Lung Transplantation
State of the Art Review including Patient Selection and Strategies for Optimizing Outcomes

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Disclosure

• Dr. Roe has none to report
• Dr. Wozniak has none to report
Objectives

• Define disease processes appropriately treated with lung transplant evaluation.
• Discuss the pre-operative and post-operative care of a lung transplant patient.
• Discuss acute and chronic rejection and treatments available.
• Review new advances in lung transplant including EVLP and ECMO.
Questions

1. True or False. It is mandatory for all patients to attend on a regular basis pulmonary rehab locally or in Indianapolis at Methodist Hospital in order to be considered for lung transplant unless stipulated by transplant team?

2. Which of the following agents are typically used for immunosuppression following lung transplant?
   - Tacrolimus (Prograf)
   - Prednisone
   - Mycophenilate (Cellcept)
   - All of the above

3. True or False  Acute rejection is only mediated by T-cell dysfunction.
All I ever needed to know about transplant I learned in...

- The Three R’s of Transplant
- The right lungs
  - Donor Selection
- The right time
  - Survival
  - Lung Allocation Score
  - PULMONARY REHAB
- The right reason
  - Disease
IU Health Methodist Thoracic Transplant

12th largest lung transplant center in United States

Lung transplants in 2010
39

Lung Transplants in 2011
41

Lung Transplants 2012
50

Lung Transplant 2013
49

Lung Transplants 2014
19
2013 Volume

• Diagnosis
  – IPF/UIP: 15
  – Emphysema/COPD: 24
  – CF: 4
  – Alpha-1: 3
  – Scleroderma – Pulmonary HTN: 1
  – Scleroderma – Restrictive: 2
2013 Volume

• Lung Allocation Score
  – Mean: 44.26, Median: 36.22
    • Mean: 2012: 44.30, 2011: 46.31, 2010: 43.43
  – Range: 30.89-94.58

• ABO
  – A: 14
  – B: 2
  – O: 30
  – AB: 3
Outcomes

• SRTR data
  – 1yr IUH 92.9% US 86.11%
  – 3 yr IUH 77.03% US 68.18%

• LOS 2013 25 days
• 30 days readmission rate 15%
• 1 month ACR rate <5%
Who are the players in the sandbox?

- **UNOS**
  - United Network for Organ Sharing
  - private, non-profit organization that operates the Organ Procurement and Transplantation Network (OPTN) under a contract with the US Department of Health and Human Services.
  - maintains data pertaining to the waiting list, organ matching, and transplants.

- **Organ Procurement Organizations**
  - OPOs are private, non-profit organizations that recover organs within their geographical territory and allocate them based on UNOS guidelines.
Players

• SRTR
  – Scientific of Registry Transplant Recipients
  – [www.ustransplants.org](http://www.ustransplants.org)
  – Large database of all centers
  – Can compare and contrast centers
  – Tracks outcomes used by CMS to help with accreditation

• Transplant Centers
Number of Transplants

- **Bilateral/Double Lung**
- **Single Lung**

Year-wise Data:
- 1985: 5, 6
- 1986: 35, 84
- 1987: 197, 427
- 1988: 713, 923
- 1989: 1111, 1235
- 1990: 1306, 1317
- 1991: 1445, 1486
- 1992: 1627, 1712
- 1993: 1834, 1901
- 1994: 1934, 2129
- 1995: 2474, 2692
- 2000: 2814, 2867
- 2005: 3154
- 2006: 3395
- 2010: 3640
- 2011: 3640

**Source:**
SCHOOL OF MEDICINE  
INDIANA UNIVERSITY
Median survival (years): A1ATD=6.3; CF=7.8; COPD=5.4; ILD=4.5; IPAH=5.2; Sarcoidosis=5.4

All pair-wise comparisons with CF were significant at p < 0.0001
A1ATD vs. COPD: p < 0.0001
A1ATD vs. ILD: p < 0.0001
COPD vs. ILD: p < 0.001
p < 0.0001
Donor Selection

• One area of “art” of medicine

• Multiple factors are considered

• Relative and absolute contraindications

• High Risk Donors
Donor Physiology

- Disruption in homeostatic regulation
  - Temperature dysregulation
  - Autonomic dysfunction

