Lung Transplantation

KEY CLINICAL POINTS

1. The Lung Allocation Score (LAS) prioritizes patients with higher acuity and older age groups, with Idiopathic Pulmonary Fibrosis (IPF) becoming a frequent indication.
2. The Composite Allocation Score (CAS) system was introduced in 2023 to incorporate factors beyond survival, including ethical considerations, blood type, and sensitization.
3. Absolute contraindications include active malignancy, active bloodstream infections (e.g., Burkholderia cenocepacia), and uncorrectable organ dysfunction.
4. Primary Graft Dysfunction (PGD) is characterized by diffuse infiltrates and PaO2/FiO2 <300 at 72h, with severe PGD defined as PaO2/FiO2 <100.
5. ECMO bridging to transplant is recommended for critically ill patients, with survival rates equivalent to direct transplant in high-volume centers.
6. Ex vivo lung perfusion (EVLP) can salvage up to 50% of unsuitable donor lungs, particularly from donors after cardiac death (DCD).
7. B. cenocepacia colonization portends the highest risk after transplant, often leading to bacteremia and early mortality.
8. Nutritional status has a U-shaped relationship with outcomes; BMI <18 or >35 increases mortality risk.
9. Surgical approaches include right/left thoracotomy, transverse thoracosternotomy (clamshell), and median sternotomy, each with specific morbidity profiles.
10. Induction immunosuppression typically involves IL-2 receptor antagonists, anti-thymocyte globulin, or corticosteroids, followed by a three-drug maintenance regimen.

FIGURES IN THIS CHAPTER

No figures extracted.

1. DEFINITION & OVERVIEW

Lung transplantation is a surgical procedure involving the replacement of one or both native lungs with donor lungs to treat end-stage lung disease. The Lung Allocation Score (LAS) was implemented in 2005 to prioritize organ allocation based on survival metrics. In 2023, the United Network for Organ Sharing (UNOS) transitioned to the Composite Allocation Score (CAS) system, which incorporates factors beyond survival,

including ethical considerations, access, and efficiency.

Table 1 **Table 309-1 Contraindications to Lung Transplantation**

Category	Absolute Contraindications	Relative Contraindications
Surgical Considerations	Anatomic abnormalities not amenable to transplant procedure	Immobilility, inability to participate in physical therapy/rehabilitation; Limited functional status as defined by 6-minute walk distance
Functional Status	Untreatable, irreversible organ dysfunction	Untreatable, irreversible psychiatric disorder with potential to impact transplant outcome
Medical Comorbidities	Active malignancy or malignancy with insufficient remission period; Active bacterial bloodstream infection resistant to treatment or of high risk for posttransplant morbidity/mortality (Burkholderia cenocepacia, Mycobacterium abscessus); Uncontrolled viral infection (HIV, hepatitis)	Active substance abuse; Other circumstances that would impede ability to participate in and comply with posttransplant care
Nutritional		BMI <18 or >30–35

1.1 Indications for Transplantation

Referral for transplant evaluation should be considered at the time of diagnosis for patients with IPF and other fibrosing lung diseases, as medical therapies slow but do not reverse disease decline. Indications include forced vital capacity <80% predicted, diffusing capacity for carbon monoxide <40% predicted, failure to respond to medical therapy, and functional decline.

1.2 Contraindications

Selection criteria are in constant evolution. Each program establishes its own algorithms. Absolute contraindications affect the ability to complete the procedure or involve untreatable organ dysfunction. Relative contraindications involve risk factors that may worsen outcomes.

2. EPIDEMIOLOGY

Historically, obstructive lung disease was the most common indication, but after LAS implementation, IPF has become an increasingly frequent indication. In 2023, UNOS transitioned to the CAS system. Under the LAS system, patients continued to die at a rate of 10–12 deaths per 100 patient-years on the wait list. Models of CAS allocation suggest expected improvements in wait-list mortality and posttransplant survival, as well as improvements in equity in access.

