Pediatric Lung Transplantation: Basic Concepts and Complications

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Disclosures

• Unfortunately, I have no financial disclosures.
• I have a lot of slides...
• I am primarily a clinician and I’m definitely not a transplant immunologist!
Objectives

• (Brief) history of lung transplantation
• Indications/Contraindications
• The “Basics” of Transplant Immunology and Immunosuppressive Treatment
• Complications (limited, with emphasis on GER/Aspiration)
• Controversies and Challenges
THE ROAD TO ENLIGHTENMENT IS LONG AND DIFFICULT, WHICH IS WHY I ASKED YOU TO BRING SANDWICHES AND A CHANGE OF CLOTHING.
History of Lung Transplantation II

• 1963: First human lung transplant by J.D. Hardy. Deceased donor. Recipient died of renal failure, 18 days (Minimal rejection, although A-B incompatible!)

J.D. Hardy, MD. 1918-2003: First human lung transplant (1963); first animal to human heart transplant (1964)
History of Lung Transplantation II

• 1963-1982:
  – Research on surgical techniques leading to improved bronchial anastomotic healing.
  – Immunosuppressives: Azathioprine, irradiation, and corticosteroids
  – By 1978: of 38 reported recipients, only 9 lived more than 14 days, none more than 1 year.
History of Lung Transplantation III

• After 1978
  – The CYCLOSPORINE A “Revolution”…
  – Calne: renal 1978
  – Starzl: liver 1981
“Probably the most interesting period of medicine has been that of the last few decades. So rapid has been this advance, as new knowledge developed, that the truth of each year was necessarily modified by new evidence, making the truth an ever-changing factor.”

Charles H. Mayo, M.D., 1919
NUMBER OF LUNG TRANSPLANTS REPORTED BY YEAR AND PROCEDURE TYPE

NOTE: This figure includes only the lung transplants that are reported to the ISHLT Transplant Registry. As such, this should not be construed as representing changes in the number of lung transplants performed worldwide.

ISHLT 2012
NOTE: This figure includes only the pediatric lung transplants that are reported to the ISHLT Transplant Registry. Therefore, these numbers should not be interpreted as the rate of change in pediatric lung procedures performed worldwide.
Recipient Selection

• Is the patient sick enough to justify the risks of lung transplantation?
• Is the patient likely to benefit from lung transplantation?
• Are there contraindications that will absolutely preclude lung transplantation?
Guidelines for Candidate Selection

• Optimal medical therapy
• Known limited survival
• Optimal treatment of comorbid conditions (e.g. DM, HTN)
• Age limits:
  – Heart-lung: 55 yrs.
  – Double lung: 60 yrs.
# Pediatric Lung Transplants: Indications (Transplants: January 1990 - June 2011)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>AGE: &lt; 1 Year</th>
<th>AGE: 1-5 Years</th>
<th>AGE: 6-11 Years</th>
<th>AGE: 12-17 Years</th>
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</thead>
<tbody>
<tr>
<td>Cystic Fibrosis</td>
<td>1</td>
<td>6</td>
<td>171</td>
<td>826</td>
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<tr>
<td>Idiopathic Pulmonary Arterial Hypertension</td>
<td>12</td>
<td>27</td>
<td>31</td>
<td>83</td>
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<tr>
<td>Re-Transplant: Obliterative Bronchiolitis</td>
<td>7</td>
<td>9</td>
<td>35</td>
<td></td>
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<tr>
<td>Congenital Heart Disease</td>
<td>14</td>
<td>9</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Idiopathic Pulmonary Fibrosis</td>
<td>9</td>
<td>21</td>
<td>15</td>
<td>39</td>
</tr>
<tr>
<td>Obliterative Bronchiolitis (Not Re-TX)</td>
<td>10</td>
<td>23</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Re-Transplant: Not OB</td>
<td>3</td>
<td>4</td>
<td>9</td>
<td>30</td>
</tr>
<tr>
<td>Interstitial Pneumonitis</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Pulmonary Vascular Disease</td>
<td>8</td>
<td>7</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Eisenmenger’s Syndrome</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Pulmonary Fibrosis, Other</td>
<td>6</td>
<td>8</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>Surfactant Protein B Deficiency</td>
<td>16</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD/Emphysema</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Bronchopulmonary Dysplasia</td>
<td>3</td>
<td>3</td>
<td>7</td>
<td>2</td>
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<tr>
<td>Bronchiectasis</td>
<td>1</td>
<td>6</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>12</td>
<td>6</td>
<td>12</td>
<td>27</td>
</tr>
</tbody>
</table>

