CARE OF LUNG TRANSPLANT RECEPIENTS: Challenges unique to developing countries

Dr Milind Baldi
LT in India

• Number of lung transplantation procedures done in India till July 2015
• Tamil Nadu: 67
• Karnataka: 0
• Kerala: 0

http://www.dmrhs.org/tnos/
Numbers...

- China*: 244 (till 2013)
- Iran#: 63 (till 2014)
- Brazil ^^: ~ 700 (till Apr 2015)

*Transplant Proc. 2013 Jan-Feb;45(1):349-55


^^ Einstein (Sao Paulo). 2015 Apr-Jun;13(2):297-304
Literature review

Case Report

Single Lung Transplantation in India: An Initial Experience

Raja Saravanan Elumalai¹, Ganesh Somasundaram¹, Kirthivasan Vaidyanathan¹, Rajesh Venkatraman², Madhusankar Nainar² and Vijil Rahulan³

Departments of Cardiac Anaesthesiology¹, Cardiothoracic Surgery² and Pulmonology and Critical Care³, Global Hospital and Health City, Chennai, India

Review Article

Lung transplantation in India: A possible treatment option

KALPAJ R. PAREKH, PRASAD S. ADUSUMILLI, G. ALEXANDER PATTERTSON
Extrapolation from...

- Other Solid organ transplant complications in developing countries &
- Lung transplant related complications in developed countries.
Complications

- PGD
- Infectious complications
- CAD
- Airway complications
- Malignancy
- Non infectious, non malignant long term complications
Primary Graft Dysfunction

**Pathology**
- DAD

**Pathophysiology**
- Ischemia Reperfusion Injury

**Clinically**
- Decreased oxygenation

**Radiology**
- Diffuse pulmonary infiltrates

**Treatment**
- Largely supportive
Primary Graft Dysfunction

- acute lung injury
- within the first 72 hours.
- pulmonary edema with diffuse alveolar damage
- progressive hypoxemia and
- radiographic pulmonary infiltrates without other identifiable causes.
Various names

• ischemia-reperfusion injury,
• re-implantation response and edema,
• reperfusion edema,
• non-cardiogenic pulmonary edema,
• early graft dysfunction,
• primary graft failure, and
• post-transplant ARDS;
Several modifications (exclusions) have been proposed since then.
PGD

• The reported incidence of PGD ranges from 10% to 25%, with 30-day mortality close to 50%

• Prediction models:
  » normal BMI,
  » COPD/CF, and
  » absent or mild pulmonary hypertension
<table>
<thead>
<tr>
<th>Category</th>
<th>Risk factors for PGD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor inherent variables</td>
<td>Age&gt;45yo, Age&lt;21yo, African American race, Female gender, <strong>History of smoking</strong> &gt;20py, &gt;10py, current, any</td>
</tr>
<tr>
<td>Donor acquired variables</td>
<td>Prolonged mechanical ventilation, Aspiration, Head trauma, Hemodynamic instability after brain death</td>
</tr>
<tr>
<td>Recipient variables</td>
<td><strong>Obesity Body mass index</strong>&gt;25, Female gender, <strong>Diagnosis of idiopathic pulmonary hypertension</strong>, Diagnosis of secondary pulmonary hypertension, Diagnosis of idiopathic pulmonary fibrosis, <strong>Diagnosis of sarcoidosis</strong>, Elevated pulmonary arterial pressure at time of surgery</td>
</tr>
<tr>
<td>Operative variables</td>
<td><strong>Single lung transplantation</strong>, Prolonged ischemic time, <strong>Use of cardiopulmonary bypass</strong>, Blood products transfusion &gt;1L, <strong>High FiO₂ &gt;=0.4 at reperfusion</strong>, Use of intra-cellular (hyperkalemic) type (Euro-Collins) preservation solution</td>
</tr>
</tbody>
</table>
Preventive Interventions

• 1) optimizing selection, matching, and management of donors and recipients preoperatively;
• 2) improving lung preservation and storage techniques; and
• 3) improving lung implantation and reperfusion techniques
Treatment

• Therapy for established PGD after diagnosis remains generally **supportive**, and is influenced by those applied in patients with ARDS, including
  – lung-protective ventilation strategies,
  – avoidance of excess fluid administration,
  – iNO or prostacycline, and
  – extracorporeal membrane oxygenation support (ECMO)
Pulmonary infections following lung transplantation

• Survival for lung transplant recipients continues to lag behind that of other solid organ transplant recipients

• a median survival ("half-life") of 5.5 years.

• **First year after transplantation**: Graft failure and non-cytomegalovirus (non-CMV) infection

• **After first year**: the most common identifiable causes for mortality are bronchiolitis obliterans syndrome (BOS) and non-CMV infection.
Higher than other solid organ transplant ...  

- **Immunosuppression**
- preoperative microorganism colonization
- transmission of infectious agents from the donor
- blunted cough mechanism due to denervation
- impaired mucociliary clearance
- poor lymphatic drainage
- ischemic large airways in the immediate postoperative period and
- constant exposure to the environment
Adult Lung Retransplants

Cause of Death (Deaths: January 1992 – June 2013)

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>0-30 Days (N = 226)</th>
<th>31 Days - 1 Year (N = 306)</th>
<th>&gt;1 Year - 3 Years (N = 215)</th>
<th>&gt;3 Years - 5 Years (N = 80)</th>
<th>&gt;5 Years – 10 Years (N = 88)</th>
<th>&gt;10 Years (N = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiolitis</td>
<td>4 (1.8%)</td>
<td>26 (8.5%)</td>
<td>78 (36.3%)</td>
<td>30 (37.5%)</td>
<td>22 (25.0%)</td>
<td>6 (33.3%)</td>
</tr>
<tr>
<td>Acute Rejection</td>
<td>6 (2.7%)</td>
<td>8 (2.6%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>0</td>
<td>4 (1.3%)</td>
<td>4 (1.9%)</td>
<td>2 (2.5%)</td>
<td>3 (3.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Malignancy, Non-Lymphoma</td>
<td>0</td>
<td>3 (1.0%)</td>
<td>11 (5.1%)</td>
<td>5 (6.3%)</td>
<td>6 (6.8%)</td>
<td>2 (11.1%)</td>
</tr>
<tr>
<td>CMV</td>
<td>0</td>
<td>5 (1.6%)</td>
<td>3 (1.4%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infection, Non-CMV</td>
<td>39 (17.3%)</td>
<td>102 (33.3%)</td>
<td>39 (18.1%)</td>
<td>16 (20.0%)</td>
<td>13 (14.8%)</td>
<td>0</td>
</tr>
<tr>
<td>Graft Failure</td>
<td>56 (24.8%)</td>
<td>49 (16.0%)</td>
<td>45 (20.9%)</td>
<td>15 (18.8%)</td>
<td>20 (22.7%)</td>
<td>2 (11.1%)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>24 (10.6%)</td>
<td>16 (5.2%)</td>
<td>10 (4.7%)</td>
<td>2 (2.5%)</td>
<td>3 (3.4%)</td>
<td>1 (5.6%)</td>
</tr>
<tr>
<td>Technical</td>
<td>31 (13.7%)</td>
<td>7 (2.3%)</td>
<td>1 (0.5%)</td>
<td>0</td>
<td>1 (1.1%)</td>
<td>1 (5.6%)</td>
</tr>
<tr>
<td>Other</td>
<td>66 (29.2%)</td>
<td>86 (28.1%)</td>
<td>24 (11.2%)</td>
<td>10 (12.5%)</td>
<td>20 (22.7%)</td>
<td>6 (33.3%)</td>
</tr>
</tbody>
</table>