2.1 Trends in Indications

- Idiopathic pulmonary fibrosis (IPF) is the most common restrictive lung disease and has become an increasingly frequent indication.
- Pulmonary vascular disease transplantation has become less frequent due to advances in medical therapy but remains an important consideration for patients refractory to treatment.
- Cystic fibrosis patients are historically considered for evaluation when FEV reaches ~30% predicted.

2.2 Wait-List Mortality

- Under the LAS system, patients continued to die at a rate of 10–12 deaths per 100 patient-years on the wait list.
- The CAS system aims to create an allocation system that addresses prioritization more continuously, rather than placing candidates within firm boundaries or groups that create hard cutoffs.

3. ETIOLOGY & PATHOPHYSIOLOGY

The text focuses on procedural and selection pathophysiology rather than disease etiology. Key pathophysiological concepts include ischemia-reperfusion injury in the allograft leading to Primary Graft Dysfunction (PGD). PGD is not related to infection or rejection but is a consequence of ischemia-reperfusion injury. It is characterized by a diffuse pattern of infiltrates on the chest x-ray and poor pulmonary gas exchange.

3.1 Primary Graft Dysfunction (PGD)

- PGD encompasses a constellation of findings resulting in poor early graft function after transplant.
- Consequence of ischemia-reperfusion injury in the allograft.
- Not related to infection or rejection.
- Characterized by diffuse pattern of infiltrates on chest x-ray and poor pulmonary gas exchange.
- Severe PGD is characterized by diffuse severe infiltrates and a PaO2/FiO2 ratio of <100 at 72 h posttransplant.
- Severe PGD portends an increased mortality risk and is a risk factor for chronic lung allograft dysfunction (CLAD).

3.2 Donor Lung Pathophysiology

- Brain death causes severe perturbations in potential donor lung allograft function.
- Development of severe neurogenic pulmonary edema often accompanies brain death.
- Hemodynamic instability and neurogenic shock are major stressors on preservation of donor allograft function.
- Primary goal of donor management is maintenance of hemodynamic stability and preservation of donor lung function.

4. CLINICAL FEATURES

Clinical features involve the assessment of disease severity, functional status, and nutritional state to determine candidacy. Functional capacity, as assessed by 6-minute walk distance, is inversely correlated with both wait list and posttransplant mortality. Frailty, independent of walk distance, has been recognized as a marker of poor outcome.

4.1 Functional Assessment

- Functional capacity assessed by 6-minute walk distance is inversely correlated with wait list and posttransplant mortality.
- Frailty, independent of walk distance, is a marker of poor outcome.
- Instruments for frailty assessment include:
  - Short Physical Performance Battery (SPPB).
  - Fried Frailty Phenotype (FFP).

- Lung Transplant Frailty Scale (LT-FS) incorporates body composition and serum biomarker measurements and is a better predictor of outcomes.

4.2 Nutritional Status

- Nutritional status has a U-shaped relationship with transplant outcomes.
- Increased mortality risk associated with underweight (BMI <18) and obesity (specifically BMI >35).
- Consultation with nutritional experts may allow for modification of this risk prior to transplant.
- In underweight patients, placement of an enteral feeding tube and initiation of enteral feedings may be considered.

4.3 Psychosocial Assessment

- Psychosocial assessment is a key component of evaluation.
- Multidisciplinary approach with transplant social work, psychiatry, and financial care coordination is often helpful.
- Assessment for and optimization of psychiatric disorders such as anxiety and depression.
- Substance abuse disorders and compliance with medical therapy recommendations are important parts of pretransplant evaluation.
- Transplant candidates require a strong support system given potential posttransplant care needs.
- Confirmation of insurance coverage and financial resources should be completed during evaluation.

5. DIFFERENTIAL DIAGNOSIS

The differential diagnosis in this context involves distinguishing between disease states eligible for transplant and those that are not. Key differentiating factors include the presence of active malignancy, active infections, and specific comorbidities that preclude transplantation.

5.1 Infectious Considerations

- Burkholderia cepacia complex (specifically B. cenocepacia) presents a unique concern, often leading to bacteremia, abscess formation, and early mortality.
- B. dolosa and B. gladioli may cause similar posttransplant complications.
- Patients colonized with other Burkholderia species appear to have posttransplant outcomes comparable with the noncolonized population.
- Mycobacterial infections, particularly with rapidly growing organisms such as M. abscessus, can lead to chronic, refractory infections.
- Fungal infection assessment includes pathogenicity, resistance patterns, and responsiveness to pretransplant treatment.

