Pediatric Lung transplantation

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Disclosures

- No financial disclosures relevant to this presentation
Pediatric lung transplant - Overview

- Indications and Contraindications
- Outcomes and Complications
- Challenges and Opportunities
Lung Transplant Indications

- Untreatable end-stage pulmonary parenchymal or vascular disease
- Low probability of recurrence
- No other significant medical diseases
- Limitation of daily activity
- Pulmonary rehabilitation potential
- Satisfactory psychosocial support system
Absolute Contraindications

- Second major organ failure
- Burkholderia Cenocepacia colonization
- HIV Infection*
- Hepatitis B or Hepatitis C* Infection
- Active malignancy within past two years
- Progressive Neuromuscular Disorder

*Becoming debatable
Relative Contraindications

Invasive Ventilation
- Risk Factor in Adults
- Less in infants

Fungal and ATM Colonization
- PreTx Eradication vs. PostTx Prophylaxis
- Problematic with Single LT

Psychosocial Issues
- Major Psychoaffective Disorders
- Refractory Nonadherence
Pediatric Lung Transplants: Diagnosis Distribution by Location

<table>
<thead>
<tr>
<th>Region</th>
<th>CF</th>
<th>ILD</th>
<th>ILD Other</th>
<th>OB (non-Retx)</th>
<th>IPAH</th>
<th>PH-not IPAH</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe (N=458)</td>
<td>80%</td>
<td>10%</td>
<td>10%</td>
<td>5%</td>
<td>1%</td>
<td>1%</td>
<td>38%</td>
</tr>
<tr>
<td>North America (N=481)</td>
<td>80%</td>
<td>10%</td>
<td>10%</td>
<td>5%</td>
<td>1%</td>
<td>1%</td>
<td>38%</td>
</tr>
<tr>
<td>Other (N=103)</td>
<td>80%</td>
<td>10%</td>
<td>10%</td>
<td>5%</td>
<td>1%</td>
<td>1%</td>
<td>38%</td>
</tr>
</tbody>
</table>

(Transplants: January 2008 – June 2017)
## Lung Transplant Diagnoses: Infancy

<table>
<thead>
<tr>
<th>Parenchymal Disease</th>
<th>Pulmonary Vascular Disease</th>
<th>Mixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChILD</td>
<td>PH related to CHD</td>
<td>CDH with pulmonary hypoplasia and PH</td>
</tr>
<tr>
<td>SPB, SPC, ABCA3, NKX2.1</td>
<td>ACD / MPV</td>
<td></td>
</tr>
<tr>
<td>Filamin A</td>
<td>Pulmonary Vein Stenosis</td>
<td></td>
</tr>
<tr>
<td>Rarely BPD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Lung Transplant in Infants & Toddlers

## Added Challenges
- Lung Function Assessment
- Bronchoscopy / Biopsy
- Lung Growth

## Specific Infant Requirements
- Weight > 3.5 kg
- EGA > 26-28 weeks
- No other organs involved
- Stable for Transport
Infant and Toddler Diagnoses

- Surfactant Disorders: 37%
- Pulmonary Venous Obstruction: 13%
- Interstitial Lung Disease: 6%
- Pulmonary Hypertension (HTN): 28%
- Inadequate Pulmonary Vascular Supply: 6%
- Pulmonary Dysmaturity: 2%
- Other: 5%
- BPD: 3%

Source: SLCH Txp Program Data
Timing of Referral

- Early! – No downside

- Cystic Fibrosis & Bronchiectasis
  - FEV$_1$ < 40-50\% predicted for children (Ramos et al. JCF 2019 18(3):321-333)

- Pulmonary Hypertension
  - Progressive disease despite therapy
  - CI < 2.0 L/min/m², RA pressure > 15 mm Hg, Mean PA pressure > 55 mm Hg
  - Hemoptyisis, syncopal episodes
  - Consider Pott’s Shunt (Aggarwal et al Circulation:cardiovascular imaging 2018 11(12))