Percentages represent % of deaths in the respective time period.
BOS

• Chronic allograft rejection is the major life-limiting complication after lung transplantation.

• Pulmonary infections with viruses, including CMV; gram-negative bacilli, especially Pseudomonas aeruginosa; and Aspergillus species have all been associated with an increased risk of BOS
Diagnosis of LTBI

• Interferon-gamma Release Assay Agreement With Tuberculin Skin Test in Pre transplant Screening for Latent Tuberculosis in High-prevalence Country

• There was a fair agreement between IGRA and TST in the study (kappa = 0.31)

• assessment of cellular immunity response in end-stage renal disease patients be a priority before reliance on IGRA
Diagnosis of LTBI

- The QFT test did not predict subsequent short-term TB development. Furthermore, a long-term and larger-scale study is needed to confirm our results
Diagnosis of LTBI
• A TST reaction of $\geq 5$ mm of induration is considered positive (in transplant recipients)*

• When compared to TST, IGRAs have some operational advantages that are particularly relevant in immunocompromised patients

• While screening of living donors is achievable, testing of deceased donors is challenging, as TST is not feasible and the performance of in vitro assays have not yet been assessed.

• When screening recipients, the decrease in test sensitivity with increasing immunosuppression has important practical consequences,
  • as screening should be carried out before administration of immunosuppressive drugs to ensure sensitivity and
  • to allow sufficient time to initiate chemoprophylaxis.
• The limited number of studies so far indicates that its value may be higher in low-prevalence countries as compared to highly endemic regions.
Predictive Value of ELISPOT

Admission at kidney transplantation units (n=324)

Exclusion (n=12)
- 1 refuse informed consent, 4 pediatric patients, 3 pancreas transplantation alone, 4 transplantation not done (1 active TB, 1 renal cell carcinoma, 1 colon ca, 1 donor kidney problem)

Kidney transplantation n=312 (LDKT n=242 (78%), DDKT n=54 (17%), PKT n=16 (5%))

Presence of clinical risk factors for LTBI n=16 (5%) → INH treatment
- 9 inadequate treated TB history, 3 recent close contact with active TB, 3 donor with inadequate treated TB history, 1 recent tuberculin skin test converter

Tuberculin skin test (+) n=24 (8%)

INH treatment

ELISPOT (+) n=18 (75%)
- TB n=0

ELISPOT (-) n=5 (21%)
- TB n=0

Tuberculin skin test (-) n=272 (87%)

No INH treatment

ELISPOT (+) n=71 (26%)
- TB n=4

ELISPOT (-) n=171 (63%)
- TB n=0
• Further longitudinal studies are needed to estimate the risk for progression to post-transplant TB after IGRA- and TST-based screening
Antibiotic prophylaxis for preventing post solid organ transplant tuberculosis

- Conducted in countries that have high prevalence of TB (India and Pakistan)
- Prophylactic administration of isoniazid reduced the risk of developing TB posttransplant
- There was no significant effect on all-cause mortality
- Substantial risk of liver damage
• We found **limited evidence of suboptimal quality** to support that anti-TB prophylaxis using isoniazid for kidney transplant recipients during the first sixth months to one year post-transplant reduced the risk of developing TB.
Transplant and Tuberculosis

- 511 cases reported worldwide
- 5-15% in India (renal transplant patients)
- Immunosuppression: Cyclosporine and Azathioprine (47%)
- Time of onset: 9 months
- Mode of acquisition: MC: reactivation of old TB, donor transmitted in 4%

*M. tuberculosis Infection in Transplant Recipients, CID 1998;27 (November)*
Epidemiology

TB in transplant recipients is

• more frequent compared to the general population (estimates state 20–74 times as frequent in SOT recipients)

• often fatal (up to 31% in SOT recipients),
<table>
<thead>
<tr>
<th>Nation</th>
<th>Risk post transplant</th>
<th>Organ assessed</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Korea</td>
<td>Incidence: 2.1%</td>
<td>Kidney</td>
<td>The IJTLD, Volume 16, Number 2, 1 February 2012, pp. 248-254(7)</td>
</tr>
<tr>
<td>China</td>
<td>Incidence: 1.1%</td>
<td>Liver</td>
<td>Transplant Proc. 2014 May;46(4):1032-5</td>
</tr>
<tr>
<td>China</td>
<td>Incidence: 3.2%</td>
<td>Kidney</td>
<td>Transplant Proc. 2014 May;46(4):1032-5</td>
</tr>
<tr>
<td>China</td>
<td>Incidence: 2.8%</td>
<td>Heart</td>
<td>Transplant Proc. 2014 May;46(4):1032-5</td>
</tr>
<tr>
<td>India</td>
<td>Incidence: 2.3%</td>
<td>Liver</td>
<td>Liver Transpl. 2014 Aug;20(8):960-6</td>
</tr>
<tr>
<td>China</td>
<td>Incidence: 2.4%</td>
<td>Liver and Kidney</td>
<td>BMC Infect Dis. 2014; 14: 387.</td>
</tr>
<tr>
<td>China</td>
<td>Incidence: 3.2%</td>
<td>kidney</td>
<td>Transplant Proc. 2014;46(2):588-91</td>
</tr>
<tr>
<td>Tunisia</td>
<td>Incidence: 3.2%</td>
<td>Kidney</td>
<td>Biomed Res Int. 2013; 2013:347103</td>
</tr>
</tbody>
</table>
• The risk is highest in lung transplant recipients
• A history of a positive TST or radiographic evidence of past TB is associated with earlier onset of disease
• Hallmark symptoms of TB, are not present universally in transplant patients eg. Fever in 64% of recipients
• a wide range of radiographic manifestations
Tb in scenarios
Latent infection with *M. tuberculosis*
Healthy