Analysis includes living donor transplants

*ISHLT* 2012

*J Heart Lung Transplant. 2012 Oct; 31(10): 1045-1095*
<table>
<thead>
<tr>
<th>Absolute Contraindications</th>
<th>Relative Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Malignancy</strong> within 2 years, with the exception of cutaneous squamous and basal cell tumors</td>
<td>Critical or unstable condition</td>
</tr>
<tr>
<td>Untreatable, advanced dysfunction of another major organ system</td>
<td>Severely limited functional status with poor rehabilitation potential</td>
</tr>
<tr>
<td>Non-curable chronic extrapulmonary infection (HIV, HepB, HepC)</td>
<td>Colonization with highly resistant or highly virulent microorganisms</td>
</tr>
<tr>
<td>Significant chest wall and/or spinal deformity</td>
<td>Severe obesity (BMI &gt;30 kg/m²)</td>
</tr>
<tr>
<td>Documented nonadherence</td>
<td>Severe malnutrition</td>
</tr>
<tr>
<td>Immunodeficiency**</td>
<td>Severe or symptomatic osteoporosis</td>
</tr>
<tr>
<td>Untreatable psychiatric or psychologic condition that will impair compliance with medical therapy</td>
<td>Mechanical ventilation</td>
</tr>
<tr>
<td>No reliable social support system</td>
<td>Suboptimally treated serious medical condition</td>
</tr>
<tr>
<td>Substance addiction within past 6 months</td>
<td></td>
</tr>
</tbody>
</table>
Evaluation for Pediatric Lung Transplantation

• Consideration
  – Underlying disease
  – Contraindications?
  – Assessed level of illness/ risk of death

• Evaluation
  – Meet the team: Transplant Coordinator
    Pulmonology/Cardiology/I.D./CT Surgery/
    Psychology/Social Work et. al.
  – Understanding of process of transplantation
Lung Allocation Score: Patients >12 yrs old, since 2005.

• Waitlist Urgency:
  – Predicts survival on the wait list over the next year

• Post-Transplant Survival
  – Predicts survival over the year following transplantation

• Both used to calculate a Raw Score, leading to the actual LAS (0-100).
Patient data required for LAS

- 6 minute walk distance
- Modified NYHA Class
- Diabetes (Y/N)
- Assisted ventilation (Y/N)
- Serum creatinine
- $O_2$ (Y/N; amt)
- FVC ( # and % pred.)
- $PCO_2$
- PA systolic; PAP; PCWP

Data updated every 6 months

Score range: 0 (healthiest) -100 (sickest)
Recent Changes to UNOS Policy

- Pediatric Donor Lungs are preferentially directed to Pediatric Recipients
- Adolescent Lung Candidates may not be large enough for lungs from previously healthy adolescent donors
Pediatric Lung Transplantation

• Surgical approach is usually bilateral sequential lung transplantation with bi-bronchial anastamoses.
  – Transverse inframammary thoracic incision
  – Bronchial arterial re-implantation usually not performed

• Lung harvesting: hypothermic pulmonary artery flush, 50 to 60 mL/kg, low potassium Dextran-glucose soln.
Fig. 6. A: A transverse sternothoracotomy is performed with the patient supine. The incision (dashed line) follows the inframammary crease. B: The fourth or fifth interspace is opened, and the sternum is divided.
CF Patient Immediately Post-Transplant
Pediatric Lung Transplantation

• The surgery, although technically challenging, is not the most difficult aspect of pediatric lung transplantation.

• Recovery post-transplant and “life after lung transplantation” are the real test of the patient, the family…and the care team
  – Immunosuppression: Life-long compliance
  – Risk of complications: e.g. Rejection; Infection
“Lung transplantation is a treatment, not a cure, and it is not a panacea.”

