Chapter

37

Lung Transplantation

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Case Scenario

A 14-year-old girl, weighing 43 kg, presents to the general operating room for routine surveillance bronchoscopy with lavage and biopsies. She has a history of cystic fibrosis and underwent double-lung transplantation 18 months ago. Her postoperative course was complicated by primary graft dysfunction and bacteremia. Today she is actively coughing during her preoperative assessment; she says that it is her "normal" cough and has been present for more than a month. She also states that she has missed several doses of tacrolimus over the past weeks. Current vital signs are temperature 38.1°C, heart rate 92 beats/minute, respiratory rate 27 breaths/minute, hemoglobin-oxygen saturation on room air 97%. Breath sounds are clear, without wheezing or rhonchi, and she does not appear to be in respiratory distress. A review of the results of her pulmonary function tests performed on the previous day shows no significant change. The chest radiograph shows questionable consolidation versus atelectasis in the right lower lobe.

Key Objectives

- Understand the anatomy and physiology of transplanted lungs.
- Describe the preoperative assessment of post–lung transplant patients.
- Review important considerations for the anesthetic management of post–lung transplant patients.
- Discuss postoperative expectations for these patients.

Pathophysiology

What are the indications for lung transplantation?

Pediatric lung transplantation is the most aggressive therapeutic option for children with end-stage pulmonary disease, but it remains a relatively rare operation. Major diagnoses necessitating transplant vary according to recipient age group. Cystic fibrosis (CF) is the most common indication in children ≥6 years, while pulmonary hypertension and surfactant disorders account for the majority of cases in infants < 1 year of age. Other indications include interstitial lung disease, bronchopulmonary dysplasia, obliterative bronchiolitis, and re-transplantation/graft failure.

What is the expected course for patients post lung transplantation?

Lung transplants have the lowest survival rate of all solid organ pediatric transplants. Lungs are unique in that they remain directly exposed to the external environment, with its infective and immunologic challenges, and therefore high levels of immunosuppression are required. The most recent report from the International Society for Heart and Lung Transplantation registry for patients transplanted between January 1990 and June 2016 disclosed a median survival of 5.5 years after pediatric lung transplantation. In patients surviving past year 1, median survival is 8.9 years [1]. The most common causes of death in the first 30 days are multiorgan failure, cardiovascular complications, graft failure, and infection. From 30 days to 1 year, infection and graft failure are the primary causes of death. Beyond 1 year, chronic allograft dysfunction and graft failure are leading causes of mortality. Bronchiolitis obliterans syndrome (BOS) is the most common form of chronic allograft dysfunction and is present in more than 50% of recipients by 5 years post-transplant [1].

Adolescents have lower survival rates compared to young children; this may be partly due to nonadherence with medical therapy leading to graft failure, compounded by transitioning from pediatric to adult care providers. Center volume and pediatric-specific expertise also affect outcome, with better survival in patients transplanted in pediatric centers with higher clinical volume [2]. Furthermore, in CF patients, lung transplantation does not confer any significant survival benefit [3].

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Table 37.1 Complications of Lung Transplantation

Immediate (First Week)	Early Phase (1–3 Months)	Late Phase (Beyond 3 Months)
Surgical complications • *Bleeding* • *Anastomotic issues* • *Airway dehiscence* Hyperacute rejection Primary graft dysfunction Infection	Acute rejection Humoral rejection Poor airway clearance Infection Medication side effects	Bronchiolitis obliterans Malignancy Medication side effects

Clinical Pearl

Lung transplants have the lowest survival rates of all solid organ transplants, and adolescents have lower survival rates compared to young children. Lung transplantation confers no significant survival benefit to cystic fibrosis patients.

What complications are commonly associated with lung transplantation?

Complications can be divided into three phases as outlined in Table 37.1.

How does acute rejection present?

Acute rejection affects the majority of lung transplant recipients and typically is seen during the first 3 months post-transplantation. It may be asymptomatic or present with nonspecific symptoms mimicking infection, including cough, fever, hypoxemia, tachypnea, or dyspnea. Many centers advocate a strict surveillance schedule including scheduled bronchoscopy, bronchoalveolar lavage, and transbronchial biopsy at multiple intervals during the first 3 months to screen for acute rejection and infection.

What is the difference between primary graft dysfunction and chronic allograft dysfunction?