Latent infection with *M. tuberculosis*

LTBI

Active TB

Transplanted graft

De novo infection

Smear-positive TB
Latent infection with *M. tuberculosis*

Active TB

Transplanted graft

Pre-transplant active TB
PREVENTION OF TB IN Tx

• Effective pre-transplant screening for LTBI may prevent significant morbidity and mortality post-transplant.
• Apart from TST- or IGRA-positive individuals after targeted screening, treatment of SOT recipients may also be indicated due to a high-risk pre-transplant exposure history (even with negative TST or IGRA)
  • residence in an endemic TB region during the early posttransplant period,
  • specific M. tuberculosis exposure post-transplant, or
  • with a donor history of untreated or incompletely treated LTBI or TB.
PREVENTION OF TB IN Tx

• **Preventive chemotherapy**: used to denote treatment of LTBI among individuals identified as having a positive immune response to M. tuberculosis antigens.

• **Chemoprophylaxis**: is used here to denote primary chemoprophylaxis to prevent TB among individuals with risk factors but without a positive immune response to M. tuberculosis antigens (either negative test or not tested).
PREVENTION OF TB IN Tx

• Risk-adapted pretransplant screening is therefore essential, for:
  • An opportunity for preventive chemotherapy in patients with LTBI, and
  • to raise the index of suspicion of active disease in those patients at high risk.

• In cases where the pre-transplant screening may be falsely negative, as with anergy to TST or an indeterminate IGRA, specialised imaging may be employed in selected patients.
PREVENTION OF TB IN Tx

• Treatment of LTBI:
  • “Treatment of LTBI is likely to be beneficial in persons with reversible risk factors that increase the chance of developing active TB”
  • Active infection should be ruled out first
PREVENTION OF TB IN Tx

• Treatment of LTBI
• Isoniazid:
  • 9-12 months
  • most commonly used.
    – But, hepatotoxicity,
    – poor compliance because of long duration,
    – presence of high primary resistance to the drug.
• Rifampin and pyrazinamide:
  • 2 months, but
    – liver injury is higher
• Isoniazid and Rifampacin:
  • 3 months
  • equivalent to standard therapy with isoniazid
  • Can be extended if intense immunosuppression or high risk
PREVENTION OF TB IN Tx

• Treatment of LTBI
• Timing of therapy?
• Pre transplant: lowers the risk of drug interactions.
• Post transplant: immunosuppression has started and the risk of reactivation TB is higher
TREATMENT OF ACTIVE TB IN TRANSPLANT RECIPIENTS

• Different from general population in two ways:
  1. as rifamycins interact with immunosuppressive drugs of the calcineurin inhibitor family (cyclosporine and tacrolimus), rapamycin and corticosteroids, rifamycin-sparing treatment regimens are preferred

   If a rifamycin is used, the risk of rejection may be increased due to lowered levels of calcineurin inhibitors; consequently, levels of cyclosporine or tacrolimus should be carefully monitored and doses should be adapted (3–5-fold increase)
• 2. adverse anti-TB drug events are more frequent. Consequently, one or more first-line drugs cannot be used and thus the recommended duration of therapy is generally longer than in the general population.
<table>
<thead>
<tr>
<th></th>
<th>ISONIAZID</th>
<th>RIFAMPICIN</th>
<th>STREPTOMYCIN</th>
<th>FLUROQUINOLONE</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEROIDS</td>
<td>↑ steroid levels</td>
<td>↓ steroid levels and efficacy</td>
<td>None</td>
<td>↑ tendon related side effects</td>
</tr>
<tr>
<td>CYCLOSPORIN A</td>
<td>None</td>
<td>↓ Cyclosporin levels, use alt. or monitor levels</td>
<td>↑ risk of nephrotoxicity, avoid or monitor</td>
<td>↑ Cyclosporin levels</td>
</tr>
<tr>
<td>TACROLIMUS</td>
<td>None</td>
<td>↓ Tacrolimus levels, monitor levels or use alternative</td>
<td>↑ risk of nephrotoxicity, avoid or monitor</td>
<td>None</td>
</tr>
<tr>
<td>SIROLIMUS / RAPAMYCIN</td>
<td>None</td>
<td>↓ Sirolimus levels, monitor levels or use alt.</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>MMF</td>
<td>None</td>
<td>↓ MMF levels, use alt. or monitor levels</td>
<td>None</td>
<td>↓ MMF levels</td>
</tr>
</tbody>
</table>

No interaction with Pyrazinamide and Ethambutol
CMV

• Despite 3 months of CMV-directed viral prophylaxis, 10% of postlung transplant pneumonias reported were caused by CMV (n= 236)

• maximum risk in Lung transplant
  • More intense immunosuppression
  • Huge viral load
  • Max risk in D+/R- combination
CMV

- Measurement of **CMV-specific CMI** as a predictor of the development of CMV viremia and disease after the completion of primary prophylaxis.
- Commercially available CD81 CMV-specific interferon g release assay to test serial CMV-specific CMI in SOT recipients during a 3-month posttransplant CMV prophylaxis period.
- Postprophylaxis CMV disease occurred in 22.9% of patients with no detectable CMV-specific CMI, versus 5.3% in patients with a positive QuantiFERON-CMV result, suggesting a possible role in predicting late-onset CMV disease.
CMV

- There are 2 generally accepted strategies for CMV prophylaxis in solid-organ transplantation:
  - universal prophylaxis (administration of antivirals to all at-risk individuals) and
  - preemptive therapy (administration of antivirals only to individuals with demonstrable viral replication).
- Significant uncertainty remains regarding the appropriate duration of prophylaxis.
- Recent trials have suggested that extending prophylaxis to 1 year or longer after transplant may reduce CMV-related complications.
- Reinitiation of CMV prophylaxis should be considered during the treatment of acute rejection if antilymphocyte antibody therapy or high-dose steroids are used.
For CMV tissue-invasive disease, oral valganciclovir 900 mg every 12 hours (adjusted for renal function) is noninferior to intravenous ganciclovir in a mixed population of SOT recipients.

Treatment should be continued for a minimum of 2 to 3 weeks and until the cessation of viral replication has been verified and any CMV attributable symptoms have resolved.

Secondary prophylaxis with lower-dose valganciclovir (900 mg daily adjusted for renal function) can be considered for high-risk patients after completion of CMV treatment, especially those in whom reduction of immunosuppression is not possible.
CMV

• This systematic review found that the antiviral agents improve outcomes for solid organ transplant recipients far beyond the primary indication for use.