Trulock EP. Am J Resp Crit Care Med 1997; 155: 789-818
The immune system can be defined as a system of biological structures and processes within an organism that protects the organism from disease resulting from specific pathogens.

The immune system identifies an allograft as “foreign” and thus a potential pathogen. The task of transplant science is to control the immune system in a way that will preserve the graft, but not lose the ability to protect against true pathogens.
Graft Rejection I

- **“Older View”:** T-cell dependent, adaptive immunity was felt to be the key (?only?) immune response
- **“Newer View”:** Combination of innate and adaptive immunity important.
  - Pattern recognition receptors (PPRs), detecting Pathogen-associated molecular patterns (PAMPs) can also detect and bind to Damage-associated molecular patterns (DAMPs).
    - DAMPs can result from tissue/organ harvesting: release of markers of injury
    - PPRs sensing DAMPs leads to local inflammatory cascade affecting the graft.
- **Other effectors** leading to graft dysfunction:
  - Complement system
  - Antibodies to mismatched HLA
Graft Rejection II: …back to T-cells

• “Three Signal” concept of T-cell activation
  – Signal 1 (Priming): interaction of T-cell receptor with donor MHC antigen(s) presented by APC.
  – Signal 2 (Costimulation): interaction of CD28-CD86 or CD80 AND CD154-CD40
  – Signal 3 (Transduction): downstream effects of Ca\(^{+2}\) increase, activation calcineurin, and increased NFAT and NFκB…leading to increased release of IL-2
T-Cell Activation: A 3 step Process

Halloran P. N Engl J Med 2004; 351:26
Graft Rejection IV

• The Effector mechanism of graft rejection involves allograft-independent and – dependent mechanisms-- examples:
  – Organ ischemia leads to a non-specific inflammatory response-and can magnify the recognition of the graft as foreign
  – Cytotoxic T-lymphocytes (CTLs) recognize “foreign” cells and interact with them. Granzymes injected into target cells, triggering apoptosis.
A “history” of immunosuppressive agents

<table>
<thead>
<tr>
<th>Date</th>
<th>Compound</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1949</td>
<td><strong>Cortisol</strong></td>
<td>Hench et al. (1949)</td>
</tr>
<tr>
<td>1959</td>
<td>Cyclophosphamide</td>
<td>Stender et al. (1959)</td>
</tr>
<tr>
<td>1959</td>
<td>6-mercaptopurine</td>
<td>Schwartz and Dameshek (1959)</td>
</tr>
<tr>
<td>1961</td>
<td>Methotrexate</td>
<td>Friedman et al. (1961)</td>
</tr>
<tr>
<td>1975</td>
<td>Mizoribine</td>
<td>Sakaguchi et al. (1975)</td>
</tr>
<tr>
<td>1976</td>
<td>Cyclosporin A</td>
<td>Borel et al. (1976)</td>
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<tr>
<td>1977</td>
<td>Rapamycin</td>
<td>Martel et al. (1977)</td>
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<tr>
<td>1978</td>
<td>Leflunomide</td>
<td>Schleyerbach (1978)</td>
</tr>
<tr>
<td>1987</td>
<td><strong>Tacrolimus</strong></td>
<td>Kino et al. (1987)</td>
</tr>
<tr>
<td>1991</td>
<td><strong>Mycophenolate mofetil</strong></td>
<td>Allison et al. (1991)</td>
</tr>
</tbody>
</table>
Other Immunosuppressives (Biologics)

- Anti-thymocyte globulin: Thymoglobulin [Rabbit] and ATGAM [Equine]
- Anti-CD3 monoclonal (OKT3)
- Anti-CD25 monoclonal (Basiliximab)
- Anti-CD52 monoclonal (Alemtuzumab)
Sites of Action of Immunosuppressive Agents

Halloran P. N Engl J Med 2004; 351:26
Immunosuppression
Long Term Management

• Corticosteroids
• Tacrolimus (alternative: Cyclosporine A)
• Mycophenolate mofetil or Azathioprine
Lung transplantation means trading one disease for another disease...except in the case of cystic fibrosis where one trades only part of one disease for another disease.
Complications of Transplantation Generally are the Rule Rather than the Exception
The lessons learned in transplantation have been taught to us at great expense by our Patients.
(Selected) Surgical Complications