Primary graft dysfunction (PGD) refers to a syndrome of acute lung injury that develops in the first 72 hours after lung transplantation. It is characterized by hypoxemia and the radiographic appearance of diffuse pulmonary opacities and represents a multifactorial injury to the transplanted lung rather than immunologic rejection. Diagnosis is made by excluding other conditions such as volume overload, acute rejection, infection, aspiration, and pulmonary thromboembolism. The severity of PGD is based on the ratio of arterial fraction of oxygen (PaO_2) /fraction of inspired oxygen (FiO_2)[4]. (See Table 37.2.)

Table 37.2 Grading Scale for Primary Graft Dysfunction

PGD Grade	Pulmonary Edema on Chest Radiograph	PaO_2/FiO_2 ratio
PGD grade 0	No	Any
PGD grade 1	Yes	>300
PGD grade 2	Yes	200–300
PGD grade 3	Yes	<200

From Christie J. D., Carby M., and Bag R. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction Part II: Definition. A Consensus Statement of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2005; **24**: 1454–9.

Primary graft dysfunction is associated with a significantly higher mortality and has been correlated with bronchiolitis obliterans. Management is primarily supportive and includes fluid restriction and avoidance of barotrauma. In severe cases, patients may require support with extracorporeal membrane oxygenation (ECMO).

Chronic allograft dysfunction (CLAD) is a term encompassing all chronic lung dysfunction after lung transplantation. Chronic allograft dysfunction is a major limitation to long-term survival post-transplantation. There are two predominant phenotypes of CLAD:

- ***Bronchiolitis obliterans syndrome***, or obliterative bronchiolitis, is the most common form of chronic allograft dysfunction and manifests clinically as obstructive lung disease. It is detected clinically as a decline in forced expiratory volume in 1 second (FEV_1)>20% from baseline and pathologically as dense fibrous tissue affecting the small airway. It is the leading cause of death after the first year of transplant and 50% of surviving children develop BOS within 5 years after transplant [1].
- ***Restrictive allograft syndrome*** (***RAS***) accounts for 30% of CLAD and manifests clinically as restrictive lung disease, with a persistent decrease in forced vital

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capacity (FVC) or total lung capacity with chronic pulmonary infiltrates. Patients with RAS have decreased survival (6–18 months) compared with 3- to 5-year survival for patients with BOS [5].

Do transplanted lungs function like native lungs?

Overall, lung transplant recipients display marked improvement in respiratory function, gas exchange, and exercise tolerance. Respiratory rate and rhythm are typically unchanged. However, transplanted lungs do have an altered physiology compared to native lungs because of the disruption to vagal and autonomic nerves, as well as pulmonary, bronchial, and lymphatic vessels that occurs during explantation of the donor lungs. The level of preservation of the cough reflex is dependent on the surgical strategy, as coughing is stimulated from remaining native lung or from sites proximal to the airway anastomosis. (See Figure 37.1.) Impaired mucociliary clearance is especially pronounced in the early post-transplant period, but remains problematic in long-term survivors, possibly due to abnormal mucus production and diminished ciliary beat frequency. The disruption of the cough reflex and mucociliary clearance, combined with chronic immunosuppression, increases susceptibility to infection. Lymphatic interruption predisposes transplanted lungs to pulmonary edema from fluid overload, especially in the early post-transplant period, and lung compliance is reduced. Single lung transplant recipients can have differential ventilation and perfusion, dependent on compliance differences between native and implanted lung and the pulmonary circulation. The hypoxic pulmonary vasoconstriction reflex remains intact, as does airway response to β_2-agonists.

Clinical Pearl

Transplanted lungs have diminished cough reflex and mucociliary clearance and are predisposed to pulmonary edema due to interruption of lymphatic drainage.

What common coexisting medical issues are frequently seen in lung transplant recipients?

Roughly half of early post-transplant patients exhibit some degree of gastrointestinal dysmotility, gastroparesis, and/or gastroesophageal reflux. Arrhythmias (e.g., supraventricular