• In addition to reducing the risk of CMV disease by 60%, these agents reduced all-cause mortality by 40%, predominantly due to
  • reduced mortality from CMV disease,
  • reducing clinical disease caused by herpes simplex and herpes zoster
  • bacterial infections, and
  • protozoal infections.

• These benefits occurred in both CMV positive recipients and CMV negative recipients of CMV positive organs.

The Cochrane Library 2013, Issue 2
CARVs

- In a significant percentage of patients, symptomatic or asymptomatic viral infection is a trigger for acute rejection and obliterative bronchiolitis/BOS
- Effective antiviral therapies for most CARVs are not available, with the notable exception of influenza virus and perhaps RSV, thus appropriate infection control strategies including hand hygiene and droplet precautions are mandatory to prevent the spread of disease
CARVs

• Influenza
• All transplant recipients and their household contacts should receive *yearly influenza vaccination* with inactivated influenza vaccine for the prevention of disease.
• Suspected cases of influenza should be treated ideally within 48 hours of symptom onset, but symptomatic recipients should be treated regardless of the duration of symptoms.
CARVs

- RSV
- **Supportive care** with the reduction of immunosuppression if possible is universally recommended
- Oral **ribavirin** appears to be an effective, well-tolerated alternative to IV or inhaled ribavirin; provides considerable cost savings and reduces length of hospital stay


J Heart Lung Transplant. 2015 Jul;34(7)
Gram negative Bacterial Infections

- Bacterial pathogens: most common cause of pneumonia after lung transplantation,
- gram-negative bacteria responsible for the bulk of disease.
- a positive donor Gram stain does not lead to poorer posttransplant outcomes if targeted, aggressive antimicrobial prophylaxis is given initially.

• No difference in the incidence of posttransplant pneumonia at 30 days or duration of mechanical ventilation between recipients of donor lungs with positive or negative Gram stains in patients treated with standard postoperative antibiotic prophylaxis (vancomycin plus a third-generation cephalosporin for 7 days)
<table>
<thead>
<tr>
<th>Microorganism</th>
<th>n (%)</th>
<th>Incidence (Number of episodes per 1,000 LT recipients/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BACTERIA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram-negative bacilli:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>14 (24.6)</td>
<td>118.6</td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>8 (14)</td>
<td>67.8</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>3 (5.3)</td>
<td>25.4</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>3 (5.3)</td>
<td>25.4</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td>3 (5.3)</td>
<td>25.4</td>
</tr>
<tr>
<td>Pseudomonas putida</td>
<td>1 (1.8)</td>
<td>8.4</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>1 (1.8)</td>
<td>8.4</td>
</tr>
<tr>
<td>Burkholderia cepacia</td>
<td>1 (1.8)</td>
<td>8.4</td>
</tr>
<tr>
<td>Gram-positive cocci:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>8 (14)</td>
<td>67.8</td>
</tr>
<tr>
<td>Nocardia sp.</td>
<td>2 (3.5)</td>
<td>16.8</td>
</tr>
<tr>
<td>Mycobacteria</td>
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<td></td>
</tr>
<tr>
<td>M. tuberculosis</td>
<td>2 (3.5)</td>
<td>16.8</td>
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<tr>
<td><strong>FUNGI</strong></td>
<td></td>
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<tr>
<td>Aspergillus fumigatus</td>
<td>4 (7)</td>
<td>33.8</td>
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<tr>
<td>Aspergillus niger</td>
<td>1 (1.8)</td>
<td>8.4</td>
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<tr>
<td>Scedosporium prolificans</td>
<td>1 (1.8)</td>
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<tr>
<td>Acremonium sp.</td>
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<td>Mucor sp.</td>
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</tr>
<tr>
<td><strong>VIRUS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>6 (10.4)</td>
<td>50.8</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>57 (107)*</td>
<td></td>
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<td>Incidence (Number of episodes per 1,000 LT recipients/year)</td>
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<td><em>Serratia marcescens</em></td>
<td>1 (1.8)</td>
<td>8.4</td>
</tr>
<tr>
<td><em>Burkholderia cepacia</em></td>
<td>1 (1.8)</td>
<td>8.4</td>
</tr>
<tr>
<td>Gram-positive cocci</td>
<td>8 (14)</td>
<td>67.8</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>8 (14)</td>
<td>67.8</td>
</tr>
<tr>
<td>Nocardia sp.</td>
<td>2 (3.5)</td>
<td>16.8</td>
</tr>
<tr>
<td>Mycobacteria</td>
<td>3 (5.3)</td>
<td>16.8</td>
</tr>
<tr>
<td><em>M. tuberculosis</em></td>
<td>2 (3.5)</td>
<td>16.8</td>
</tr>
<tr>
<td><em>M. avium</em></td>
<td>1 (1.8)</td>
<td>8.4</td>
</tr>
<tr>
<td><strong>FUNGI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Aspergillus fumigatus</em></td>
<td>4 (7)</td>
<td>105.8</td>
</tr>
<tr>
<td><em>Aspergillus niger</em></td>
<td>1 (1.8)</td>
<td>8.4</td>
</tr>
<tr>
<td><em>Scedosporium prolificans</em></td>
<td>1 (1.8)</td>
<td>8.4</td>
</tr>
<tr>
<td><em>Acremonium sp.</em></td>
<td>1 (1.8)</td>
<td>8.4</td>
</tr>
<tr>
<td><em>Mucor sp.</em></td>
<td>1 (1.8)</td>
<td>8.4</td>
</tr>
<tr>
<td><strong>VIRUS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>6 (10.4)</td>
<td>50.8</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>57 (107)*</td>
<td></td>
</tr>
</tbody>
</table>


Fungal Infections

Fungal infections have a **bimodal** presentation:

• early onset, in relation to difficult postsurgeries and prior colonizations, and

• late onset, primarily in relation to chronic rejection and terminal renal insufficiency

