Lung Transplantation: Perioperative Care

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No disclosures
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New Lung Allocation System: May 2005

LTXP is not a therapy of last resort
New Lung Allocation System

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LTXP is not a therapy of last resort
Source of UW lung donors
Donor Optimization

General:
- Ventilator Management
- Pulmonary Toilet
- Pain control
- Immunosuppression

Complications
- Coagulopathy
- Atrial tachyarrhythmias
- Infection vs Rejection
- Hyperammonemia

- Inotropes and Pressors
- Fluids
- Antibiotics
- GI complications
- Pleural space issues
- Rejection
Primary Graft Dysfunction
grading
support
Severely ill potential recipients
Ventilator Management

- Ppk >40 cm H2O
- Ppk <35 cm H2O
- Pplat <25 cm H2O

Fernandez-Perez et al Anesthesiology 105(2006) 14-18
Van der Werf et al Chest 111 (1997) 1278-1284
Slinger PD Anesthesiology 105 (2006) 2-8
Turnage, Lunn Chest 103 (1993) 1646-50
Ventilator Management

Pressure control  (Ppl < 25mmHg, Ppk <35mmHg)

80%  extubated within 24 hours

Wean FIO$_2$ for SaO$_2$ >90% or PaO2 > 70

Reasonably approximate effective Vt in the donor

PEEP: at least 5cm H$_2$O (not for COPD   SLT)
Acute Native Lung Hyperinflation
Acute Native Lung Hyperinflation

**Predictors:** PAP >32, FEV$_1$ < 427ml, RV>4450 ml

**Effects:** paradoxical ↑ PBF / ↑ V/Q mismatch, hemodynamic/repiratory failure 4%

J Heart Lung Transplant 1998;17(2):192-201 (Manchester)
Acad Radiol 1998;5(10):688-93
Acute Native Lung Hyperinflation

**Long Term Effects:** unclear (FEV$_1$, FVC, RV)

**Therapy:** Differential lung ventilation*
LVRS / bullectomy
pneumonectomy

*J Cardiothorac Vasc Anesth 2002.16(4) 459-62 (Harefield)
Pulmonary Toilet

Ineffective airway clearance and breathing pattern:

denervation: cough and mucocilliary clearance
infection
pain
altered chest wall musculoskeletal function
Pulmonary Toilet

Early Extubation \((esp \ CF)\)
Bronchoscopy prior to extubation
Positioning
  - SLT : operative side up
  - DLT : 90° side to side q 1-2 hours
Physiotherapy
  - vibropercussion and postural drainage q2-4 hrs
Suctioning : sterile technique
Incentive Spirometry
Fluids

• Lungs have increased capillary permeability
• Disrupted lymphatic drainage

*Keep as hypovolemic as possible*

- MAP 50-60mmHg
- UOP brisk
- SvO2 >65%
- Adequate mentation

PHTN patients more volume dependent early

Avoid bolus fluid administration

Use of IL-2ra / CNI-hold
CHOICE OF REPLACEMENT FLUID:
Distribution of Resuscitation Solutes into the Interstitium

• Sodium ............... 8 minutes
• Albumin ............... 12 minutes
• Hetastarch ............ 20 minutes
CHOICE OF REPLACEMENT FLUID:
Exposure of Albumin Binding Sites in the Interstitium
Lung Perfusion Scan

Radiolabeled albumin
Fluids

- PRBC
- FFP
- Platelets
- Crystalloid
  
  X Colloid
Avoid Colloid in the Donor and Recipient...

