Lung Transplantation 2.0:

Updates on Indications/Contraindications, Donor Selection, Surgical Technique and Post-transplant complications

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• None
Learning Objectives

• To review the current indications and contraindications for lung transplant based on the 2014 consensus guidelines from the Pulmonary Council of the International Society for Heart and Lung Transplantation

• To discuss donor selection criteria

• To describe the surgical techniques for lung transplantation

• To discuss the current clinical and imaging findings of post-transplant pulmonary parenchymal and non-pulmonary parenchymal complications, with particular focus on chronic lung allograft dysfunction
General candidacy considerations:

- >50% risk of death within 2 years if lung transplantation not performed
- >80% likelihood of surviving >90 days after lung transplantation
- >80% likelihood of 5-year post-transplant survival, provided there is adequate graft function

### Indications: Adult Lung Transplants 1995-2015

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Obstructive Pulmonary Disease (COPD)</td>
<td>31.3%</td>
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<tr>
<td>Idiopathic Pulmonary Fibrosis (IPF) + other IIP</td>
<td>24.5%</td>
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<tr>
<td>Cystic Fibrosis (CF)</td>
<td>15.8%</td>
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<tr>
<td>Interstitial Lung Disease (ILD) – non IIP</td>
<td>5.2%</td>
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<tr>
<td>Alpha-1 Antitrypsin Deficiency (A1AD)</td>
<td>5.2%</td>
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<tr>
<td>Retransplant</td>
<td>4.1%</td>
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<tr>
<td>Idiopathic Pulmonary Arterial Hypertension (IPAH)</td>
<td>2.9%</td>
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<td>Others, including:</td>
<td></td>
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<tr>
<td>- Non CF-bronchiectasis</td>
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<tr>
<td>- Sarcoidosis</td>
<td></td>
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<tr>
<td>- Pulmonary Hypertension - Not IPAH</td>
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<tr>
<td>- Lymphangioleiomyomatosis (LAM)</td>
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<tr>
<td>- Langerhans Cell Histiocytosis (LCH)</td>
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<tr>
<td>- Connective Tissue Disease</td>
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<tr>
<td>- Cancer</td>
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<tr>
<td>- Bronchiolitis Obliterans</td>
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Adapted from the Registry of the International Society for Heart and Lung Transplantation 2016
Indications

Emphysema

- Chronic obstructive pulmonary disease (COPD):
  - CT topogram: Hyperaerated lungs with flattening of diaphragm.
  - CT: Upper lobe predominant severe centrilobular emphysema with large bullae.

- Alpha-1-antitrypsin deficiency:
  - Radiograph: Paucity of upper lobe lung marking, suggestive of bullous emphysema.
  - CT: Lower > upper lobe panlobular emphysema.

Bronchiectasis

- Cystic Fibrosis (CF)
- Non-CF bronchiectasis, including:
  - Common variable immune deficiency
  - Kartagener’s Syndrome
  - Primary Ciliary Dyskinesia

Cystic fibrosis:
- Varicoid bronchiectasis with bronchial wall thickening and mucus plugs.
- Mosaic attenuation due to air trapping.
Indications: Pulmonary Fibrosis

**Idiopathic Pulmonary Fibrosis (IPF)**
- Poor prognosis, median survival of 2-3 years from diagnosis
- Only 20-30% survive > 5 years after diagnosis

**Interstitial Lung Disease (ILD)**

**Non-IPF**
- Connective Tissue Disease
- Hypersensitivity pneumonitis
- Sarcoidosis
- Inhalational/occupational lung disease
- Idiopathic interstitial pneumonias

**Usual interstitial pneumonia (UIP) fibrosis:**
- Lower > upper lobe, subpleural > peribronchovascular reticulation, architectural distortion
- Honeycombing, traction bronchiectasis

**Sarcoidosis:**
- Upper > lower lobe end-stage pulmonary fibrosis
- Calcified mediastinal and hilar nodes

**Scleroderma:**
- Nonspecific interstitial pneumonia pattern of fibrosis
- Lower > upper lobe, peribronchovascular > subpleural textured groundglass, reticulation
- Traction bronchiectasis
- No honeycombing
- Patulous esophagus
Indications