• Fungal infections occur in 15–35% of patients after lung transplantation

• overall mortality of 80%
<table>
<thead>
<tr>
<th>IFI Type</th>
<th>Kidney (n = 332)</th>
<th>Liver (n = 378)</th>
<th>Pancreas (n = 128)</th>
<th>Lung (n = 248)</th>
<th>Heart (n = 99)</th>
<th>Small bowel (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidiasis</td>
<td>164 (49)</td>
<td>255 (68)</td>
<td>97 (76)</td>
<td>56 (23)</td>
<td>48 (49)</td>
<td>19 (85)</td>
</tr>
<tr>
<td>Aspergillosis</td>
<td>47 (14)</td>
<td>42 (11)</td>
<td>6 (5)</td>
<td>109 (44)</td>
<td>23 (23)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Zygomycosis</td>
<td>8 (2)</td>
<td>9 (2)</td>
<td>0 (0)</td>
<td>8 (3)</td>
<td>3 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other mold</td>
<td>10 (3.0)</td>
<td>9 (2.4)</td>
<td>4 (3.1)</td>
<td>49 (19.8)</td>
<td>7 (7.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Unspecified mold</td>
<td>7 (2.1)</td>
<td>8 (2.1)</td>
<td>0 (0)</td>
<td>7 (2.8)</td>
<td>2 (2.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>49 (15)</td>
<td>24 (6)</td>
<td>6 (5)</td>
<td>6 (2)</td>
<td>10 (10)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Endemic mycoses</td>
<td>33 (10)</td>
<td>17 (5)</td>
<td>8 (6)</td>
<td>3 (1)</td>
<td>3 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pneumocystosis</td>
<td>5 (1)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>4 (2)</td>
<td>3 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other yeast</td>
<td>6 (1.8)</td>
<td>9 (2.4)</td>
<td>5 (3.9)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Unspecified yeast</td>
<td>3 (0.9)</td>
<td>5 (1.3)</td>
<td>1 (0.8)</td>
<td>6 (2.4)</td>
<td>0 (0.0)</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>
Aspergillus

• **pretransplant airway colonization** was once considered as a risk factor for IA, but subsequent studies have not found the same.

• **Galactomannan assay**: approved in hematopoietic stem cell transplant population, approved for use as a twice weekly

• LT recipients: mixed results, BAL better sensitivity and specificity than serum
Aspergillus

• Prophylaxis:
Majority of centers aim to target Aspergillus and Candida infection.
Monotherapy with either voriconazole or inhaled amphotericin B mostly variable time periods (40% 3-6 months; 30% ≥12 months)
TDM (itraconazole/voriconazole) was used in 86% of centers.
Aspergillus

- Prophylaxis:
- A uniform approach on the optimal agent, dose, frequency, route of administration, type and duration of antifungal prophylaxis in LTx recipients, has not been established.
- Despite the lack of RCTs, the majority of existing studies suggested that antifungal prophylaxis can reduce the incidence and risk of IA among LTx recipients, with tolerable ADRs.
Aspergillus

- **Treatment:**
  - Voriconazole for Aspergillus tracheobronchitis
  - along with reduction of immunosuppression,
  - with attention paid to drug interactions with calcineurin inhibitors and to
  - potential side effects including hepatotoxicity and visual hallucinations.
  - Duration of treatment is guided by bronchoscopic surveillance.
Aspergillus

• Treatment
  • Treatment of IA also relies on voriconazole
  • Reduction of immunosuppression is again an important component of treatment.
  • Surgical intervention
  • Interferon gamma immunotherapy studied in renal transplant recipient
Candida

• Risk Factors
  • prolonged stays in the intensive care unit,
  • Prolonged indwelling catheters and
  • broad-spectrum antibiotic therapy and
  • parenteral nutrition, and
  • heavy growth of Candida from the donor lung

• Culture remains the gold standard for the diagnosis of candidal infections

• given the increasing use of azole prophylaxis (both fluconazole and voriconazole) in lung transplant patients experts recommend empiric therapy with an echinocandin or liposomal amphotericin B
Early Pleural Space Infection Following Lung Transplantation

- Pleural effusions requiring drainage occurred in 27% of recipients (124/455)
- Pleural space infection occurred in 27% (34/124)
- MC infectious etiology: Fungal (60%)
- *Candida albicans* was the predominant organism

*Chest. 2009 Feb; 135(2): 484–491.*
<table>
<thead>
<tr>
<th>Infection</th>
<th>Viruses/Organisms</th>
<th>Common Prophylaxis Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral</td>
<td>Herpes simplex virus CMV</td>
<td>Acyclovir, 200 mg, po twice daily indefinitely</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High risk (D⁺/R⁻)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Valganciclovir, 900 mg, po daily for 6–12 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medium Risk (D⁺/R⁺, D⁻/R⁺)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Weekly CMV polymerase chain reaction, treat when test result is positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Valganciclovir, 900 mg, po daily for 3–12 mo</td>
</tr>
<tr>
<td></td>
<td>Pneumocystis jiroveci</td>
<td>Pneumocystis jiroveci</td>
</tr>
<tr>
<td>pneumonia</td>
<td></td>
<td>Trimethoprim/sulfamethoxazole, 160/800 mg, po 3 times weekly indefinitely</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alternatives for sulfa intolerant, all continued indefinitely</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Atovaquone, 1500 mg, po daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Pentamidine, 300 mg, inhaled monthly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Dapsone, 100 mg, po daily</td>
</tr>
<tr>
<td>Fungal</td>
<td>C albicans</td>
<td>Until corticosteroid dose weaned postoperatively or 3 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Nystatin, 5 mL, po 4 times daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Fluconazole, 100 mg, po daily</td>
</tr>
<tr>
<td></td>
<td>Aspergillus species</td>
<td>When colonized preoperatively or immediately postoperatively, continued until cultures negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Voriconazole, 200 mg, po twice daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Itraconazole, 200 mg, po twice daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Amphotericin, 20–40 mg, inhaled daily</td>
</tr>
</tbody>
</table>
Immunosuppression

• One of the factors that has led to significant improvements in post transplant survival in the current era of solid organ transplantation
• targeting multiple pathways
• Unfortunately, these agents have not been as effective in lung transplantation where graft rejection remains a major obstacle to long-term survival
Conventional approaches

• Some variability
• **Maintenance regimens** typically involve administration of three distinct classes of immunosuppressive agents:
  • Calcineurin inhibitors (eg, cyclosporine, tacrolimus),
  • Antiproliferative agents (eg, azathioprine, mycophenolate mofetil, sirolimus),
  • Corticosteroids
Induction therapy

• In addition, approximately 60% of lung recipients receive **induction therapy** to augment immunosuppression in the early posttransplant period

• a potent immunosuppressive agent
  ▪ to reduce risk of acute rejection
  ▪ permit more gradual initiation of maintenance immunosuppression.

• specifically target T-lymphocytes
• high quality studies comparing one regimen to another are also absent.

• Transplant center practices regarding induction therapy are based largely on retrospective studies, registry reports, and small prospective single-center investigations as well as institutional experiences and expert opinion.
• retrospective study of almost 4000 lung transplant recipients in the ISHLT

• registry transplanted between January 2000 and March 2004, induction therapy with either an IL-2R antagonist or polyclonal ATG remained independently associated with improved survival at 4 years (IL2R antagonist, 64%; ATG, 60%; no induction, 57%).