- Primary graft dysfunction
- Diffuse alveolar damage/ischemia-reperfusion injury
- Anastomotic complications: vascular or airway
- Phrenic/vocal cord paresis
- Gastroparesis
(Selected) Medical Complications I

- Acute Rejection
- Infection: viral, bacterial, fungal, protozoal
- Toxicity of immunosuppressives:
  - Nephrotoxicity, Hypertension
  - Hirsutism
  - Gingival hyperplasia
  - PRES (Posterior Reversible Encephalopathy Syndrome)
- Diabetes
Acute Cellular Rejection

- Determined with TBBx or OLB
- Peri-vascular lymphocytic infiltration
- Treatment: High-dose methylprednisolone succinate (Solu-Medrol), 10 mg/kg I.V. daily X 3 days
Acute Cellular Rejection

- Peri-vascular lymphocytic infiltrate
- Blood vessel
(Selected) Medical Complications II

• Hyperlipidemia
• Post-Transplant Lymphoproliferative Disease (PTLD)
  – B-cell driven lymphoma
  – EBV-related
• Obliterative Bronchiolitis
• Other malignancy
Obliterative Bronchiolitis

• “The thorn in the side of transplantation.”
• “…a riddle wrapped in a mystery inside an enigma”
• Is obliterative bronchiolitis truly chronic rejection?
  – Affects airways, not vessels
• Difficult to diagnosis on biopsy---BOS
• Does not respond well to steroids (or other therapy)
Freedom from Bronchiolitis Obliterans Syndrome For Pediatric Lung Recipients (Follow-ups: April 1994-June 2011)

ISHLT

Why are lungs so “delicate”? 

Benden C J Heart Lung Transpl 33: 1025-1033, 2014
What is the underlying “cause” of BOS

• Many factors have been associated with the development of BOS
  – Primary graft dysfunction
  – CMV mismatch and CMV pneumonitis
  – Respiratory viral illness
  – Gastroesophageal reflux and/or aspiration
  – Multiple episodes of acute rejection
  – Development of Donor HLA-specific Abs by recipient
Bronchiolitis Obliterans: Recent Experimental Evidence

- “Uncovering” of a usually hidden potential antigen, possibly secondary to organ harvesting or ischemia-reperfusion injury
  – Collagen Type V, κα1-Tubulin?
- Possible role of IL-17 in perpetuating airway damage?
Why are lungs so “delicate”? 

- A scaffolded and “collapsible” system with interdependent features
- Two blood supplies normally, reduced to one with transplantation
- Receives entire cardiac output
- Immunologically active organ; AMs are derived from monocytes (donor origin)
- Exposure to external environment
- Reliance on external muscles for function
- Denervated lungs post-transplant
GER and Lung Transplantation: Inconvenience or Complication?
8 y/o boy 5 days post H-L Txplt with abdominal pain and “mass”
Gastroparesis following lung transplantation

- 3-year follow up of 38 adult lung or heart-lung recipients.
- 16/38 (42%) experienced GI complaints (pain, dyspepsia, N/V, satiety)
- Evaluation led to 27 diagnoses in the 16 patients
- Gastroparesis confirmed with endoscopy (retained food after fasting) and scintigraphy in 9/16
- 44% of patients with gastroparesis developed OB vs 29% in those without gastroparesis

Berkowitz N. Chest 1995; 108:1602-07
The phrenic and vagus nerves course through the thorax.
What about GER?

Lung Transplantation Exacerbates Gastroesophageal Reflux Disease*

Lisa R. Young, MD; Denis Hadjiliadis, MD, MHS; R. Duane Davis, MD, FCCP; and Scott M. Palmer, MD, MHS, FCCP

Chest 2003; 124: 1689-1693
GER Increases following Lung Transplantation

- Duke study, 2003: 23 patients (mean age 51.5 yrs) studied with pH probe, esophageal manometry, and gastric emptying pre- and post-transplant (median 100 days)
- Emphysema (11), CF (4), and IPF (3) most common diagnoses.
- GER present pre-transplant in 8/23 (35%), but in 15/23 (65%) post-transplant. 80% of patients were asymptomatic!

