patients who receive a BLT for pulmonary hypertension, although single lung transplant recipients should also experience normalization of hemodynamic parameters. Exercise tolerance improves greatly and allows most recipients to perform activities of daily living without limitation or need for supplemental oxygen. However, cardiopulmonary exercise testing reveals that maximum oxygen consumption is limited to 50–60% predicted at peak exercise. Deconditioning, and a possible myopathy that is linked to the immunosuppressant regimen or other factors, likely accounts for this limited exercise capacity, because cardiopulmonary reserve appears to be maintained. Recipients of heart, liver and kidney transplants have similar limitations on cardiopulmonary exercise, suggesting that factors other than organ function may account for the subnormal maximum oxygen consumption at peak exercise.

Quality of life and cost-effectiveness have been scrutinized as important outcome factors in lung transplantation. Recently, a plethora of research has been published on QoL in lung transplant recipients. Most patients who have undergone lung transplantation have been found to be happy with their decision to undergo the procedure. The recipient approval rating of their lung transplantation is approximately 75%, and over 90% of those who have had the procedure would elect to have it again. Over 80% of survivors at 1, 3, and 5 years post-transplantation have no activity limitations. However, only 20% of recipients are working full-time at 1 year post-transplantation despite their lack of activity limitation. Improvements in QoL appear to have a lasting effect even at 7 years post-transplantation, and there does not seem to be a difference in QoL when comparing single with bilateral lung transplant recipients. Cost-effectiveness data are relatively scarce, and results inconclusive.

Recurrence of lung disease is very unusual. Sarcoidosis and lymphangioleiomyomatosis are diseases that may recur after lung transplantation. In addition, there have been case reports of recurrence in recipients transplanted for Langerhans' cell histiocytosis, giant cell interstitial pneumonitis, pulmonary alveolar proteinosis, and diffuse panbronchioloitis.

Re-transplantation

PGD, severe airway complications, refractory acute rejection, and progressive BOS can lead to irreversible allograft dysfunction and respiratory failure after lung transplantation. Re-transplantation can be performed to treat these complications if refractory to all other interventions, but outcomes after re-transplantation have been significantly worse than outcomes after primary lung transplantation. Due to ethical concerns about proper organ distribution when an overall organ scarcity prevents successful transplantation of many wait-listed candidates and various reports of poor outcome after re-transplantation, the value of re-transplantation has been open to question. More recent data suggest that survival after re-transplantation for certain recipient groups approaches that for primary lung transplantation, and outcomes after lung re-transplantation have generally improved. Early re-transplantation (within 30 days) and re-transplantation for PGD have the worst outcomes, whereas re-transplantation for BOS appears to provide survival rates that are similar to long-term survival rates for primary lung transplantation. Re-transplantation should be considered on a case-by-case basis for recipients of primary lung transplantation whose allografts have developed severe dysfunction that is refractory to non-surgical interventions.

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Addendum: glossary

α_1-Antitrypsin deficiency: a deficiency of a protein produced in the liver that blocks the destructive effects of certain enzymes.This inherited condition can be associated with emphysema and/or liver disease.

Atelectasis: absence of gas from a part or the whole of the lungs, due to failure of expansion or resorption of gas from the alveoli.

ARDS: acute respiratory distress syndrome – a malfunction of the lung resulting from injury to the small air sacs and the capillaries of the lungs. Upon injury, blood and fluid leak into the air sacs, making breathing difficult. The condition can be fatal.

BAL: Bronchoalveolar lavage – a technique that allows the recovery of both cellular and non-cellular components from the epithelial surface of the lower respiratory tract and differs from bronchial washings, which refer to the aspiration of either secretions or small amounts of instilled saline from the large airways.

BiPAP: bilevel positive airway pressure – a non-invasive means to deliver both inspiratory and expiratory pressure for ventilatory support.

BO/BOS: bronchiolitis obliterans/bronchiolitis obliterans syndrome – irreversible scarring of the terminal and respiratory bronchioles which may either partially or totally obliterate the lumen of the airway.