Vascular

- Idiopathic pulmonary arterial hypertension (IPAH)
- Pulmonary hypertension – non-IPAH, including:
  - Connective tissue
  - Thromboembolic
  - Pulmonary capillary hemangiomatosis (PCH)
  - Pulmonary veno-occlusive disease (PVOD)
  - Congenital defect

Cystic Lung Disease

- Lymphangioleiomyomatosis:

  53 years old female with:
  - Diffuse thin-walled cysts with little normal intervening lung parenchyma

- Langerhans cell histiocytosis:

  64 years old male, former smoker:
  - Upper lobe predominant irregular reticulation, microcysts, micronodules, and architectural distortion
## Contraindications

### Absolute

- Recent malignancy:
  - 5-year disease free interval for hematologic malignancy, sarcoma, melanoma, breast, bladder, kidney
  - 2-year disease free interval for non-melanoma localized skin cancer that has been treated appropriately

- Medical comorbidities:
  - Another major organ system untreatable dysfunction (unless combined organ transplantation)
  - Untreatable atherosclerotic disease with end-organ ischemia
  - Uncorrectable bleeding diathesis
  - Chronic infection – poorly controlled
  - Class II or III obesity body mass index (BMI) ≥ 35 kg/m²

- Mechanical: Significant chest wall or spinal deformity expected to cause severe restriction after transplantation

- Social: substance abuse, medical therapy nonadherence, lack of social support

### Relative

- Age:
  - No upper limit as absolute contraindication, but >75 years old unlikely to be candidates
  - Age >65 years old associated with low physiologic reserve and/or other relative contraindications

- Medical comorbidities:
  - Atherosclerotic disease at risk for end-organ disease after transplant. With coronary artery disease, may undergo preoperative percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) or combined lung transplant and CABG
  - Infection: hepatitis B/C, human immunodeficiency virus (HIV), highly virulent organisms
  - Class I Obesity – BMI 30-34.9 kg/m²

- Severe malnutrition or osteoporosis

- Extensive prior chest surgery with lung resection

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Donor Selection Criteria

- During the first decade of lung transplantation, used stringent “ideal” donor criteria
- Organ donor shortage with long waiting time for listed patient -> 10-15% risk of dying before transplantation
- Many programs now use “extended” donor criteria, called marginal donors
- Mixed data on survival outcome with marginal vs ideal donors

- **Age**
  - Ideal is < 55 years old
  - Marginal donor > 55 years old, similar short-term outcomes compared with younger donor age with some studies showing lower 10-year survival
  - Donor age is borderline risk factor for 1-year mortality but a significant factor for 5-year mortality

- **Radiographic findings**
  - Ideal is clear serial chest X-rays
  - Limited role as an isolated criterion in determining donor suitability given subjective process as often interpreted by an inexperienced person
  - No current data on the role of CT scan

- **Tobacco history**
  - Ideal is < 20 pack-years; marginal donor > 20 pack-years
  - No data on the upper limit of donor cigarette exposure

- **Other “ideal” donor criteria:**
  - Normal gas exchange
    - ($\text{PaO}_2 > 300 \text{ on } \text{FiO}_2 = 1.0, \text{PEEP } 5 \text{ cm H}_2\text{O}$)
  - ABO compatibility
  - Size match with prospective recipient
  - No chest trauma
  - No evidence of aspiration/sepsis
  - No prior cardiopulmonary surgery
  - No purulent secretions at bronchoscopy or organisms on sputum gram stain
  - No history of primary pulmonary disease or active pulmonary infection
Surgical Technique

- **Bilateral vs. unilateral lung transplant:**
  - Bilateral for chronic pulmonary sepsis, ie. cystic fibrosis or non-CF bronchiectasis, to prevent transbronchial spread of infection from the residual native lung
  - Single or bilateral lung transplant for nonseptic lung disease, ie. COPD, IPF, primary pulmonary hypertension
  - Institutional preference and practices: have to consider social benefit of more transplant recipients with single lung transplants
  - Data showing bilateral lung transplant has better survival than single lung transplant – median of 7.1 years for bilateral vs 4.5 years for single lung transplants