- Disturbances in endocrine function
  - Thyroid and Diabetes Insipidus

- Intense inflammatory reaction

- Aspiration / nosocomial pneumonia
Basic donor criteria

- Age < 65 yr
- ABO blood group compatibility
- Clear chest radiograph
- $P_{aO_2} \geq 300$ mm Hg on fractional inspired oxygen of 1.0 and positive end-expiratory pressure $5$ cm $H_2O$
- <40- pack-year smoking history
Donor Management

• Manipulation of vent
  – Lung recruitment
  – ARDSnet strategy

• Hemodynamic monitoring and management

• Increased presence in donor management with IOPO
  – On call and discuss all Indiana donors
COPD

- Chronic Obstructive Pulmonary Disease
  - Emphysema, Chronic Bronchitis, Asthma
  - 20 pts. with COPD are non-smokers (alpha-1)
  - Occupational exposures
  - FEV1/FVC < .70

- Refer to Tx
  - FEV1 < 25%
  - PCO2 > 55
  - Oxygen needs
  - Pulmonary hypertension
Interstitial Lung Disease

- **IPF/UIP**
  - Usual Interstitial Pneumonia
  - Expansion of the interstitial compartment (that portion of the lung parenchyma sandwiched between the epithelial and endothelial basement membranes)

- Refer to Transplant
  - At diagnosis
  - FVC < 70%
  - DLCO <50%
Cystic Fibrosis

- Most common fatal autosomal recessive disease among Caucasian populations
- Persistent pulmonary infection, pancreatic insufficiency, and elevated sweat chloride levels
- Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) protein, a complex chloride channel
- Lung, Pancreas, Sinus
- Lung Tx
  - FEV1 < 30%
  - Hemoptysis
  - Malnutrition
  - PCO2 > 50 PO2 < 55
Barriers in CF Lung Txp

• Compliance
  – Younger recipients

• MDR Pseudomonas
  – Close collaboration with peds pulm and CF center
  – Aggressive sinus protocol decontamination with chlorpactin and surgical changes

• Weight
  – Increase pre-op feeding tubes/Nissen
Pulmonary Hypertension

• Mean pulmonary artery pressure greater than 25 mmHg at rest
Transplant Refer

• NYHA III-IV
• Cardiac Index < 2
• RAP > 15
• mPAP > 55mmHg
Recipient Selection

- Initial screen with Pre-Tx Coordinator
- Initial consult with transplant pulmonologist
- Transplant Work-up
  - Blood work, PFT’s, six minute walk, Info session
  - CT scans, GB US, Cancer screening, Dentist
  - R and L heart cath, V/Q scan, MUGA
  - pH probe and esophageal manometry
  - Social work, Dietary, Financial, Transplant Surgeon
  - Lung measurements
- Transplant Committee
Recipients

1. Maintain goal weight
2. Enroll in pulmonary rehab
3. Maintain pulmonary rehab
4. Social Support Structure
Rehab

- "bridging to transplant“
  - improving strength, endurance and mobility
  - intensive motivation and knowledge transfer can prepare patients as good candidates

- rehabilitation after LTx
  - regaining physical abilities and health related quality of life using the increased breathing capacities

- Introduction of Strength Training
  - Resistance training in hospital
Contraindications

- Uncontrolled or untreatable pulmonary or extrapulmonary infection
- Malignancy in the last two years
- Significant dysfunction of other vital organs
- Significant coronary artery disease or heart failure
- Significant chest wall/spinal deformity
- Active tobacco smoking
- Drug or alcohol dependency
- Unresolved psychosocial problems or noncompliance with medical therapy
- HIV infection
- Ongoing hepatitis B or C viral infection
- Absence of a consistent or reliable social support system
Lung Allocation Score

Forced Vital Capacity
- Pulmonary Artery Pressure
- O2 requirements (L/min) at rest
- Age
- Body Mass Index
- Diabetes (IDDM)

- NYHA Classification
- 6’ walk test
- Ventilator use
- PCWP
- Creatinine
- Diagnosis
LAS

- Sicker patients transplanted first
- Less death on list awaiting transplant
- Increase in transplants
- More IPF
Intraoperative Interventions

• Use of ECMO
• Lower FIO2
• Surgical approach tailored
• Chlorpactin
Goals of Immunosuppression

• Allow transplanted organ to function normally for as long as possible
  – Prevent rejection

• Achieve a balance between unwanted adverse effects and efficacy

• Avoid over-immunosuppressing the patient to prevent unwanted infectious and oncologic complications
Immunosuppressive Regimens: What will it be?