Bronchiectasis: chronic dilation of bronchi. It can be the result of inflammation, infection, and/or lung tissue fibrosis (traction bronchiectasis).

Bronchoscopy: the direct visualization of the trachea and bronchi through a rigid or flexible tube (bronchoscope).

CPB: cardiopulmonary bypass – to surgically insert a shunt to bypass a chamber of the heart to carry blood directly to the aorta.

COPD: Chronic obstructive pulmonary disease – a progressive lung disease process characterized by difficulty breathing, wheezing, and a chronic cough. Airflow obstruction usually does not improve after inhaled bronchodilator medications.

CF: cystic fibrosis – an inherited disease (autosomal recessive) that affects the lungs, exocrine pancreas and gastrointestinal system resulting in chronic lung disease.

DVT: deep venous thrombosis – blockage of the deep veins; particularly common in the leg.

Diffuse panbronchiolitis: an idiopathic chronic obstructive airway disease more commonly affecting Japanese individuals. Lymphocytic and plasma cell infiltration of bronchial walls occurs.

DIOS: distal intestinal obstructive syndrome – inspissation of intestinal contents in the terminal ileum, cecum, and proximal colon in patients with CF.

ECMO: extracorporeal membrane oxygenation – a technique that is used to oxygenate blood by passing it through an external membrane.

Eisenmenger's syndrome: the process in which a left-to-right shunt in the heart causes increased flow through the pulmonary vasculature, resulting in pulmonary hypertension, which causes increased pressures in the right side of the heart and reversal of the shunt into a right-to-left shunt.

Empyema: the presence of pus in a body cavity, especially the pleural cavity.

FEV_1: forced expiratory volume in 1 s – the volume of air that can be exhaled during the first second of a forced exhalation.

FVC/VC: forced vital capacity/vital capacity – the maximum volume of air that can be (forcibly) expired from the lungs.

ILD: interstitial lung disease – a disorder resulting in scarring of lung tissue or the lining of the air sacs (alveolus); often results in poor oxygen diffusion from the alveolus into the bloodstream.

IVC filter: inferior vena cava filter – a device placed in the inferior vena cava intended to disrupt the flow of a blood clot from the lower extremities to the lungs.

IPF: idiopathic pulmonary fibrosis – scarring or thickening of lung parenchyma of unknown etiology.

NO: nitric oxide – a free radical gas synthesized from arginine by nitric oxide synthase. It is one of the endothelium-dependent relaxing factors released by the vascular endothelium and mediates vasodilation. It also inhibits platelet aggregation, induces disaggregation of aggregated platelets, and inhibits platelet adhesion to the vascular endothelium.

PCR: polymerase chain reaction – a technique for amplifying DNA sequences in vitro by separating the DNA into two strands and incubating it with nucleotide triphosphates.

Pleuredesis: the surgical or medical creation of a fibrous adhesion between the visceral and parietal layers of the pleura, thus obliterating the pleural cavity.

PE: pulmonary embolism – lodging of a blood clot in the lumen of a pulmonary artery, causing dysfunction in respiratory function. PEs often originate in the deep leg veins and travel to the lungs through the blood circulation. Symptoms include sudden shortness of breath, chest pain, and rapid heart and respiratory rates.

PGD primary graft dysfunction: reperfusion injury that occurs after implantation and causes parenchymal infiltrates and impaired gas exchange.

Pulmonary hypertension: elevated blood pressure in the pulmonary circulation. Primary pulmonary hypertension indicates that the etiology is not secondary to diseases of the heart or lungs.

Sarcoidosis: a multisystem disorder characterized in affected organs by a type of granulomatous inflammation. The etiology is unknown.

Six-minute walk test: 6MWT – a test that measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 min. It evaluates the global and integrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism.

TBLB: transbronchial lung biopsy – a lung biopsy obtained during bronchoscopy in which tiny forceps are passed to the distal bronchi and air sacs to obtain tissue.