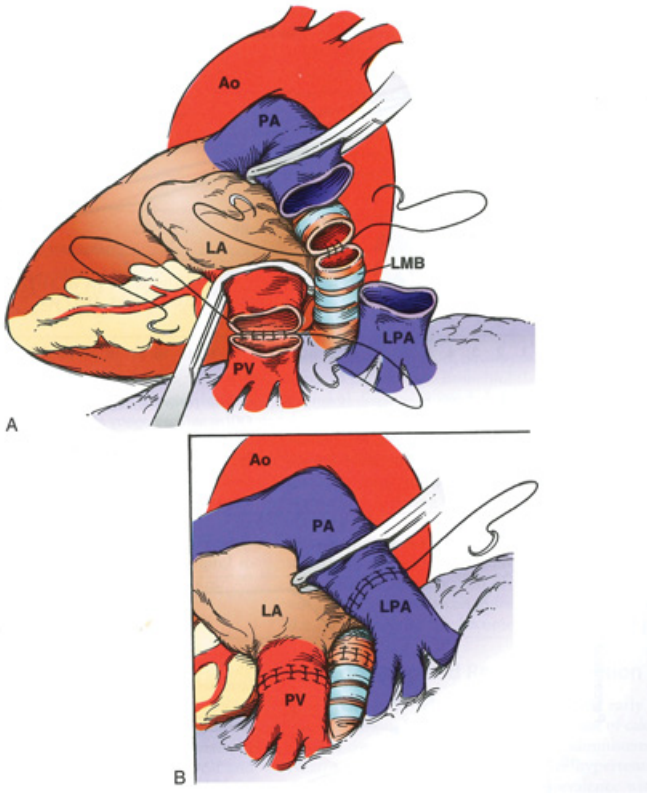

Figure 37.1 **(A) Lung implantation.** Typically, the bronchus is anastomosed first, followed by the left atrial/pulmonary venous connection. **(B)The implantation is completed with the left pulmonary artery anastomosis.** Ao, aorta; LA left atrium; LMB, left mainstem bronchus; LPA, left pulmonary artery; PA, pulmonary artery; PV, pulmonary vein. From Ryan T. D., Chin C., and Bryant R. III. Heart and Lung Transplantation. In Ungerleider R. M., Meliones J. N., McMillan K. N., et al., eds. *Critical Heart Disease in Infants and Children*, 3rd ed. Elsevier, 2019; 868–84. With permission.

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tachycardia, atrial flutter, atrial fibrillation) related to the left atrial cuff suture line may also be present but can be treated with conventional therapies and are often self-limited.

A host of medical issues can be attributed to chronic immunosuppression therapy.

- ***Cardiovascular***: Hypertension may develop due to the pressor effects of corticosteroids and calcineurin inhibitors and affects approximately 70% of patients within 5 years. Hyperlipidemia is also common, developing in 18% of survivors by 5 years [6].
- ***Renal***: Long-term use of calcineurin inhibitors can also result in renal dysfunction, with almost one-third of patients affected within 5 years post-transplant [6]. Early postoperative renal insufficiency, however, is more likely related to preexisting renal dysfunction.
- ***Neurologic***: Calcineurin inhibitors can cause neurologic symptoms including seizures.
- ***Endocrine***: Diabetes may result from immunosuppression with steroids and calcineurin inhibitors and is more common in CF patients with pancreatic disease. Prevalence ranges from 18.8% within 1 year to 28.6% at 5 years [1].
- ***Orthopedic***: Steroid-induced osteoporosis markedly increases the risk of fractures, and avascular necrosis is most commonly seen in the lumbar spine, ribs, and femoral heads.
- ***Oncologic***: Ten percent of transplant survivors develop malignancy by 5–7 years, most commonly a lymphoma variant termed post-transplant lymphoproliferative disease [1].

Clinical Pearl

Lung transplant recipients develop comorbidities related to chronic immunosuppression. Hypertension, renal dysfunction, diabetes, hyperlipidemia, and osteoporosis are frequently seen. Chronic steroid use also leads to osteoporosis and avascular necrosis.

Anesthetic Implications

What special considerations exist when assessing a post–lung transplant patient preoperatively?

The patient's transplant team is an excellent point of contact during the preoperative evaluation, as they will have detailed knowledge of their patient's history, current status, ongoing morbidity, medication regimen, and medical compliance.

The following factors should be considered in the preoperative evaluation of patients with transplanted lungs:

- ***Assessment of pulmonary graft function*** and possible rejection/infection is crucial. Red flag signs such as increasing dyspnea or the need for supplemental oxygen, fever, cough, infiltration on chest radiograph, and deterioration of pulmonary function should be noted. If any of those are present, discussion with the patient's multidisciplinary team, particularly the patient's pulmonologist, should take place prior to surgery.
- ***Immunosuppressive medications*** should be continued throughout the perioperative period. Triple-drug immunosuppression is standard and typically consists of a calcineurin inhibitor (e.g., tacrolimus, cyclosporine), a cell cycle inhibitor (e.g., mycophenolate mofetil, azathioprine), and corticosteroids, with the International Pediatric Lung Transplant Collaborative advocating tacrolimus, mycophenolate mofetil, and prednisolone as the predominant regimen [7]. It is important to appreciate side effects and potential toxicities of commonly used immunosuppressive agents. (See Table 37.3.)
- The ***indication for the surgical procedure*** should be taken into account, as the nature of the condition requiring surgery may affect the transplanted lungs. For instance, patients presenting with acute changes in lung function may require anesthesia to undergo transbronchial biopsy and bronchioalveolar lavage to differentiate between rejection and infection. Both intrathoracic and intraabdominal surgeries may result in diaphragmatic splinting and impaired respirations. If infection is the indication for surgery, septicemia is a major concern given the patient's immunocompromised status.
- The ***underlying disease process necessitating transplant*** and the associated comorbidities remain important, especially in CF patients where multiple "distant" organs are involved.

Preoperative testing and labs should evaluate end-organ function. In addition to pulmonary function tests, the following labs are appropriate: complete blood count, creatinine, blood urea nitrogen, glucose, electrolytes, liver function tests, and a coagulation panel.

In this patient, one should be concerned about the cough with mild tachypnea, mild temperature elevation, and questionable consolidation on chest radiograph. Combined with the history of medical nonadherence, underlying rejection or infection is a distinct possibility.

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Table 37.3 Side Effects and Toxicity of Commonly Used Immunosuppressive Agents

Agent	Side Effect/Toxicity
Tacrolimus (calcineurin inhibitor)	Nephrotoxicity Hypertension Neurotoxicity (headache, tremor, paresthesia, seizure) Glucose intolerance Thrombocytopenia
Mycophenolate mofetil (cell cycle inhibitor)	Hypertension Hyperkalemia/hypophosphatemia Anemia Arrhythmias (tachycardia) Muscle weakness
Corticosteroids	Hypertension Fluid retention Glucose intolerance Adrenal suppression Electrolyte abnormalities Peptic ulcerations, pancreatitis Osteoporosis, myopathy, aseptic necrosis Poor wound healing Psychological disturbance, mood change
Azathioprine (cell cycle inhibitor)	Hepatotoxicity Myelosuppression (anemia, leukopenia, thrombocytopenia) Pancreatitis Nausea, vomiting Arthralgia, rash, stomatitis
Cyclosporine (calcineurin inhibitor)	Nephrotoxicity Hypertension Hepatotoxicity Neurotoxicity (tremor, paresthesias, headache, confusion, seizures) Gastric atony Hyperkalemia/hypomagnesemia

Clinical Pearl

Preoperative evaluation of lung transplant patients should include the following:

- *Ensuring that the transplant team is aware of the planned surgery*
- *Evaluation of pulmonary graft function*
- *Consideration for rejection and/or infection*
- *Effects of the immunosuppressive regimen on other organ systems*
- *Effect(s) of other organ dysfunction on transplanted lungs*
- *Medical noncompliance risk, especially in adolescent patients*
- *Indication for the surgical procedure and potential effects on the lungs*

Are there specific anesthetic management goals for a post–lung transplant patient?

- ***Premedication***: As these patients are frequent visitors to the medical environment, they may experience significant anxiety preoperatively. Anxiolytic premedication is appropriate, provided the patient has adequate ventilatory function. Supplemental perioperative steroid administration should also be considered for major invasive surgeries in patients on chronic steroid therapy or those who have recently completed steroid therapy.
- ***Monitoring***: The use of invasive monitors intraoperatively should be dictated by the severity of the patient's condition and the intended surgery. The risk of infection during line placement cannot be underestimated.
- ***Induction***: Unless hemodynamic instability exists, all induction agents may be considered safe. In the face of compromised cardiopulmonary function, the use of etomidate or ketamine should be considered. Rapid-sequence induction is indicated for patients with severe GERD or gastroparesis.
- ***Airway management***: A recognized side effect of chronic steroid treatment is the rounded Cushingoid moon face, which can adversely impact the ability to mask ventilate a patient. While a laryngeal mask airway (LMA) may be appropriate for procedures of short duration, it is not advisable for patients with active mucositis or those who are at risk of aspiration from gastric atony. Tracheal intubation is preferable for longer procedures and those performed in the nonsupine position. Positioning of the endotracheal tube with the cuff just distal to the vocal cords avoids traumatizing tracheal or bronchial anastomotic suture lines. Especially in the early post-transplant period, direct visualization with a fiberoptic scope may be desirable, and certainly if advanced lung-isolation techniques are required. Long-term airway complications such as stenosis, bronchomalacia, granulomas, and mechanical bronchial distortion can complicate lung-isolation techniques. Avoidance of reactive bronchospasm, especially during airway manipulation, is a high priority, as bronchodilators are less effective, particularly if there is underlying rejection.