**Induction Therapy**
- Polyclonal anti-thymocyte globulin (Thymoglobulin)
  - OR
  - Basiliximab (Simulect)
  - OR
  - Alemtuzumab (Campath)

**Maintenance Therapy**
- Calcineurin inhibitor
  - Tacrolimus (Prograf)
  - Cyclosporin
  - OR
  - mTOR inhibitor
    - Sirolimus (Rapamune)
  - OR
  - Antiproliferative agent
    - Mycophenolate (Cellcept)
    - Azathioprine (Imuran)
  - OR
  - Glucocorticoid
IU Health: Freedom From Grade 2 Rejection at 6 months
Medications

- Prograf
  - Tacrolimus
  - Calcineurin inhibitor
- Prednisone
- Cellcept
  - Mycophenalate mofetil
  - Cell cycle inhibitor
- Rapamune
  - Sirolimus
  - mTOR inhibitor
- Imuran
  - Azathioprine
- Bactrim
  - PCP
- Valcyte
  - CMV
- Vfend (Voriconazole)
  - Aspergillus
- Nystatin
  - Thrush
Sites of Drug Action

Antigen-presenting cell

- CTLA-4-Ig
- CD80, 86
- CD28
- CD40
- CD154
- CD25
- Cell membrane
- Interleukin-2
- Interleukin-15
- Sirolimus, Everolimus
- JAK3 inhibitor
- MPA
- FK778
- Anti-CD52 mAb
- CD52 (depletion)
- FTY720
- Cyclosporine, Tacrolimus
- Azathioprine
- mTOR
- Nucleotide synthesis
- PI-3K
- JAK3
- Calcineurin
- MAP kinases
- IKK
- NFAT
- AP-1
- NF-κB
- S
- G1
- Cell cycle
- mRNA
- T cell
Acute Cellular Rejection

• Dx by spirometry and TBBX
  – Lymphocytes perivascular and bronchiolitis
  – Grade A1-A4, B

• Treat with solumedrol first line
  – Refractory with Campath

• Can be antibody mediated—TBBX and serum
  – Monitor DSA (Donor Specific Antibody)
  – Treat with IVIG, plasmapheresis, Rituximab, Velcade
Chronic Rejection

• BOS vs RAS
  – Slow vs rapid
  – Macrolide therapy
  – Can treat with steroids and campath
  – Have used photopheresis in selected cases
  – Look to retransplant
Advances in Txp

• ECMO
  – Bridge to txp
  – Transition during lung txp
  – Post txp

• Ex-Vivo

• Transmedics
1. Severe hypoxemia (P:F <80) despite 6 hours of ARDS appropriate ventilation
2. Refractory acidemia (pH <7.15) from ARDS
3. Excessively high inspiratory plateau pressures caused by ARDS
CO2 Removal
Adjust Sweep gas flow (The SWEEP)

Oxygenation
Adjust FdO2
Adjust Blood Flow
Cannulas

• Dual lumen catheters
  – Avalon (VV ECMO)
    • Placed in the IJ: drains from the distal right atrium (to the IVC) and returns just past the tricuspid valve
      – The blood mixes with native venous return on the right side of the heart.
    • Position is KEY
  • Single lumen catheters
    – VA ECMO
      • Fem vein and artery, IJ, R. Common Carotid
    – VV ECMO
      • IJ and Femoral Vein
Avalon bi-caval dual lumen catheter
After Cannulation

• Anticoagulation
  – Use of unfractionated heparin (Goal PTT 40-60 secs)

• Ventilator management—REST
  – No strict guidelines, varies center to center
  – Volume-control with lung protective ventilation settings with minimal FiO2
  – CESAR trial
    • Pressure control ventilation ($P_{\text{peak}}$ 20-25, PEEP 10, Rate 10, FiO2 < 30%)
Patient Case