• There was also a significantly higher rate of infection in both induction therapy groups compared with patients who did not receive induction therapy
To induce or not to induce...

- *United Network for Organ Sharing* registry from 2001 to 2012 for adult
- deceased donor lung transplants who received no induction *(NONE)* or the contemporary agents of basiliximab, alemtuzumab, thymoglobulin, antilymphocyte globulin, or antithymocyte globulin *(INDUCED)*.
- Amongst the 23,951 lung transplants performed with 12,858 meeting the inclusion criteria; 5,713 (44%) were INDUCED.
- Being INDUCED significantly increased overall survival *(p < 0.0001)*.
- Median INDUCED survival was 71.3 months (confidence interval [CI]: 65.7–75.5) as compared with 63.2 months (CI: 60.1–65.9).
- There was less rejection in INDUCED patients (37%), as compared to NONE (42%; *p* < 0.0001).
Chronic Allograft Dysfunction

- first described in 1984
- Lung biopsy: intraluminal polyps of fibromyxoid granulation tissue, which tends to obliterate the lumen of terminal bronchioles, and dense submucosal eosinophilic fibrous scars
• The small airway lesions have a patchy distribution,
• can hardly be demonstrated by TBB
• As a result, in order to establish the diagnosis of BO without the need for open lung biopsy, in 1993, the ISHLT proposed a clinical definition based on pulmonary function criteria.
## Updated classification

<table>
<thead>
<tr>
<th><strong>Table 1</strong></th>
<th>Bronchiolitis obliterans syndrome classification system</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1993 Classification</strong></td>
<td><strong>2002 Classification</strong></td>
</tr>
</tbody>
</table>
| FEV$_1$ 80% or more of baseline | FEV$_1$ >90% of baseline and  
FEF$_{25-75}$ >75% of baseline  
FEV$_1$ 81% to 90% of baseline  
*and/or* FEF$_{25-75}$ = or <75% of baseline | BOS 0 |
| BOS 1 | FEV$_1$ 66% to 80% of baseline | BOS 1 |
| BOS 2 | FEV$_1$ 51% to 65% of baseline | BOS 2 |
| BOS 3 | FEV$_1$ 50% or less of baseline | BOS 3 |

J Heart Lung Transplant 2002;21:297–310
Conditions to be satisfied for a patient to be classified in the staging system

1. The functional loss to be present for at least 3 weeks.
2. The loss had to include a decrease in both FEV1 and FEV1/vital capacity ratio, and
3. Confounding conditions that may produce a decrease in FEV1 should be excluded – eg, infection, acute rejection, anastomotic complications, disease recurrence, and progression of disease in native lung is needed to be excluded.
# Adult Lung Transplants

Cumulative Morbidity Rates in **Survivors** within 1 Year Post Transplant (Follow-ups: April 1994 – June 2013)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Within 1 Year</td>
<td>Total number with known response</td>
</tr>
<tr>
<td>Hypertension</td>
<td>50.8%</td>
<td>(N = 5,982)</td>
</tr>
<tr>
<td>Renal Dysfunction</td>
<td>26.1%</td>
<td>(N = 5,991)</td>
</tr>
<tr>
<td>Abnormal Creatinine ≤ 2.5 mg/dl</td>
<td>15.8%</td>
<td></td>
</tr>
<tr>
<td>Creatinine &gt; 2.5 mg/dl</td>
<td>8.3%</td>
<td></td>
</tr>
<tr>
<td>Chronic Dialysis</td>
<td>2.0%</td>
<td></td>
</tr>
<tr>
<td>Renal Transplant</td>
<td>0.0%</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>16.3%</td>
<td>(N = 6,264)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>20.1%</td>
<td>(N = 5,959)</td>
</tr>
<tr>
<td>Bronchiolitis Obliterans Syndrome</td>
<td>9.4%</td>
<td>(N = 5,592)</td>
</tr>
</tbody>
</table>

*JHLT. 2014 Oct; 33(10): 1009–1024*
Adult Lung Transplants
Cumulative Morbidity Rates in **Survivors** within 10 Years Post-Transplant
(Follow-ups: April 1994 – June 2013)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Within 10 Years</th>
<th>Total number with known response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Dysfunction</td>
<td>73.5%</td>
<td>(N = 1,270)</td>
</tr>
<tr>
<td>Abnormal Creatinine ≤ 2.5 mg/dl</td>
<td>41.1%</td>
<td></td>
</tr>
<tr>
<td>Creatinine &gt; 2.5 mg/dl</td>
<td>19.4%</td>
<td></td>
</tr>
<tr>
<td>Chronic Dialysis</td>
<td>7.8%</td>
<td></td>
</tr>
<tr>
<td>Renal Transplant</td>
<td>5.3%</td>
<td></td>
</tr>
<tr>
<td>Bronchiolitis Obliterans Syndrome</td>
<td>63.4%</td>
<td>(N = 946)</td>
</tr>
</tbody>
</table>
Adult Lung Transplants

Freedom from Bronchiolitis Obliterans Syndrome
Conditional on Survival to 14 days (Follow-ups: April 1994 – June 2013)
Adult Lung Transplants

Freedom from Bronchiolitis Obliterans Syndrome by Diagnosis Conditional on Survival to 14 days
(Follow-ups: April 1994 – June 2013)

No pair-wise comparisons were significant at p < 0.05 except CF vs. COPD
Adult Lung Transplants
Freedom from Bronchiolitis Obliterans Syndrome
by Induction Use Conditional on Survival to 1 Year
(Follow-ups: April 1994 – June 2013)

% Free from Bronchiolitis Obliterans Syndrome

p = 0.0003

N at risk = 40

N at risk = 20

No induction (N = 7,891)
Induction (N = 7,262)

0 1 2 3 4 5 6 7 8 9 10 11 12 13
0 20 40 60 80 100

Years
Classical BOS

• BOS may affect all lung transplant recipients irrespective of donor and recipient characteristics, type of transplantation, and pretransplant disease.

• BOS may present as an acute illness and imitate a respiratory infection, but in most patients it starts as an asymptomatic process that produces an insidious decline in lung function.
• **Auscultation** of the lungs is often normal, but squeaks and coarse crackles may be heard.

• High-resolution CT may reveal **air trapping** and **bronchiectasis**, without significant parenchymal infiltrate.