- Infants with congenital respiratory failure (SBP, ABCA3, NKX2.1), PVS - soon

- Other Diseases Less Clear
# Lung Transplant Evaluation

<table>
<thead>
<tr>
<th>Pulmonary Function Testing</th>
<th>Studies</th>
<th>Laboratory</th>
<th>Psychosocial Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Spirometry</td>
<td>• CXR</td>
<td>• Comprehensive Metabolic Panel</td>
<td>• Social Work</td>
</tr>
<tr>
<td>• Lung Volumes</td>
<td>• Chest CT</td>
<td>• Viral Serologies</td>
<td>• Psychology</td>
</tr>
<tr>
<td>• DLCO</td>
<td>• Echo / Cath?</td>
<td>• Sputum Culture</td>
<td>• Child Life</td>
</tr>
<tr>
<td>• Blood Gases</td>
<td>• Consider VQ</td>
<td>• HLA Antibodies</td>
<td>• Financial</td>
</tr>
<tr>
<td></td>
<td>• 6 MWT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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*Children's Hospital in St. Louis*

*Washington University School of Medicine*
Pre-Transplant Case #1

- Full term infant with Respiratory Distress Syndrome
  - 3.9 kg infant born at 40 weeks.
  - Respiratory distress at birth
  - Intubated in the Delivery Room.
  - CXR with ground glass infiltrates.
  - Minimal response to surfactant administration.
  - Now 2 weeks old with slowly increasing respiratory support.
  - Open lung biopsy with alveolar proteinosis.
Pre-Transplant Case #1

- For this term infant with RDS, what is the least likely diagnosis?
  a) ABCA3 Transporter Deficiency
  b) Surfactant Protein B Deficiency
  c) NKX2.1 Mutation
  d) Surfactant Protein C Deficiency
Pre-Transplant Case #1

- For this term infant with RDS, what is the least likely diagnosis?
  a) ABCA3 Transporter Deficiency
  b) Surfactant Protein B Deficiency
  c) NKX2.1 Mutation
  d) **Surfactant Protein C Deficiency**
Lung Transplant Operation

- **Bilateral Sequential**
  - Most Common in Pediatrics
  - Clamshell incision
  - CPB or ECMO

- **En bloc**
  - Median sternotomy
  - Tracheal anastomosis

- **Single Lung Transplant**
  - Rare
Lung Transplant Operation

- Heart Lung Transplant
  - LV failure
  - Irreparable congenital cardiac abnormality
  - Waiting times longer
  - Outcomes track with lung transplant
Initial Post-transplant Therapies

- **Empiric Antibiotics**
  - Cover pre-transplant organisms
  - Cover any organisms in donor

- **Prophylactic Antibiotics**
  - Antifungals (i.e. posaconazole)
  - CMV/HSV (Valgan / Valacyclovir)
  - PJP (TMP/SMX)
  - Candida (Nystatin)
Pediatric lung transplant - Overview

Indications and Contraindications

Outcomes and Complications

Challenges and Opportunities
Pediatric Lung Transplants: Kaplan-Meier Survival by Diagnosis

No pair-wise comparisons were significant at p < 0.05.

- CF (N=1,203)
- ILD (N=98)
- ILD Other (N=96)
- OB (non-Retx) (N=100)
- IPAH (N=217)
- PH-not IPAH (N=115)

Median survival (years): CF=5.4; ILD=4.4; ILD Other=6.3; OB (non-Retx)=NA; IPAH=7.2; PHT Other=3.2

(Transplants: January 1990 – June 2016)
Lung Transplants: Kaplan-Meier Survival Conditional on Survival to 1 Year by Recipient Age Group

Median survival (years):
Adult = 8.2; Pediatric = 8.9

(Transplants: January 1990 – June 2016)
Pediatric Lung Transplants: Kaplan-Meier Survival by Era

Median survival (years):

1988-1999 vs. 2000-2007: p=0.0024
1988-1999 vs. 2008-6/2016: p<0.0001
2000-2007 vs. 2008-6/2016: p=0.3260

(Transplants: January 1988 – June 2016)
Pediatric Lung Transplants: Relative Incidence of Leading Causes of Death