1) **Approach:**

- **Bilateral lung transplant:**
  - Clamshell incision (sternothoracotomy)
  - Median sternotomy (concomitant cardiac surgery)
  - Right atrium and ascending aorta accessed for cardiopulmonary bypass (CPB)
- **Single lung transplant:**
  - Antero/posterolateral thoracotomy
  - If left-sided single lung transplant, main pulmonary artery and descending aorta cannulated for CPB

2) **Pneumonectomy:**
   - Recipient lung with least perfusion on preoperative V/Q scan is transplanted first

3) **Hilar dissection for allograft implantation:**
   - Pericardium opened for mobilization of pulmonary vein and artery
   - Important not to denude recipient bronchus as the peribronchial connective tissue carries collateral vessels -> avoid ischemic complications

4) **Allograft implantation:**
   - Anastomoses order bronchus -> pulmonary artery -> pulmonary vein (posterior to anterior hilar structures)
   - Bronchial anastomosis: end-to-end vs telescope technique
   - Bronchial arterial circulation not reestablished, thus need 2-4 weeks time to for rearterialization via recipient bronchial arteries

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B type of telescope anastomosis technique allows well-vascularized recipient bronchus to serve as a “stent” to the relatively more ischemic donor bronchus.

Post-Transplant Complications

Non-pulmonary Parenchymal
- Airway
- Pleural
- Vascular
- Mechanical

Pulmonary Parenchymal
- Primary Graft Dysfunction
- Infection
- Rejection
- Malignancy
- Recurrent Disease
Post-Transplant Complications

Non-pulmonary Parenchymal
- Airway
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Airway Complications

• Bronchial arteries not re-anastomosed during surgery -> healing of bronchial anastomoses dependent on retrograde collateral perfusion from pulmonary arterial circulation

• **Dehiscence:**
  • 2-3% of cases
  • Typically occurs 2-4 weeks post-transplant
  • Imaging: Extraluminal air, bronchial wall defect or irregularity, new/persistent pneumothorax or pneumomediastinum

• **Stenosis**
  • 10% of cases
  • Occurs average of 3 months postsurgery
  • Anastomosis vs distal non-anastomotic stenosis

• **Tracheobronchomalacia**
  • Cross-sectional area of airway decreased by >50% on expiration
  • Occurs within 4 months postsurgery

• **Infection**
  • Mostly within the first 6 months

### Bronchial dehiscence
- 3 week post bilateral lung transplant for CF
- **Localized extraluminal air** adjacent to right mainstem bronchial anastomosis
- 4mm **fistulous connection** between extraluminal air and right mainstem bronchus

### Bronchial stenosis
- 5 months post single left lung transplant for COPD
- **Focal narrowing** of the left upper lobe bronchus (arrow)

### Status post bronchial dilatation
Vascular Complications

- Pulmonary vascular anastomotic stenosis
  - Arterial > venous
  - Rare; < 4% cases
- Pseudoaneurysms
- Pulmonary embolism (PE)

Stenosis of pulmonary artery anastomosis, 1 month post single left lung transplant for IPF

Pseudoaneurysm:
- 2 months post bilateral lung transplant for IPF
- CT angiogram shows *enlarging 5cm collection* subjacent to right pulmonary artery anastomosis
- *Central enhancement on arterial phase and peripheral nonenhancing thrombus*, likely from pulmonary artery anastomosis
- Medialized left atrial appendage exclusion clip (black arrow)
Pleural Complications

- Common 22-34%

- **Effusion**
  - Usually self limiting and resolves within 2 weeks
  - If persistent, think empyema, chylothorax, hematoma, rejection

- **Pneumothorax**
  - Self limiting with chest tube placement
  - If new or persistent, think air leak
  - May occur after transbronchial biopsy

**Mechanical Complications**

- **Size mismatch**
  - Size difference of 25% acceptable
  - May have simultaneous volume reductions surgery if large donor lung
  - Small allograft may be compressed by native lung emphysema

- **Pulmonary torsion**, imaging:
  - Inappropriate hilar displacement associated with atelectatic lobe
  - Abnormal position of pulmonary vasculature and bronchi