• As the disease progresses, permanent airway **colonization** with pathogens, such as Pseudomonas aeruginosa and Aspergillus fumigatus, frequently develops.
Types of CAD (other than BOS)

(1) a reversible phenotype characterized by airway neutrophilia and functional improvement with azithromycin
(2) a phenotype characterized by a restrictive ventilatory impairment associated with upper lobe fibrosis or persistent parenchymal or pleural abnormalities,
(3) exudative or follicular bronchiolitis, and
(4) large airway stenosis/malacia..
Pathogenesis and Risk factors

• BO represent a final common pathway lesion secondary to multiple, repetitive insults to the airway epithelium

• Alloimmune Risk Factors: high number of HLA mismatches have an unfavorable impact on survival.

• Other risk factors:
  – direct injury to airways: gastric aspiration and/or
  – augment the alloimmune response via activation of the innate immune system, as is the case for respiratory bacterial and viral infections.
Diagnosis

• Lung functions: spirometry
• Exhaled biomarkers: distribution of ventilation
• eNO and eCO
Treatment

• Optimization and/or Change in Immunosuppressive Regimen: no evidence
• Macrolides: may be used, for ppx also*
• Statins
• Retransplantation
Malignancies following lung transplantation

• SOT recipients have **three- to four-fold** increased risk of developing cancer

• malignancy accounts for 13% of deaths between 5 and 10 years after lung transplantation

• Decrease in T cell mediated immune surveillance

Br J Cancer 2003;89(7): 1221–7
Adult Lung Transplants
Freedom from Malignancy (Follow-ups: April 1994 – June 2013)

% Free from Malignancy

Years

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17

All malignancy  Lymphoma  Skin  Other
## Adult Lung Transplants

### Cumulative Post Transplant Malignancy Rates in Survivors (Follow-ups: April 1994 – June 2013)

<table>
<thead>
<tr>
<th>Malignancy/Type</th>
<th>1-Year Survivors</th>
<th>5-Year Survivors</th>
<th>10-Year Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Malignancy</td>
<td>18,644 (96.4%)</td>
<td>5,600 (84.3%)</td>
<td>1,049 (72.2%)</td>
</tr>
<tr>
<td>Malignancy (all types combined)</td>
<td>701 (3.6%)</td>
<td>1,042 (15.7%)</td>
<td>403 (27.8%)</td>
</tr>
<tr>
<td>Skin</td>
<td>237</td>
<td>724</td>
<td>284</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>261</td>
<td>101</td>
<td>43</td>
</tr>
<tr>
<td>Other</td>
<td>176</td>
<td>263</td>
<td>113</td>
</tr>
<tr>
<td>Type Not Reported</td>
<td>27</td>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>
Extrapolated from Renal transplant...

• Epidemiology differs according to region

<table>
<thead>
<tr>
<th>Region</th>
<th>Malignancy</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>America</td>
<td>Skin</td>
<td>Pathol Oncol Res. 2007;13(1):63–9</td>
</tr>
<tr>
<td>Australia</td>
<td>Lip</td>
<td>JAMA. 2006;296(23):2823–31</td>
</tr>
<tr>
<td>China</td>
<td>Urothelial</td>
<td>Med Oncol. 2014 Jul;31(7):32</td>
</tr>
</tbody>
</table>
• Patients should receive education on avoidance of sun exposure particularly between 11 AM and 3 PM, the use of protective clothing and sunscreen, performing self-examination, and obtaining dermatologic screening at least yearly
Airway complications

• complication rates: 10% to 15%
• with a related rate of mortality of 2% to 3%
AC can be grouped

- **anatomically** (anastomotic or distal to the anastomosis),
- **descriptively** (stricture, granulation tissue, infection, necrosis, dehiscence, and fistula formation),
- **temporally** (early or late), or
- **by cause** (ischemic, infectious, iatrogenic, or idiopathic)
Description of MDS standardized grading

\[ M \text{ (macroscopic aspect)} \]
M0: scar tissue
M1: protruding cartilage
M2: inflammation/granulomas
M3: ischemia/necrosis
- Extent of abnormalities in regard to the anastomosis
  a. Abnormalities localized to the anastomosis
  b. Abnormalities extending from the anastomosis to the bronchus intermedius or to the extremity of the left main bronchus, without lobar involvement
  c. Abnormalities extending from the anastomosis to lobar or segmental bronchi
  d. Abnormalities affecting the lobar and/or segmental bronchi, without anastomotic involvement

\[ D \text{ (diameter)} \]
D0: normal to a fixed reduction less than 33%
D1: expiratory reduction (malacia) greater than 50%
D2: fixed reduction from 33% to 66%
D3: fixed reduction greater than 66%
- Extent of abnormalities in regard to the anastomosis
  a. Abnormalities localized to the anastomosis
  b. Abnormalities extending from the anastomosis to the truncus intermedius or to the extremity of the left main bronchus, without lobar involvement
  c. Abnormalities extending from the anastomosis to lobar or segmental bronchi
  d. Abnormalities affecting the lobar and/or segmental bronchi, without anastomotic involvement

\[ S \text{ (sutures)} \]
S0: absence of dehiscence
S1: limited dehiscence (<25% of circumference)
S2: extensive dehiscence (from 25% to 50%)
S3: very extensive dehiscence (>50%)
- Localization: e: anteriorly; f: other localizations
<table>
<thead>
<tr>
<th>Stenosis/stricture</th>
<th>Anastomotic bronchial stenosis</th>
<th>Nonanastomotic bronchial stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Stenosis &lt;50% of bronchial diameter</td>
<td>• Stenosis &gt;50% of bronchial diameter</td>
<td></td>
</tr>
<tr>
<td>• Stenosis &gt;50% of bronchial diameter</td>
<td>• Stenosis &lt;50% of bronchial diameter</td>
<td></td>
</tr>
<tr>
<td>• Stenosis &gt;50% of bronchial diameter</td>
<td>• Stenosis &gt;50% of bronchial diameter</td>
<td></td>
</tr>
<tr>
<td>Necrosis and dehiscence</td>
<td>Grade I</td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>• No slough or necrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Well-healed anastomosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade II</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Any necrotic mucosal slough observed but no bronchial wall necrosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade III</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bronchial wall necrosis within 2 cm of anastomosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Extensive bronchial wall necrosis extending &gt;2 cm from anastomosis</td>
</tr>
</tbody>
</table>
Exophytic granulation tissue

- Obstructing <50% of the bronchial lumen
- Obstructing >50% of the bronchial lumen
Fistula

- Bronchomediastinal fistula
- Bronchopleural fistula
- Bronchovascular fistula
<table>
<thead>
<tr>
<th>Infectious</th>
<th>Anastomotic infections</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Bacterial</td>
</tr>
<tr>
<td></td>
<td>• Fungal</td>
</tr>
<tr>
<td></td>
<td>Nonanastomotic infections</td>
</tr>
<tr>
<td></td>
<td>• Bacterial</td>
</tr>
<tr>
<td></td>
<td>• Fungal</td>
</tr>
<tr>
<td></td>
<td>• Viral</td>
</tr>
</tbody>
</table>
BRONCHIAL ARTERY REVASCULARIZATION