5.2 Malignancy Considerations

- Patients with a history of malignancy are generally required to have experienced a period of remission prior to consideration.
- Necessary length of disease-free survival varies by program based on type of malignancy, stage at diagnosis, and likelihood of recurrence.

6. INVESTIGATIONS & DIAGNOSIS

Evaluation involves donor and recipient assessments. Donor evaluation includes medical and social history, physical examination, laboratory examination, chest imaging, arterial blood gases, bronchoscopy, and

serologic tests. Recipient evaluation includes PFTs, imaging, and infectious workup.

Table 2 Table 309-2 Characteristics of the Ideal Lung Donor

Characteristic	Criteria
Donor age	<55 years
ABO compatibility	Identical
Chest radiograph	Clear
PaO2/FiO2	>300 on PEEP 5 cmH2O
Tobacco history	<20 pack-years
Chest trauma	Absent
Evidence of aspiration	Absent
Prior thoracic surgery	None
Sputum Gram stain	Negative
Bronchoscopy findings	No purulent secretions

6.1 Donor Evaluation

- Standard evaluation includes donor medical and social history, physical examination, and laboratory examination.
- Chest imaging is mandatory.
- Arterial blood gases are required.
- Bronchoscopy is required.
- Serologic tests for cytomegalovirus (CMV), Epstein-Barr virus (EBV), hepatitis B and C, HIV, Toxoplasma, rapid plasma reagin, and herpes simplex virus.

6.2 Recipient Evaluation

- Pulmonary function test (PFT) data (e.g., FEV1 <25% predicted).
- Functional assessments (e.g., 6-minute walk distance).
- Infectious history and colonization with resistant organisms.
- Nutritional status assessment.
- Psychosocial assessment.

6.3 Diagnostic Criteria for PGD

- Mild PGD: Diffuse pattern of infiltrates on chest x-ray and poor pulmonary gas exchange with PaO2/FiO2 ratios <300.
- Severe PGD: Diffuse severe infiltrates and a PaO2/FiO2 ratio of <100 at 72 h posttransplant.

7. MANAGEMENT & TREATMENT

Management includes surgical approaches, induction of immunosuppression, perioperative considerations, and postoperative care. ECMO is an alternative strategy for mechanical circulatory support. EVLP is used to assess marginal donors.

7.1 Surgical Approaches

- Right or left thoracotomy: Allows explant and implant without cardiopulmonary bypass (CPB); preferred for single-lung transplant.
- Transverse thoracosternotomy (clamshell): Offers increased exposure; can be used for bilateral lung transplants; allows possibility of avoiding CPB.
- Median sternotomy: Can be used for bilateral lung transplant; offers fewer wound complications, less postoperative pain, and flexibility with complex cardiac procedures; manages use of CPB.

7.2 Procurement Operation

- Prior to incision, thorough bronchoscopic evaluation is completed.
- Anatomy of donor airways is defined.
- Secretions evacuated; airways examined for lesions/masses.
- Epithelial lining inspected for friability/hemorrhage.
- Median sternotomy incision employed.
- Pleural spaces opened; lungs inspected, palpated, recruited.
- Donor systemically heparinized.
- Main pulmonary artery cannulated.
- Prostacyclin introduced 15 minutes prior to explant to ensure adequate pulmonary flush.
- Heart arrested first, then pulmonoplegia solution instilled.
- Topical iced-saline solution instilled into pleural spaces.
- Heart explanted; individual pulmonic veins flushed retrogradely.
- Lungs re-expanded; trachea clamped.
- Explanted allograft stored in ice-cold saline solution for transport.

7.3 Recipient Operation

- Recipient operation divided into two parts: explant of native lung and implant of new lung.
- Hilar structures isolated and divided.
- Bronchial anastomosis completed first; checked for security by insufflating lung under saline.
- Donor left atrial cuff incorporating pulmonary vein connected to native left atrium.
- Donor right or left pulmonary artery connected to native pulmonary artery.
- Lungs gently reperfused.
- Lung-protective ventilation strategies employed; oxygen tension reduced.
- Patient transitioned to normal ventilation; drains placed; wounds closed.