**Disruption of thoracotomy sutures**, 2 months post bilateral lung transplant for IPF:
- Patient noticed new right chest wall bulge following coughing paroxysm
- New hydro pneumothorax communicating with new chest wall emphysema
- Blood clot within chest wall emphysema.
Post-Transplant Complications

Non-pulmonary Parenchymal
- Airway
- Pleural
- Vascular
- Mechanical

Pulmonary Parenchymal
- Primary Graft Dysfunction
- Infection
- Rejection
- Malignancy
- Recurrent Disease
Primary Graft Dysfunction

- **Terminology**: also referred to as ischemia-reperfusion injury, reimplantation response, reperfusion edema
- **Mechanism**: noncardiogenic pulmonary edema; multifactorial pathogenesis with oxidative damage from reactive oxygen species major contributor
- **Timeframe**: within 72 hours after surgery, generally resolves by day 10 but may continue up to 2 months
- **Imaging**: nonspecific features, perihilar and basal consolidations, groundglass opacities, interlobular septal thickening, pleural effusions
- Wide spectrum of presentation from mild edema to severe acute lung injury

- Incidence 10-25%; leading cause of early <30 days post-transplantation morbidity and mortality
- Need to exclude left ventricular failure, fluid overload, transplant rejection and infection
- Risk factor for development of bronchiolitis obliterans syndrome
Infection

**Imaging**, similar to nontransplant:
- Consolidations, groundglass opacity, tree-in-bud nodularity, ill-defined nodules, septal thickening, pleural effusion
- Cavitary nodules in bacterial or fungal infections

**Bacterial:**
- Peak incidence within 1st month post-transplant
- Common organisms *Pseudomonas aeruginosa*, and *Klebsiella* species

**Fungal:**
- Peak incidence within first 3 months
- Common organisms *Candida* and *Aspergillus*
- Imaging: ill-defined nodules, cavitary opacities, consolidation, groundglass opacities

**Viral:**
- Cytomegalovirus (CMV) most common opportunistic infection
- CMV peak incidence at 1-4 months

Aspergillus infection:
- 6 years post single left lung transplant for rheumatoid arthritis related UIP fibrosis
- Left upper lobe cavitary nodule and groundglass opacity and nodularity in lingula and left lower lobe. Biopsy of cavitary nodule positive for *Aspergillus*

CMV viremia:
- 1 year post single left lung transplant for COPD and ILD
- New patchy and nodular groundglass opacities in the lingula and left lower lobe
Rejection: Hyperacute -> Acute -> Chronic Lung allograft Dysfunction (CLAD)

- **Hyperacute Rejection:**
  - Fulminant graft failure <24 hours posttransplant
  - Due to preformed recipient antibodies reacting with donor organ HLA or ABO antigens
  - Imaging: diffuse homogeneous opacification of allograft

- **Acute Rejection:**
  - Commonly occurs between 2-3 weeks post-transplant, but can have repeated episodes months-years post-transplant
  - Increases risk of chronic rejection
  - Imaging: nonspecific, groundglass opacities, consolidation, interlobular septal thickening, nodules, pleural effusion
  - Transbronchial biopsy often performed to exclude infection
  - Significant improvement of imaging abnormality 48-72 hours following steroid treatment

3 weeks post single right lung transplant for PCH/PVOD:
- Radiograph: new patchy airspace opacities through the right allograft
- CT: coalescent groundglass opacities, intralobular septal thickening, new small pleural effusion

3 days later following treatment with steroid:
- Resolved airspace opacities in the right allograft
Rejection

- Imaging features of acute rejection, primary graft dysfunction, and infection are nonspecific and often overlap
- Need transbronchial biopsy to exclude infection
- May utilize post-transplant timeframe to help decide between acute rejection and primary graft dysfunction, but may be difficult if recently post-surgery

**Acute rejection**, 5 weeks post single right lung transplant for PCH/PVOD

**Primary graft dysfunction**, 4 days post single left lung transplant for UIP from hypersensitivity pneumonitis

**CMV pneumonia**, 2 months post single left lung transplant for COPD

- All three cases demonstrate shared imaging features of coalescent groundglass opacities, interlobular septal thickening, and two cases with pleural effusions
Chronic Lung Allograft Dysfunction