• routine lung transplantation does not restore the bronchial artery supply
• Allowing the anastomosis of bronchial arteries and preservation of blood flow to the airways shows early promising results
Long term, non pulmonary, non infectious, medical complications

- Renal Failure
  25 % at 1 year, 37 % at 5 years

Calcineurin inhibitor nephrotoxicity
  (tacrolimus < cyclosporine)

ACE inhibitors prevents
Adult Lung Transplants
Freedom from Severe Renal Dysfunction* Conditional on Survival to 1 Year
(Follow-ups: April 1994 – June 2013)

* Severe renal dysfunction = Creatinine > 2.5 mg/dl (221 μmol/L), dialysis or renal transplant

Freedom from Severe Renal Dysfunction (N=16,952)

% Free from Severe Renal Dysfunction

Years

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

0 20 40 60 80 100

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

* Severe renal dysfunction = Creatinine > 2.5 mg/dl (221 μmol/L), dialysis or renal transplant
DIABETES MELLITUS

- 24.3% at 1 year after transplant *
- 33.5% at 5 years after transplant*
- glucocorticoid use and calcineurin inhibitor use
- Guidelines for treatment of diabetes for solid organ transplants recommend intervention when patients have fasting glucose levels greater 126 mg/dl and hemoglobin A1C levels greater than 6.5%^.

CARDIOVASCULAR COMPLICATIONS

- Statins
- Follow general population guidelines

<table>
<thead>
<tr>
<th></th>
<th>@1 year</th>
<th>@ 5 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>51.9 %</td>
<td>85.6 %</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>20.5%</td>
<td>52.2%</td>
</tr>
</tbody>
</table>

J Heart Lung Transplant 2007;26:782–795
OSTEOPOROSIS

• use of corticosteroids and other immunosuppressive medication
• minimum of 1,000 mg/day of calcium and 800 IU/day of vitamin D
• The greatest effect of bisphosphonates in reducing bone loss occurred when medication was started before transplantation when patients were on the waiting list.^
OSTEOPOROSIS

• evaluate all pre-transplant candidates for osteoporosis by DEXA scan, and begin bisphosphonate therapy on anyone with defined osteopenia or osteoporosis and to continue treatment for at least 6 to 12 months after transplantation

AVASCULAR NECROSIS:

- 3 to 22%
- Hip pain: MRI
HEMATOLOGIC COMPLICATIONS

- Cytopenia: immunosuppression medication and prophylactic antiinfectious medication
- Anemia: renal failure, iron deficiency
- Infections such as parvovirus B19, CMV, EBV
- CCI: HUS/TTP
THROMBOEMBOLIC DISEASE

- Incidence of 8.6 to 29%
- high risk for pulmonary infarction, given the dual blood supply from the bronchial artery is absent or poorly developed

Chest 2007;132:547–553
GASTROINTESTINAL COMPLICATIONS

• over 60% of patients who have undergone lung transplant have at least one gastrointestinal complaint
• Nausea, GERD
NEUROLOGIC COMPLICATIONS

• 26% of patients having a neurologic complication in the form of severe headaches, seizures, strokes, and confusion
• calcineurin inhibitor toxicity or infections

J Heart Lung Transplant 1998;17:185–191
## Adult Lung Transplants

**Cause of Death (Deaths: January 1992 – June 2013)**

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>0-30 Days (N = 2,905)</th>
<th>31 Days - 1 Year (N = 5,098)</th>
<th>&gt;1 Year - 3 Years (N = 4,797)</th>
<th>&gt;3 Years - 5 Years (N = 2,746)</th>
<th>&gt;5 Years – 10 Years (N = 3,263)</th>
<th>&gt;10 Years (N = 1,092)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiolitis</td>
<td>8 (0.3%)</td>
<td>233 (4.6%)</td>
<td>1,230 (25.6%)</td>
<td>804 (29.3%)</td>
<td>806 (24.7%)</td>
<td>219 (20.1%)</td>
</tr>
<tr>
<td>Acute Rejection</td>
<td>96 (3.3%)</td>
<td>93 (1.8%)</td>
<td>75 (1.6%)</td>
<td>17 (0.6%)</td>
<td>18 (0.6%)</td>
<td>2 (0.2%)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1 (0.0%)</td>
<td>114 (2.2%)</td>
<td>84 (1.8%)</td>
<td>42 (1.5%)</td>
<td>60 (1.8%)</td>
<td>35 (3.2%)</td>
</tr>
<tr>
<td>Malignancy, Non-Lymphoma</td>
<td>5 (0.2%)</td>
<td>144 (2.8%)</td>
<td>380 (7.9%)</td>
<td>300 (10.9%)</td>
<td>448 (13.7%)</td>
<td>135 (12.4%)</td>
</tr>
<tr>
<td>CMV</td>
<td>0</td>
<td>116 (2.3%)</td>
<td>48 (1.0%)</td>
<td>7 (0.3%)</td>
<td>4 (0.1%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Infection, Non-CMV</td>
<td>550 (18.9%)</td>
<td>1,803 (35.4%)</td>
<td>1,041 (21.7%)</td>
<td>506 (18.4%)</td>
<td>586 (18.0%)</td>
<td>182 (16.7%)</td>
</tr>
<tr>
<td>Graft Failure</td>
<td>702 (24.2%)</td>
<td>844 (16.6%)</td>
<td>906 (18.9%)</td>
<td>493 (18.0%)</td>
<td>558 (17.1%)</td>
<td>181 (16.6%)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>329 (11.3%)</td>
<td>257 (5.0%)</td>
<td>210 (4.4%)</td>
<td>138 (5.0%)</td>
<td>182 (5.6%)</td>
<td>83 (7.6%)</td>
</tr>
<tr>
<td>Technical</td>
<td>330 (11.4%)</td>
<td>180 (3.5%)</td>
<td>45 (0.9%)</td>
<td>14 (0.5%)</td>
<td>28 (0.9%)</td>
<td>8 (0.7%)</td>
</tr>
<tr>
<td>Other</td>
<td>884 (30.4%)</td>
<td>1,314 (25.8%)</td>
<td>778 (16.2%)</td>
<td>425 (15.5%)</td>
<td>573 (17.6%)</td>
<td>246 (22.5%)</td>
</tr>
</tbody>
</table>

THANK YOU