7.4 Induction of Immunosuppression

- Initiation starts with induction under general anesthesia.
- Induction agents: IL-2 receptor/CD25 antagonist, antithymocyte globulin, anti-CD52 monoclonal antibodies, or other induction agents.
- Systemic corticosteroids and purine modulators administered after induction is complete.
- If IL-2 receptor antagonist utilized, second dose administered 4 days after original dose.
- Additional dose of methylprednisolone administered after allograft reperfusion in operating room.
- Three-drug immune suppression initiated with calcineurin inhibitor, purine modulator, and continued systemic corticosteroids.
- In severe acute renal dysfunction, calcineurin inhibitor initiation may be delayed.

7.5 Perioperative Considerations

- Anesthetic monitoring: Arterial pressure, pulse oximetry, continuous ECG, temperature, urine output.
- Large-bore IV access and central venous access vital.
- Selective pulmonary artery pressure monitoring and transesophageal echocardiographic monitoring may be useful.
- Double-lumen endotracheal tubes mandatory for patients without planned CPB; can be avoided for patients transplanted on CPB.
- Careful attention to avoid entrainment of air into ECMO circuit mandatory.

7.6 ECMO and EVLP

- ECMO allows patients to be weaned from ventilator, maintain physical activity, and be in state of greater robustness.
- Posttransplant survival rate of patients bridged to transplant with ECMO is equivalent to those transplanted without ECMO in experienced, high-volume centers.
- ECMO requires much lower levels of anticoagulation than CPB.
- EVLP can be used to assess marginal donors prior to transplant.
- EVLP can salvage up to 50% of selected unsuitable donor lung allografts.

7.7 Infection Management

- Bacterial, viral, and fungal infections are leading causes of morbidity and mortality.
- Early infections (within first month) commonly bacterial (gram-negative bacilli) and manifest as pneumonia, mediastinitis, urinary tract infections, catheter sepsis, skin infections.
- Viral infections (CMV) can lead to severe recipient disease and early loss of graft.
- Majority of programs employ antiviral prophylaxis in early transplant period.
- Invasive fungal infections peak between 10 days and 2 months after transplantation.
- Fungal prophylaxis regimens vary widely.
- Treatment consists of inhaled amphotericin B in setting of airway infection and/or azole therapy with more advanced or invasive disease.
- Oral trimethoprim-sulfamethoxazole (or atovaquone or inhaled pentamidine for sulfa-allergic patients) has effectively prevented Pneumocystis pneumonia.

8. PROGNOSIS & COMPLICATIONS

Early morbidity and mortality most commonly are sequelae of primary graft dysfunction or infection. Hyperacute rejection is extremely uncommon with robust systems to ensure ABO and HLA compatibility. Severe PGD at 72 h posttransplant portends an increased mortality risk and is a risk factor for chronic lung allograft dysfunction (CLAD).

8.1 Primary Graft Dysfunction (PGD)

- Incidence of severe PGD has been steady over past two decades at approximately 10–15% in most programs.
- Severe PGD at 72 h posttransplant portends increased mortality risk.
- Severe PGD is a risk factor for chronic lung allograft dysfunction (CLAD).

8.2 Infection Risks

- The lung is one of the few solid organs in continuous contact with the environment.

- Each breath has potential to introduce new organisms.
- Reduced lymphatic function and mucociliary clearance in transplanted lung increase risk of serious infection.
- Highest incidence of infection is early after lung transplant and coincides with intensity of immune suppression.

8.3 Nutritional and Psychosocial Outcomes

- Nutritional status has U-shaped relationship with outcomes.
- Psychosocial assessment is key component.
- Strong support system required for potential posttransplant care needs.

9. SPECIAL CONSIDERATIONS

Special considerations include donor management, ECMO bridging, nutritional status, and psychosocial factors. Donor management focuses on maintenance of hemodynamic stability and preservation of donor lung function. DCD donors are patients who present with irreversible brain injury but without overt brain death.