- **Definition**: decline in forced expiratory volume in 1 second (FEV1) to < 80% baseline for ≥ 3 weeks
- Pathologic confirmation of chronic rejection difficult without surgical lung biopsy, thus use FEV1 as clinical surrogate marker
- Occurs > 3 months post-transplant, based on time needed to establish baseline and document FEV1 decline
- **Two subtypes**: Restrictive vs Obstructive CLAD

Restrictive CLAD = Restrictive allograft syndrome (RAS)

- **Definition**: CLAD with total lung capacity (TLC) <90% baseline for ≥ 3 weeks
- **Pathology**: peripheral lung inflammation and fibrosis, diffuse alveolar damage
- **Imaging**: peripheral, upper lobe predominant pulmonary fibrosis with early groundglass opacities, peripheral consolidation with reticulation, architectural distortion, volume loss and bronchiectasis

Bilateral lung transplant for cystic fibrosis 13 years ago: Progressive bilateral right > left apical consolidation with volume loss, architectural distortion and traction bronchiectasis.
CLAD: Restrictive Allograft Syndrome

- Trichrome stain of transplanted lung on autopsy, magnification 2X
- **Peripheral lung fibrosis** with myofibroblast infiltration of alveolar interstitium, and interlobular septa
- **Thickened pleura** of transplanted lung
- Preserved **alveolar airspaces**

- 25-35% of CLAD cases
- Worse prognosis compared to bronchiolitis obliterans syndrome (BOS):
  - Median survival of RAS is 541 days vs BOS is 1421 days

Pathology slide courtesy of Dr. W. Dean Wallace, Department of Pathology, David Geffen School of Medicine
Chronic Lung Allograft Dysfunction

- Major contributor to lung transplant mortality limiting 5-year survival to approximately 55%
- 50% lung transplant recipients develop CLAD by 5 years
- Once develop CLAD, median survival is 2 years

**Obstructive CLAD = Bronchiolitis obliterans syndrome (BOS)**

- **Definition:** CLAD with TLC >90% baseline
- **Pathology:** obliterative bronchiolitis
- **Imaging:** airway centered disease with bronchial wall thickening, bronchiectasis, mosaic attenuation with expiratory air trapping

Bilateral lung transplant for COPD 8 years ago: mosaic attenuation on inspiratory phase which persists and is accentuated on expiratory phase, indicating air trapping.
CLAD: Bronchiolitis Obliterans Syndrome

- Leading cause of death for recipients who survive beyond 1 year post-transplant
- Risk factors of BOS: repeated episodes of acute rejection, infection, gastroesophageal reflux, primary graft dysfunction

- Hematoxylin and eosin stain of transplanted lung on autopsy, magnification 10X view of a bronchiole
  - Fibroproliferation and inflammatory cell infiltration of bronchiolar wall
  - Narrowed airway lumen

- Two subset of BOS: azithromycin-responsive allograft dysfunction (ARAD) vs fibrous BOS (fBOS)
  - ARAD responds to azithromycin therapy with improvement in FEV
  - ARAD also called neutrophilic reversible allograft dysfunction (NRAD) as associated with neutrophil percentage >15% on bronchoalveolar lavage (BAL)
  - fBOS not responsive to azithromycin, less airway inflammation on BAL
  - Recommendation is 3-month trial of azithromycin in all patients with BOS, with or without BAL neutrophilia

Pathology slide courtesy of Dr. W. Dean Wallace, Department of Pathology, David Geffen School of Medicine
Chronic Lung Allograft Dysfunction

*Diagnostic criteria: FEV1 ≤80 % of baseline

**Restrictive Allograft Syndrome**
- Upper lobe, peripheral fibrosis with traction bronchiectasis, architectural distortion, and volume loss

**Bronchiolitis Obliterans Syndrome**
- Inspiratory phase: mosaic oligemia
- Expiratory phase: mosaic attenuation reflecting air trapping