(Deaths: January 2000 – June 2017)
### Complications - Overview

<table>
<thead>
<tr>
<th>Three Phases of Transplant</th>
<th>Four Complication Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Immediate (First Week)</td>
<td>• Immunologic (rejection)</td>
</tr>
<tr>
<td>• Early (1 Week to 3 Months)</td>
<td>• Infectious</td>
</tr>
<tr>
<td>• Late (after 3 Months)</td>
<td>• Surgical</td>
</tr>
<tr>
<td></td>
<td>• Other</td>
</tr>
</tbody>
</table>
Immediate Complications

- Hyperacute Rejection
  - Rarely seen
- Early Graft Dysfunction
  - Aka “reimplantation response”, “ischemia/reperfusion injury”
- Infection
- Surgical Complications
  - Bleeding
  - Anastomosis Breakdown
  - Vascular complications
Post-Transplant Case #1

- You are caring for a 12 y/o patient with pulmonary hypertension who had a lung transplant 6 hours ago.
  - Ischemic times 7:00 R, 7:45 L
  - Pre-transplant PRA 0%

- In the past 2 hours he has developed:
  - diffuse pulmonary infiltrates
  - poor lung compliance
  - moderate gas exchange abnormalities
Post-Transplant Case #1

What is the most likely diagnosis for this lung transplant recipient with severe graft dysfunction:

a) Acute rejection
b) Donor viral infection
c) Pulmonary vein obstruction
d) Primary Graft Dysfunction
What is the most likely diagnosis for this lung transplant recipient with severe graft dysfunction:

a) Acute rejection
b) Donor viral infection
c) Pulmonary vein obstruction
d) **Primary Graft Dysfunction**
Early Complications - Infection

- **Bacterial**
  - Community Acquired Organisms
  - MRSAPseudomonas

- **Fungal**
  - Aspergillus (azole prophylaxis)
  - Candida

- **Viruses**
  - CMV (ganciclovir prophylaxis)
  - Adenovirus
  - RSV

- **Opportunistic**
  - PJP

Photo: Yousem, S. 3rd Banff Conference on Allograft Pathology
Early Complications – Acute Rejection

Acute Rejection: Symptoms / Findings
- Cough, respiratory difficulty
- Fever, inspiratory crackles
- Elevated WBC
- Decreased FEV1
- Perihilar Infiltrates
- Pleural Effusions

Images Courtesy F. White, Washington University
Early Complications – Acute Rejection

- Acute Rejection – Treatment
  - Pulse steroids (methylprednisolone 10 mg/kg IV x 3 doses)
  - Reassess (i.e. biopsy 2 wk post rx)
  - Consider additional therapy if worse (more steroids, Antithymocyte globulin)
Early Complications – Humoral Rejection

- Humoral Rejection – Symptoms / Findings
  - Can be asymptomatic
  - Inspiratory crackles
  - Decreased FEV1
  - Presence of donor specific HLA antibodies
  - Positive C4d capillary loop staining

Image Courtesy F. White, Washington University

Capillaritis
Positive C4d Staining

Images Courtesy F. White, Washington University
Early Complications – Humoral Rejection

- Humoral Rejection – Treatment
  - Many options - Controversial
  - Plasma Exchange
  - Proteosome Inhibitors (carfilzomib)
  - B-Cell depletion (rituximab)
  - Complement Inhibition (eculizumab)
  - Pulse Steroids
  - Antithymocyte globulin

Image Courtesy F. White, Washington University

Capillaritis
Early Complications

- **Surgical Complications**
  - **Airway anastomosis narrowing / malacia:**
    - More common in infants, related to ischemic injury to mainstem bronchi
    - Present with respiratory difficulty, obstruction on spirometry
    - Treated by serial dilation with balloon catheter
    - Rarely require placement of endobronchial stent
  - **Airway dehiscence:**
    - Can be asymptomatic
    - Can present with pneumomediastinum on CXR / CT
  - **Diaphragm Paresis**
    - Cases with recurrent infection/atelectasis treated with plication
  - **Vocal Cord Paresis**
Early Complications