Increased Esophageal Acid Contact Time Following Lung Transplant

Can Prevention of GER Improve Transplant Outcome?

Early Fundoplication Prevents Chronic Allograft Dysfunction in Patients With Gastroesophageal Reflux Disease

Edward Cantu III, MD, James Z. Appel III, MD, Matthew G. Hartwig, MD, Hiwot Woreta, BA, Cindy Green, PhD, Robert Messier, MD, PhD, Scott M. Palmer, MD, MPH, and R. Duane Davis, Jr, MD

Department of Surgery, Department of Medicine, Duke University Medical Center; Duke Clinical Research Institute, Durham, North Carolina

Early Fundoplication and Graft Dysfunction


• Stratified first by ICD-9 code for GER
  – No history of reflux n=180
  – History of reflux, no fundoplication n=125
  – History of reflux and early (<90 Days) fundoplication n=14
  – History of reflux and late fundoplication n=62

Fig 2. Freedom from BOS in ICD-9 segregated groups. ■ = no history of reflux; □ = reflux, no surgery; ▲ = reflux, early surgery; △ = reflux, late surgery. (BOS = bronchiolitis obliterans syndrome; ICD = international classification of diseases.)
Are CF patients at higher risk for GER post transplant?

Gastroesophageal reflux disease in lung transplant patients with cystic fibrosis

Bernardino M. Mendez, M.D.\textsuperscript{a}, Christopher S. Davis, M.D., M.P.H.\textsuperscript{a}, Cynthia Weber, M.D.\textsuperscript{a}, Raymond J. Joehl, M.D., F.A.C.S.\textsuperscript{a,b}, P. Marco Fischella, M.D., F.A.C.S.\textsuperscript{a,b,*}

\textsuperscript{a}Department of Surgery, Loyola University Chicago, Stritch School of Medicine, 2160 South First Avenue, Room 3226, Health Sciences Campus, Maywood, IL 60153, USA; \textsuperscript{b}Hines VA Hospital, Hines, IL, USA

Am J Surg 2012; 204: e21-26
CF and lung transplantation: Higher risk for GER?

- pH probe monitoring, esophageal manometry, gastric emptying scans, and Ba swallow studies in patients with CF (n=10) compared with patients without CF (n=78). Average time from transplant to GER studies was 30 months.
- Prevalence of GERD in CF patients was 90% (vs 54% in non-CF recipients). Proximal reflux in 70% of CF vs 29% of non-CF recipients.

Mendez BM Am J Surg 204: e21-6, 2012
What about other diseases and biomarkers as a risk for GER?

Pepsin concentrations are elevated in the bronchoalveolar lavage fluid of patients with idiopathic pulmonary fibrosis after lung transplantation

Christopher S. Davis, MD, MPH,^a^ Bernardino M. Mendez, MD,^a^ Diana V. Flint, MD,^a^ Karen Pelletiere, RN, BSN,^b^ Erin Lowery, MD, MS,^b^ Luis Ramirez, BS,^a^ Robert B. Love, MD, FACS, FRCS,^c^ Elizabeth J. Kovacs, PhD,^a^ and P. Marco Fischella, MD, FACS[^a,*]

^a^Department of Surgery, Loyola University Chicago Health Sciences Campus, Maywood, Illinois
^b^Division of Pulmonary and Critical Care Medicine, Department of Medicine, Loyola University Chicago Health Sciences Campus, Maywood, Illinois
^c^Department of Thoracic and Cardiovascular Surgery, Loyola University Chicago Health Sciences Campus, Maywood, Illinois

J Surg Res 2013; 185: E101-8
Pepsin in BAL fluid post-transplant

• Gastric pepsin measured in 252 BAL samples from 100 recipients.

• Correlation of pepsin with biopsy results, Ba swallows, esophageal functional studies, and gastric emptying scans was sought—but <50% of patients were studied…

• Underlying disease leading to transplant was another variable studied.