9.1 Donor Management

- Brain death causes severe perturbations in potential donor lung allograft function.
- Development of severe neurogenic pulmonary edema often accompanies brain death.
- Hemodynamic instability and neurogenic shock are major stressors.
- Primary goal is maintenance of hemodynamic stability and preservation of donor lung function.
- Judicious fluid resuscitation and avoidance of excessive resuscitation should be employed.
- Volume replenishment limited to maintain central venous pressure between 5 and 8 mmHg.
- Crystalloid fluid boluses avoided.
- Diabetes insipidus common; requires use of intravenous vasopressin to prevent excessive urine loss.
- Blood transfusions avoided; if necessary, CMV-negative and leukocyte-filtered blood used.
- Hypothermia avoided as it predisposes to ventricular arrhythmias and metabolic acidosis.
- Excessive oxygen delivery minimized to prevent free radical injury.
- Positive end-expiratory pressures maintained to avoid atelectasis.
- Airway pressure release modes utilized to preserve lung function and minimize barotrauma.

9.2 Donor Contraindications

- Absolute contraindications: Radiographic evidence of chronic lung disease (emphysema, pulmonary fibrosis), active malignancy, radical donor history of severe asthma requiring multiple hospitalizations, positive HIV status.
- Relative contraindications: Older donor age, severe thoracic trauma with extensive pulmonary contusions, presence of pulmonary hypertension, prolonged donor hypotension or acute hypoxemia.

9.3 Nutritional and Psychosocial Optimization

- Nutritional status optimization prior to transplant.
- Consultation with nutritional experts may allow for modification of risk.
- Enteral feeding tube and initiation of enteral feedings considered in underweight patients.
- Psychosocial assessment key component.

• Multidisciplinary approach with transplant social work, psychiatry, and financial care coordination helpful.

• Optimization of psychiatric disorders such as anxiety and depression.

• Substance abuse disorders and compliance with medical therapy recommendations important.

• Strong support system required.

• Confirmation of insurance coverage and financial resources completed during evaluation.

• Fundraising opportunities and subsidies for medications may need to be pursued.

9.4 Medical Management of Wait-Listed Patients

• Underlying disease in wait-listed patients will almost always continue to worsen.

• Prioritization determined by CAS system.

• Oxygen prescribed to maintain adequate systemic oxygenation.

• Patients enrolled in pulmonary rehabilitation programs if available.

• Continue daily physical exercises.

• Patients with pulmonary vascular disease need special attention to maintain adequate right ventricular function.

• Use of pulmonary vasodilator therapy recommended and should not be stopped prior to transplant.

• Patients with secondary pulmonary hypertension assessed for utility of direct pulmonary vasodilator therapy.

• Periodic assessment of right ventricular function with echocardiography recommended.

• In restrictive lung disease patients, consideration given to continuation of immune modulators and/or antifibrotic therapy.

• Increased pulmonary vascular resistance can occur as disease progresses.

• Acute exacerbations associated with severe acute decrease in right ventricular function.

• Steroids utilized in management of acute exacerbations; negative sequelae of chronic steroid use on wound healing well established.

• Steroid use should be limited as much as possible and tapered rapidly if unavoidable.

• Patients with CF can have pancreatic dysfunction leading to difficulty maintaining normal blood glucose levels.

• Uncontrolled diabetes mellitus can make management of posttransplant blood glucose very challenging.

• Optimization of diabetes management pursued prior to transplantation.

10. KEY PEARLS & CLINICAL TRAPS

• LAS prioritizes patients with IPF and higher acuity of disease.

• CAS system introduced in 2023 to incorporate factors beyond survival.

• B. cenocepacia colonization portends highest risk after transplant.

• Severe PGD at 72 h posttransplant portends increased mortality risk.

• ECMO bridging survival rate equivalent to direct transplant in high-volume centers.

• EVLP can salvage up to 50% of unsuitable donor lungs.

• Nutritional status has U-shaped relationship with outcomes.

• Frailty independent of walk distance is a marker of poor outcome.