Other Complications
- Hypertension – common side effect of CNI use
- Seizures / posterior reversible encephalopathy syndrome (PRES)
  - Associated with elevated CNI levels
- Renal Failure
  - Usually in patients with preexisting renal dysfunction
- Gastrointestinal
  - Delayed Gastric Emptying
    - May make reflux more likely
    - Aspiration can be a major issue
  - DIOS in CF Patients
- Arrhythmias
  - Often SVT
Post-Transplant Case #2

- You are evaluating an 8 y/o with CF, 2 months post transplant with fever and cough
  - Vitals: tachypnea, SaO2: 92-94% RA
  - PFTs: refuses at home, down in lab
  - Exam: mild distress, crackles at bases
  - CBC: WBC 18K, no left shift  
    CXR: perihilar infiltrates, small right pleural effusion
  - Bronchoscopy: anastomoses intact and patent, no airway mucus, BAL gram stain – moderate polys, no organisms
Post-Transplant Case #2

What is the most likely diagnosis for this transplant recipient with fever and cough:

a) Community acquired pneumonia
b) Acute Cellular Rejection
c) Viral Pneumonia
d) Bacteremia
Post-Transplant Case #2

- What is the most likely diagnosis for this transplant recipient with fever and cough:
  a) Community acquired pneumonia
  b) **Acute Cellular Rejection**
  c) Viral Pneumonia
  d) Bacteremia
Late Complications

- Infection, Acute and/or Humoral Rejection…
- Developmental delay (particularly in infants)
- Renal Failure
- Diabetes
  - Malignancy
- Chronic Lung Allograft Dysfunction (CLAD)
# Pediatric Lung Transplants

Cumulative Morbidity Rates in **Survivors** within 1, 5 and 7 Years Post-Transplant *(Transplants: January 1994 – June 2016)*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Within 1 Year</th>
<th>Total N with known response</th>
<th>Within 5 Years</th>
<th>Total N with known response</th>
<th>Within 7 Years</th>
<th>Total N with known response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Renal Dysfunction&lt;sup&gt;1&lt;/sup&gt;</td>
<td>2.0%</td>
<td>(N = 843)</td>
<td>6.1%</td>
<td>(N = 327)</td>
<td>7.8%</td>
<td>(N = 204)</td>
</tr>
<tr>
<td><em>Creatinine &gt; 2.5 mg/dl</em></td>
<td>1.5%</td>
<td></td>
<td>4.3%</td>
<td></td>
<td>5.9%</td>
<td></td>
</tr>
<tr>
<td><em>Chronic Dialysis</em></td>
<td>0.4%</td>
<td></td>
<td>1.2%</td>
<td></td>
<td>1.0%</td>
<td></td>
</tr>
<tr>
<td><em>Renal Transplant</em></td>
<td>0.1%</td>
<td></td>
<td>0.6%</td>
<td></td>
<td>1.0%</td>
<td></td>
</tr>
<tr>
<td>Diabetes&lt;sup&gt;2&lt;/sup&gt;</td>
<td>18.8%</td>
<td>(N = 848)</td>
<td>28.6%</td>
<td>(N = 336)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Bronchiolitis Obliterans Syndrome</td>
<td>9.3%</td>
<td>(N = 794)</td>
<td>36.9%</td>
<td>(N = 260)</td>
<td>45.1%</td>
<td>(N = 153)</td>
</tr>
</tbody>
</table>

<sup>1</sup> Severe renal dysfunction = Creatinine > 2.5 mg/dl (221 μmol/L), dialysis or renal transplant

<sup>2</sup> Data are not available 7 years post-transplant.
Late Complications

- Infection, Acute and/or Humoral Rejection…
- Developmental delay (particularly in infants)
- Renal Failure
- Diabetes

- Malignancy
  - Post Transplant Lymphoproliferative Disease (PTLD)
  - Other malignancies

- Chronic Lung Allograft Dysfunction (CLAD)
  - Bronchiolitis Obliterans (OB)
  - Restrictive Allograft Syndrome (RAS)
# Pediatric Lung Transplants

Cumulative Post-Transplant Malignancy Rates in Survivors

(Transplants: January 1994 – June 2016)

<table>
<thead>
<tr>
<th>Malignancy/Type</th>
<th>1-Year Survivors</th>
<th>5-Year Survivors</th>
<th>7-Year Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Malignancy</td>
<td>814 (95.0%)</td>
<td>316 (90.8%)</td>
<td>203 (90.2%)</td>
</tr>
<tr>
<td>Malignancy (all types combined)</td>
<td>43 (5.0%)</td>
<td>32 (9.2%)</td>
<td>22 (9.8%)</td>
</tr>
</tbody>
</table>

* Recipients may have experienced more than one type of malignancy so the sum of individual malignancy types may be greater than the total number with malignancy.