<table>
<thead>
<tr>
<th>RAS</th>
<th>BOS</th>
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<tbody>
<tr>
<td>Restrictive; Peripheral lung</td>
<td>Obstructive; Small Airways</td>
</tr>
<tr>
<td>Peripheral lung inflammation and fibrosis</td>
<td>Obliterative bronchiolitis</td>
</tr>
<tr>
<td>Poor</td>
<td>Variable</td>
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</tbody>
</table>
Malignancy

- 3- to 4-fold increase of cancer incidence in immunosuppressed organ allograft recipients
- COPD and IPF as major indications for lung transplant = pool of recipients with an even higher baseline risk profile

**Subsets:**
- Common malignancies affecting organ transplant patients (not lung transplant specific):
  - Post-transplant lymphoproliferative disease (PTLD)
  - Increased incidence of skin cancers, cervical intraepithelial neoplasia, vulval and vaginal carcinomas, Kaposi sarcoma, renal cell carcinoma, hepatocellular carcinomas, and non-Hodgkin’s lymphoma
- Malignancy in the native lung
- Malignancy in the allograft

8 years post bilateral lung transplant for COPD: centrally necrotic, peripherally FDG avid right axillary mass, biopsy proven squamous cell carcinoma
Post-transplant Lymphoproliferative Disease

- Usually occurs within the first year, peak incidence at 3-4 months
- More common with lung transplant than with other solid organ transplants
- Associated with Epstein-Barr Virus infection
- Imaging:
  - Solitary or multiple pulmonary nodules/masses
  - +/- hilar/mediastinal adenopathy, thymic enlargement, pleural effusion

6 months post bilateral lung transplant for IPF: Bilateral masslike consolidations with peripheral FDG avidity. PTLD on biopsy with central necrosis
Primary lung carcinoma in allograft

Bilateral lung transplant 8 years for IPF: Enlarging right upper lobe part solid 15mm pulmonary nodule, biopsy-proven invasive adenocarcinoma.

De novo carcinoma in native lung

Single left lung transplant for emphysema: Enlarging FDG-avid 12mm part solid pulmonary nodule in right upper lobe of native emphysematous lung, biopsy non-small cell carcinoma with squamous and adenocarcinoma features.

- Incidence of lung carcinoma in the native lung after single lung transplant is 0.25-6.9%
- Presence of native lung is the strongest risk factor for developing lung cancer after transplantation
De novo malignancy in native lung

- History of single left lung transplant for IPF with rapidly enlarging right lower lobe mass in the native fibrotic right lung over the span of 8 months. Biopsy proven squamous cell carcinoma.

- Incidence of lung cancer in IPF is 4-48% with cumulative incidence of 3% at 1 year, 15%, at 5 years and 55% at 10 years

- Upward trend of reported lung cancer in post transplant patients over the last two decades, multifactorial: marginal donors, longer survival time, effect of immunosuppressive therapy, increase in number of lung transplants performed for pulmonary fibrosis
Recurrent disease

- Rare, affects 1% of transplant recipients
- Sarcoid (most common), lymphangioleiomyomatosis, bronchoalveolar carcinoma, Langerhans cell histocytosis, pulmonary capillary hemangiomatosis

52 yo female with pulmonary hypertension, pretransplant 2003:
- Diffuse ill-defined centrilobular groundglass micronodules
- Dilated pulmonary artery 42mm
- Pulmonary capillary hemangiomatosis (PCH) on explant pathology

Same patient, 6 month post bilateral lung transplant:
- New diffuse ill-defined centrilobular nodules and groundglass attenuation
- Dilated main pulmonary artery 44mm
- Recurrent PCH on biopsy
### Post-transplant Complication Time Course

<table>
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<tr>
<th>Category</th>
<th>Timeframe</th>
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<td><strong>Airway</strong></td>
<td>&lt;24 hrs, 7 days</td>
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<tr>
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<td>4 weeks, 2 months</td>
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<td>4 months, 6 months</td>
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<td>&gt;1 year</td>
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<td>Dehiscence, infection</td>
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<td>Stricture, tracheomalacia</td>
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<td><strong>Vascular</strong></td>
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<td>Stenosis, pseudoaneurysm, PE</td>
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<td>Malignancy: non-PTLD</td>
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References


References


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