Clinical Pearl

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- ***Ventilation strategy***: Particularly in recently transplanted lungs, when utilizing positive pressure ventilation, maintenance of a low peak inspiratory pressure (PIP) is desirable to minimize stress on surgical anastomoses. Most programs suggest a "lung protective" ventilation strategy with the following limits: tidal volume <7 mL/kg body weight, PIP <30 cm H_2O, plateau pressure 20–25 cm H_2O, positive end-expiratory pressure 5–8 cm H_2O, and adjustment of respiratory rate to provide appropriate minute ventilation with $PaCO_2$ at a level similar to preoperative baseline values for each patient [8]. Infection, rejection, or bronchiolitis obliterans can cause high PIP and plateau pressures.
- ***Anesthetic maintenance***: A balanced anesthetic technique utilizing volatile anesthetic or propofol along with short-acting opioids and/or neuromuscular blocking agents is usually well tolerated. The goal is rapid emergence from anesthesia with full muscular strength recovery. Opioids should be used judiciously to balance analgesic effects against the risks of respiratory depression and attenuation of cough reflex. Multimodal analgesia with local and regional/neuraxial anesthesia techniques should be considered if appropriate.
- ***Fluid balance***: Transplanted lungs are susceptible to fluid overload, most notably in the early post-transplant period, so large-volume fluid resuscitation for treatment of hypotension is generally discouraged. Furthermore, patients with concomitant renal dysfunction are further predisposed to fluid retention. Vasopressors such as phenylephrine should be considered early for treatment of hypotension.
- ***Weaning from mechanical ventilation***: Early postoperative extubation is always encouraged, as prolonged intubation carries a significant risk of respiratory infection. Neuromuscular blockade must be reversed to promote robust respiratory mechanics. The presence of compromised airway reflexes emphasizes the importance of having an awake patient with an effective cough prior to removing an invasive airway. Extubation to a noninvasive ventilation system to assist the patient's spontaneous efforts may be prudent.

For the patient in this scenario, who is hemodynamically stable, premedication with intravenous midazolam would be acceptable. After preoxygenation, induction with propofol 2 mg/kg and fentanyl 1 mcg/kg should be well tolerated. The patient could be maintained on either volatile anesthetic or a propofol infusion, with orotracheal intubation and controlled ventilation. Invasive monitors are not required for this procedure. If there is indeed ongoing infection or rejection, one should anticipate the possibility of the need for admission and temporary oxygen requirement post-procedure.

What complications can occur with bronchoscopic procedures?

Bronchoscopy remains the gold standard for evaluating lung allograft in post–lung transplant management programs. While generally safe, complications do occasionally occur and can be divided into three categories as set forth in Table 37.4. Hypoxia and hypercapnia are a direct result of ineffective oxygenation and ventilation occurring when the bronchoscope occludes the airway device. Repeated lavage and excessive suctioning can also contribute. Significant hypoxia may result in bradycardia. The most effective management involves temporary cessation of the procedure, withdrawal of the bronchoscope, and administration of alveolar recruitment breaths with applied positive pressure. Laryngospasm and bronchospasm can arise in the setting of light anesthesia or inadequate topical anesthesia.

Thankfully, serious complications like pneumothorax and hemorrhage are rare, with an incidence of 0.8%–3.4% and 1%–5% respectively [9]. Biopsies should be restricted to a single side to avoid bilateral pneumothoraces or hemorrhage. Uremia and thrombocytopenia have both been identified as risk factors for bleeding and should be addressed prior to lung biopsy.

Can this procedure be performed as an outpatient procedure?

Generally, bronchoscopy with lavage and biopsies can be done as an outpatient procedure. However, the patient should be admitted if there is refractory hypoxemia requiring prolonged oxygen supplementation, persistent ineffective ventilation with hypercapnia, hemodynamic instability, or severe complications associated with the procedure such as pneumothorax or significant bleeding.

Table 37.4 Complications of Bronchoscopic Procedures

Physiologic	Mechanical	Bacteriologic
Hypoxia	Pneumothorax	Iatrogenic infection
Hypercapnia	Hemorrhage	Fever
Arrhythmia, hypotension	Mucosal edema	
Laryngospasm/ bronchospasm		

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Suggested Reading

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