**Malignancy Type**

- **Lymphoma**: 40 31 21
- **Other**: 2 1 0
- **Skin**: 1 0 1
- **Type Not Reported**: 0 1 0

“Other” includes liver and primitive neuroectodermal tumor.

2018 JHLT. 2018 Oct; 37(10): 1155-1206
Malignancies

- **PTLD**
  - Usually B-cell non-Hodgkins lymphoma
  - 5-15% of patients
  - Associated with EBV infection
  - Risk factors include CF and acute rejection episodes
  - Elevated EBV PCR sensitive but not specific
  - Initial therapy: rituximab ± low dose cyclophosphamide / prednisone
  - Some patients require chemotherapy

- **Other malignancies**
  - Skin Cancer
PTLD
Late Complications

- Infection, Acute and/or Humoral Rejection…
- Developmental delay (particularly in infants)
- Renal Failure
- Diabetes
- Malignancy
  - Post Transplant Lymphoproliferative Disease (PTLD)
  - Other malignancies

- Chronic Lung Allograft Dysfunction (CLAD)
  - Bronchiolitis Obliterans (OB)
  - Restrictive Allograft Syndrome (RAS)
Pediatric Lung Transplants

Freedom from Bronchiolitis Obliterans Syndrome by Age Group

No pair-wise comparisons were significant at p<0.05.

(Transplants: January 1994 – June 2016)
Chronic Lung Rejection

Chronic Lung Allograft Dysfunction (CLAD)

- Primarily Obstructive Bronchiolitis Obliterans - Histology (BO)
- Bronchiolitis Obliterans Syndrome – PFTS (BOS)

- Primarily Restrictive Restrictive Allograft Syndrome – PFTs (RAS)

J Heart Lung Transplant 2014;33:127–133
Chronic Lung Allograft Dysfunction

Percent Predicted

-24 -12 0 12 24 36

Months Post Transplant

FEV1 Pct
FVC Pct
FEF2575 Pct
BDResp
Bronchiolitis Obliterans

Early small airway fibrosis

Constrictive bronchiolitis/
Obliterative bronchiolitis

Images Courtesy F. White, Washington University
Bronchiolitis Obliterans

Constrictive bronchiolitis/Obliterative bronchiolitis

Image Courtesy F. White, Washington University
CLAD Outcomes

Sato et al., *J HeartLungTransplant* 2011;30:735–42
CLAD – Risk Factors

- Acute Rejection Episodes
- Lymphocytic Bronchitis / Bronchiolitis
- Gastroesophageal Reflux
- HLA / Donor Specific Antibodies
- Autoantibodies (K-α1-tubulin, Collagen V)
- Infections
- Primary Graft Dysfunction
CLAD – Treatment

- Augmented Immunosuppression (T-cell directed Cytolytic therapy)
- Azithromycin
- Address GERD
- Photopheresis
- Retransplant

NO CONSISTENTLY EFFECTIVE THERAPY
Post-Transplant Case #3

- You are seeing a 16 m/o who is 9 months post transplant who presents with persistent fever, poor PO intake

  - Treated x 3 in last two months for otitis, bronchitis.
  - CXR: nothing new, WBC normal
  - EBV PCR elevated (since 3 months post transplant)
  - Bronch: Mild right sided narrowing. Some mucus on right.
  - BAL :Gram stain negative. Culture 20 K alpha strep.
  - TBBx: Lymphocytic bronchitis, no rejection
  - CT Chest / Abdomen: focal nodules in left base, and kidney. Mesenteric thickening
Post-Transplant Case #3