- Inverse relationship between volume of intraoperative colloid and acute graft function

  - Lower $P_aO_2 / FIO_2$ ratios at 12 hrs
  - Prolonged time to extubation

- McIlroy et al, Br J Anesth 2009, 102(4) 506-514
Physiology of Alveolar Fluid Clearance

Alveolar epithelial cells

\[ \text{Na}^+ / \text{K}^- \text{ATPase} \]

\[ \text{Na}^+ \]

\[ \text{K}^+ \]

\[ \text{Na}^+ \]

\[ \text{Na}^+ \]

\[ \text{Na}^+ \]

\[ \text{Na}^+ \]
Sodium Pump Inactivation

Alveolar epithelial cells
Sodium Pump Inactivation

Na$^+$ Pump Inactivation

Rx:
Preservation at 10°C
Extracellular-type solutions w/ colloid

Alveolar epithelial cells
**Sodium Pump Inactivation**

**Rx:**
- dopamine (D1)
- dobutamine
- terbutaline
- isoproterenol

**Rx:**
- dopamine (D2)
- steroids
- growth factors
- β agonists

**mRNA / protein translation**
(MAPK / Ras-Raf-MEK)

**Alveolar epithelial cells**
Inotropes and Pressors

• Milrinone vs Dobutamine (myocardial suppression)

• Vasopressin (impaired vasomotor tone for 24-36 hrs, no receptors in pulmonary bed)

• Dopamine (renal dose only)
Antibiotics

Routine: cefuroxime x 48hrs

Extend and alter coverage based on donor cultures and related findings

Cystic Fibrosis: coverage based on preop cultures and sensitivities as well

Chest 1999; 115:1312-1315
Immunosuppression

Induction therapy (IL-2ra)

- Steroids
- Calcineurin inhibitor
- Nucleotide synthesis inhibitor
Drugs that alter Cyclosporin, Tacrolimus and Sirolimus levels

<table>
<thead>
<tr>
<th>Increase</th>
<th>Decrease</th>
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<tbody>
<tr>
<td>Fluconazole</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Phenobarbitol</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Nafcillin</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Amiodorone</td>
<td>St. John’s wort</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td></td>
</tr>
<tr>
<td>Allopurinol</td>
<td></td>
</tr>
<tr>
<td>Nefazadone</td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td></td>
</tr>
<tr>
<td>Nicardipine</td>
<td></td>
</tr>
<tr>
<td>Grapefruit juice</td>
<td></td>
</tr>
</tbody>
</table>
Epidural

- faster extubation
- diminished ileus
- decreased ICU days

Timing:  
- preop (low risk CPB)
- post op (prior to extubation normal coags)
Coagulopathy

**Contributing factors:**
CPB / heparin
Preoperative warfarin
complicated pleural space (*topical hemostasis: argon beam, sealants*)

**Therapy:**
Platelets (<100)
Cryoppt (fibrinogen <200)
FFP (INR >1.6)
Aprotinin

..............................>200cc/hr (several hrs)......re-explore
Aprotinin

• Reduces transfusion rates in LTXP requiring CPB

• Reduces transfusion rates in LTXP NOT requiring CPB

• Reduces severity of reperfusion injury (18 vs 8%, in perfusate)

• Not associated with CVA or renal failure in LTXP

Interact Cardio Vasc Surg 2009;8:45-48
Atrial Tachyarrhythmias

34 – 47% incidence
Most common POD #4
RFs: age, IPF, CAD, LAE, pressors

ICU and overall LOS
hospital mortality

Medical Rx (89%) (beta-blockade, amiodarone)
Cardioversion (11%)
Anticoagulation (40% bleeding complications)

2004 J Intens Care Med ; 19(2):83-104
Pleural Space

*Mostly Avoidable:*
Size matching
Chest tube removal: <150cc/24hrs

*Issues:*
Retained effusions
Empyema (3.6%) (28% mortality)
## GI Complications

### Non-Surgical

<table>
<thead>
<tr>
<th>Esophagitis</th>
<th>Peptic ulcers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatitis</td>
<td>Gastritis</td>
</tr>
<tr>
<td>Gastric atony</td>
<td>GI bleeding</td>
</tr>
<tr>
<td>GERD</td>
<td>CMV hepatitis</td>
</tr>
<tr>
<td>CMV colitis</td>
<td>Diverticulitis</td>
</tr>
<tr>
<td>Diverticulitis</td>
<td>Cholecystitis</td>
</tr>
<tr>
<td>C. Difficile colitis</td>
<td></td>
</tr>
</tbody>
</table>

*Anesthesiology 1992;77;A858*
GI Complications

Surgical (4-17%)