Pepsin levels in lung recipients

- In IPF patients, those with higher pepsin levels had increased frequency of acute rejection.
- Effect on chronic rejection /BOS not reported.

GER common post-transplant despite the underlying diagnosis…

• All 4 groups had high prevalence of GERD and delayed gastric emptying post-transplant
• Patients with CF and AAT had highest incidence of proximal (high) GER
• All 4 groups had high incidence of delayed gastric emptying.
• IPF patients had higher incidence of acute rejection
• However: BOS, mortality, and length of follow-up was not different among the 4 groups.

Is pepsin a satisfactory biomarker for GER post-transplant?

• Possibly:
  – Pepsin found in BAL samples post-transplant, with negative findings in BAL from healthy controls. (Ward C. Thorax 2005; 60:872)

• Are there alternative biomarkers?
  – Bile acids: (D’Ovidio F. Am J Transplant 2006; 6: 1930)
Mechanisms of graft injury associated with GER/Aspiration.

- Bile acids in BAL fluid may be more sensitive and specific markers for aspiration
- Could they also be a surrogate marker of inflammation leading to airway damage/BOS??

Neujahr DC Am J Transplantation. 2014; 14:841
384 BAL samples 51 recipients in first post-txplt year

40/51 Recipients had BAL samples positive and negative for bile acids.

29/40 had NO infection or rejection when BAL + for bile acids

Two BAL samples (bile acid + and -) from each patient (n=58) subjected to Metabolomic Profiling

Neujahr DC Am J Transplantation. 2014; 14:841
Metabolomic Profiling

- Liquid chromatography coupled to high-resolution mass spectrometry.
- Molecules identified using mass/charge (m/z) ratio and a specific software.
- False discovery rate (FDR) analysis used to control the expected proportion of incorrectly rejected null hypotheses (“false discoveries”). This is a commonly used technique in settings of large data sets…

Neujahr DC Am J Transplantation. 2014; 14:841
Metabolomic Profiling (2)

- 7608 individual metabolic peaks seen with LC-MS
- Using FDR, 2302 molecules that were significantly different. Most of these were small (m/z 80-500).
- Refinement to 472 was done by identifying top 5% of metabolites that contributed to 95% separation of bile acid + and – samples.

Neujahr DC Am J Transplantation. 2014; 14:841
Metabolomic Profiling (3)

- Many of the molecules identified as increased in Bile acid + BAL were associated with:
  - Microbial metabolism
  - Biomarkers of lung injury including
    - T-cell Granzyme B level
    - Chemoattractants CXCL9 and CXCL10

- This suggests that aspiration leads to upregulation of inflammatory mediators, potentially leading to graft damage or dysfunction

Neujahr DC Am J Transplantation. 2014; 14:841
Limitations/Questions

• Vast majority of studies involve adults
• Some studies show that GER is common post-transplant but is not linked to development of BOS. (see Blondeau Eur Resp J 31:707, 2008)
• Limited information/studies on medical management options for gastroparesis or GER (see Lidor AO Domperidone for delayed gastric emptying post transplant Prog. Transplantation 2014; 24: 27 or Mertens V Azithromycin reduces GER and aspiration post-transplant Dig. Dis. Sci. 2009; 54:972)
• Should all potential lung recipients be evaluated for GER prior to transplant?
• When is optimal time for surgical management of GER?
• Interruption of the metabolic consequences of aspiration: Is it feasible? Will it help prevent BOS?
Lung Transplantation: A “Team Effort”, with thanks

- Transplant Coordinators
- Cardiology and C.T. Surgery
- Pulmonology
- I.D.
- Psychology and Social Work
- Pathology, Radiology, Immunology, Clinical/Micro Labs
Acknowledgements:

(With key current physicians/staff in Red)

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• Diana Shellmer
• Csaba Galambos, Jennifer Picarsic
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Other References for GER/Aspiration and Lung Transplant

- Mohammed A. Gastroesophageal Reflux Disease and Graft Failure Following Lung Transplantation Transplant Rev 2010; 24: 99-103
- Garrity ER. Gastroesophageal reflux disease and bronchiolitis obliterans syndrome: Where are we today? J Heart Lung Transpl 2013; 32: 577-580