- What is the most likely diagnosis for this transplant recipient with persistent fever:
  a) Acute Rejection
  b) Post-Transplant Lymphoproliferative Disorder
  c) Bronchiolitis Obliterans
  d) Fungal Pneumonia
Post-Transplant Case #3

- What is the most likely diagnosis for this transplant recipient with persistent fever:
  a) Acute Rejection
  b) **Post-Transplant Lymphoproliferative Disorder**
  c) Bronchiolitis Obliterans
  d) Fungal Pneumonia
Pediatric lung transplant - Overview

- Indications and Contraindications
- Outcomes and Complications
- Challenges and Opportunities
Pediatric Lung Transplants: Number of Transplants by Pediatric Center Volume

Analysis includes deceased and living donor transplants.

Source: JHLT. 2018 Oct; 37(10): 1155-1206
Cystic Fibrosis Median Survival

Median Predicted Survival Age, 1986–2016  In Five Year Increments

*Using the currently recommended method for calculating median predicted survival.

Cystic Fibrosis Foundation 2016 Registry Report
Pulmonary Hypertension Survival

![Graph showing survival rates over time from diagnosis.](image-url)

- **Predicted survival by NIH equation**
- **REVEAL weighted to match NIH cohort**

**Time from Diagnosis (years)**: 0, 1, 2, 3, 4, 5, 6, 7

**No. at Risk**: Matched REVEAL
- 279 at 0 years
- 377 at 1 year
- 390 at 2 years
- 388 at 3 years
- 328 at 4 years
- 240 at 5 years
- 153 at 6 years
- 88 at 7 years

**Survival (%)**
- 100 at 0 years
- 93.3% at 1 year
- 77.7% at 2 years
- 70.4% at 3 years
- 66.1% at 7 years

**Chest. 2012;142(2):448-456.**
Pediatric Lung Transplants: Diagnosis by Year (Number)

Number of Transplants

Transplant Year

CF  ILD  ILD Other  OB (non-Retx)  IPAH  PH-not IPAH  Retx  Other

JHLT. 2018 Oct; 37(10): 1155-1206
Adult Lung Transplants: Major Diagnoses by Year (Number)

- COPD
- A1ATD
- CF
- IIP
- ILD-not IIP
- Retransplant

Number of Transplants

Transplant Year


JHLT. 2018 Oct; 37(10): 1155-1206
Challenges

- More even distribution of pediatric transplants across centers
- Population of pediatric lung transplant candidates changing (less CF, less IPH)
- Increasing competition for adult transplant (numbers, high acuity candidates)
- Increasing Candidate Acuity
- Ultimately, Patient Outcomes are at Risk
Bridges to Transplant

- Historical Paradigm –
  - End Stage Lung Disease
  - Respiratory Failure
  - Mechanical Ventilation with escalating support
  - Extracorporeal Life Support (ECLS)
    - Historically meant VA ECMO
    - Complication rate increases with time
    - Sedation / muscle relaxant requirements may limit rehabilitation potential
    - Outcomes poor…
Bridges to Transplant

Evolving Approach

- Historically Dismal Outcomes with VA ECMO
Bridges to Transplant

Evolving Approach

- **VV ECMO in Selected Cases**
  - Early Tracheostomy when Possible
  - Active Rehabilitation (a work in progress)
  - Several successful cases

- **Pumpless Oxygenator for Refractory Pulmonary Vascular Diseases – PA to LA configuration**
  - Four patients, one bridged to recovery, one successfully transplanted
  - All with significant vascular complications

Gazit et al. *J Thorac Cardiovasc Surg* 2011; 141(6) e48-e50
Hogansen et al. *J Thorac Cardiovasc Surg* 2014;147(1):420-6
Virtual Table Exercise (10 minutes)

- Introduce yourselves
- Identify a spokesperson
- Discuss and develop answers to the assigned case from the materials provided
- Be prepared to provide answers and rationale
Key Points

- Pediatric lung transplantation is an accepted therapy
- Long term outcomes remain an issue
- Increasing competition for organs drives
  - Need to increase lung donor utilization
  - Evolution of bridging strategies
Thanks!