- Bowel perforation
- Appendicitis
- Cholecystitis
- Colitis
- Pneumatosis Intestinalis
- PTLD (intussusception, perforation)

Br J Surg 2001;88:433-438
GI Complications

Surgical (4-17%)
- Bowel perforation
- Appendicitis
- Cholecystitis
- Colitis
- Pneumatosis Intestinalis
- PTLD (intussusception, perforation)

*Aggressive investigation and Early intervention*

Br J Surg 2001;88:433-438
Hyperammononemia

Occurs in first 3-4 weeks
4% incidence
67% mortality

Most are symptomatic:
encephalopathy, seizures, lethargy,
agitation, tremors, coma

Ann Intern Med 2000;132:283-7
Ann Intern Med 1997;127:446-9
Gastroenterology 1997;112:236-240
Arch Neurol 1999;56:481-4
Hyperammonemia

Risk factors:
- GI complications, TPN, PHTN

Treatment:
- limit nitrogen intake, calories to catabolism, lactulose, neomycin, dialysis, supplements for congenital urea cycle defects
Infection vs Rejection

- bronchoscopy
- purulence
- no purulence
- PGD
- Antibody -mediated Rejection
- Acute Cellular Rejection
- Other…
DAYS POST LUNG TRANSPLANT

0

14

…TIMING OF PRESENTATION……

PGD

Antibody –mediated rejection

INFECTION

ACR
Antibody Mediated Rejection

- **Diagnosis:**
  - Timing: “Hyperacute” vs Delayed
  - Hypoxemic respiratory failure
  - Donor-specific HLA Abs
  - Endothelial C4d deposition

- **Treatment**
  - Methylprednisolone
  - Plasmapheresis
  - IVIG
  - Anti-CD-20
Primary Graft Dysfunction
Primary Graft Dysfunction

10-20% of recipients
Hypoxia
Impaired compliance / ventilation
Diffuse infiltrates / Alveolar edema
Pulmonary hypertension
Right ventricular strain
Impaired global perfusion
## Primary Graft Dysfunction

<table>
<thead>
<tr>
<th>Grade</th>
<th>P:F ratio</th>
<th>Infiltrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&gt;300</td>
<td>no</td>
</tr>
<tr>
<td>1</td>
<td>&gt;300</td>
<td>yes</td>
</tr>
<tr>
<td>2</td>
<td>200-300</td>
<td>yes</td>
</tr>
<tr>
<td>3</td>
<td>&lt;200</td>
<td>yes</td>
</tr>
</tbody>
</table>
Primary Graft Dysfunction

**TREATMENT IS SUPPORTIVE:**

- Diuresis
- Maximal ventilatory support
- Positioning (lateral, prone)
- Sedation / paralysis
- Inhaled beta agonists
- Low dose dobutamine / dopamine
- Nitric Oxide
- ECMO
Nitric Oxide

*Prophylactic use does not prevent reperfusion injury*

Decrease mean PAP by 10-15%
Improves VQ matching
Marked improvement in P:F ratios within 1 hour

**Hemodynamic effects within 15 minutes**
- CVP
- PAP
- CO
- SBP

*Optimal response may take up to two hours*

Transplantation 2001;72 (1): 112-115
JTCVS 1996; 111:193
Nitric Oxide

*Initial dose 20-40ppm*  
*Methemoglobinemia at 40-80ppm*

rapid wean to 5ppm (6-12 hours)  
slower wean from 5 to 0 ppm (24-48 hours)

Assess: oxygenation, CO > PAP

*....as infiltrates clear and oxygenation improves*
ECMO support after LTXP

**Timing:**

- Initiate Early (within 24 hrs)
- Wean within 7 days

**Cannulation:**

- Central
- Dual Lumen VV
ECMO Post-TXP

- Concerns.....
  - Bleeding risk with heparin

Kahn et al J Cardiothorac Surg 2007 (2)28
Kilic et al Interact CardioVasc Thorac Surg 2009(8)442-443
Harry et al Ped surg Int 1990 (5) 302-306
ECMO Post-TXP