- 67 yr. old white male fireman and ballroom dancer
- ILD-IPF from RA. On oxygen. Former smoker
- Hx GERD and Migrane HA
- On MTX and prednisone
- Admitted with worsening hypoxia and abd. pain
- Diverticulitis. Right Heart Cath no pul HTN
Patient 2

- Mild distress O2 sat 90% 6-8L oximizer
- Rales throughout chest
- Mild abd. pain
- CXR and CT to view
- Single right lung txp on 10/24/13
- Developed PGD III, PO2 50 on 50%
- FOB with mild secretions
- Worsening CXR, PIP, Plat, increased FIO2
Prevention of PGD

• Clinical risk factors for PGD after lung txp
  – Am J Repsir Crit Care 2013
    • LTOG data 2002-2010 1255 pts
    • 211 pts with PGD III (16.8%)

Independent Risk Factors

- Hx of donor smoking
- bypass
- single lung txp
- obesity
- sarcoid or pul HTN Dx
- Pulm HTN
- FIO2 during allograft reperfusion
ECMO - Indications

• Acute severe cardiac or pulmonary failure that is potentially reversible and unresponsive to conventional management

• Earlier the better
  – 5-7 days
ECLS (ECMO)

• Initial Consideration:
  • P/F ratio <100
  • A-aDO2 >600mmHg
  • FIO2 at 1.0 and PIP <35 cm H2O on less than 7 days support with reversible lung injury despite optimal treatment
  • Age 18-70
  • Refractory hypercapnia pH<7.2
ECMO

- Hypercapnic Resp. Failure
- Hypoxic Resp. Failure
- Cardiogenic shock
- Cardiac arrest
- Primary Graft Dysfunction (PGD)
- Bridge to transplant
ECMO Program Structure

- Surgical Director--Tom Wozniak MD
- Medical Director—David Roe MD
- ECMO Program Coordinator—Tracie Layne MSN, RN, CCRN
- ECMO Clinicians
  - 18 total with 9 CVCC Nurses and 9 RT
  - Home Training Program
    - Didactic lessons, wet labs (Perfusion, SIM Center), circuit time 50 hours
- Current Model of Staffing
  - E1, E2, E3--One circuit one clinician—changed
- ELSO Certified Adult ECMO Center
MH ECMO Patient Volume and Survival: 2011 to 2014 (as of 04/07/2014)

- 91 patients Supported with ECMO
- V-V pts = 59
  - Survival off ECMO = 52/60 (87%)
  - Survival to discharge = 43/57** (75%)
- V-A pts = 28
  - Survival off ECMO = 16/29 (55%)
  - Survival to discharge = 8/29 (28%)
- eCPR pts = 4
  - Survival off ECMO = 3/5 (60%)
  - Survival to discharge = 2/5 (40%)
2014 Data YTD (as of 04/07/2014)

• 26 patients supported with ECMO

• V-V pts = 18
  – Survival = 17/18 (94%)
  – Survival to discharge = 12/15 (80%)

• V-A: pts = 8
  – Survival = 3/8 (38%)
  – Survival to discharge = 1/8 (13%)
Blue = Veno-venous ECMO Run
Red = Veno-arterial ECMO Run

YTD = 321 ECMO Patient Days (as of 01-03-2014)

Calendar Days with Multiple patients on ECMO = 69 days
Blue = Veno-venous ECMO Run
Red = Veno-arterial ECMO Run

YTD = 189 ECMO Patient Days (as of 04-07-2014)
Calendar Days with ECMO patients = 89
Calendar Days with no ECMO patients = 8
Calendar Days with Multiple patients on ECMO = 59 days
Breakdown of Diagnoses – 2014 YTD (as of 04-07-2014)

- Bridge to Transplant – 1
  - Cystic Fibrosis – 1
- Transition during transplant – 11
- ARDS – 7
  - Influenza A – 7
- Cardiogenic Shock – 8
  - Post-cardiotomy – 7
    - 2 following VSD repair
    - 3 transported from outlying hospital on ECMO
    - 2 post heart transplant
- Cardiac Arrest – 2
Portable ECMO