• Concerns…..
  – Bleeding risk with heparin

**Table Two: Blood loss and required heparin dose between patient circuit groups**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>8 hours</th>
<th>24 hours</th>
<th>48 hours</th>
<th>Time on ECLS</th>
<th>p between times</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total blood loss mL/kg</td>
<td>ECMO I</td>
<td>35 (32)</td>
<td>81 (67)</td>
<td>107 (83)</td>
<td></td>
<td>0.0313</td>
</tr>
<tr>
<td></td>
<td>ECMO II</td>
<td>26 (18)</td>
<td>35 (12)</td>
<td>40 (29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heparin drip IU/kg/hr</td>
<td>ECMO I</td>
<td>4.2 (3.5)</td>
<td>6.8 (7.6)</td>
<td>7.9 (7.5)</td>
<td></td>
<td>0.0140</td>
</tr>
<tr>
<td></td>
<td>ECMO II</td>
<td>1.3 (0)</td>
<td>4.7 (0)</td>
<td>6.7 (4.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Mean (median); ANOVA Test p-values; p is the chance of a Type I statistical error; ANOVA interactions between circuit types and time on ECLS were not significant. *Statistical power is low at n = 11 patients per group.
ECMO Support Post-LTXP

**VV vs VA**

**Outcomes vs non-ECMO**

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**Fig 1.** Kaplan-Meier 5-year survival after extracorporeal membrane oxygenation support for lung transplantation, both venoarterial (VA [solid line]) and venovenous (VV [dashed line]).

**Fig 2.** Kaplan-Meier 5-year survival in patients weaned off extracorporeal membrane oxygenation (Ecmo-weaned [dashed line]) compared with all lung transplant patients (solid line).
**ECMO post-TXP:**

<table>
<thead>
<tr>
<th></th>
<th>ECMO 1 year</th>
<th>ECMO 2 year</th>
<th>Control 1 year</th>
<th>Control 2 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>2.41</td>
<td>2.61</td>
<td>2.73</td>
<td>2.79</td>
</tr>
<tr>
<td>FEV₁</td>
<td>1.89</td>
<td>2.01</td>
<td>2.05</td>
<td>2.03</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>72.1</td>
<td>73.2</td>
<td>70</td>
<td>69.1</td>
</tr>
</tbody>
</table>

*Ann Thor Surg 2009; 87: 854-860*
Advanced Strategies Protocols

Pulmonary Graft Failure

Conventional therapy
- Specialized ventilation
- Dehydration
- Inhaled nitric oxide
- Lateral positioning (if appropriate)

Responders

Nonresponders: 32

Unilateral pathology: 22

- 7
  - No further treatment and died: 9
  - Differential ventilation: 15
    - Responders: 13
    - Nonresponders: 2

Bilateral pathology: 10

- 2
  - ECMO: 10
Transplantation of the Severely Ill

• Mechanically ventilated

• Pre-Transplant ECMO support
Mechanical Ventilation

Ventilator dependence initially thought to be a strong relative contraindication to transplant:

- Airway microbial colonization
- Long-term immobility
- Nosocomial sinusitis
- DVT
- Swallowing dysfunction
- Depression
ISHLRT Registry shows increase risk of death with mechanical ventilation

ISHLRT Registry \(^1\)
- 1-year mortality risk=1.57 (1.29-1.97)*
- 5-year mortality risk=1.32 (1.04-1.68)*

\(^{*}p<0.0001\)

\(^{1}\) Christie 2009
Survival is Worse after Mechanical Ventilation in the US

- UNOS Registry study 1987-2008
- Total n=15,883; 586 mechanically ventilated
- Matched by propensity analysis to 566 controls

<table>
<thead>
<tr>
<th>Time since transplant (months)</th>
<th>Unsupported (% alive)</th>
<th>Ventilated (% alive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>93</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>85</td>
<td>67</td>
</tr>
<tr>
<td>12</td>
<td>79</td>
<td>62</td>
</tr>
<tr>
<td>24</td>
<td>70</td>
<td>57</td>
</tr>
</tbody>
</table>

ISHLT: 1-year mortality risk=1.57

Mason 2010
Mechanical Ventilation and Careful Selection / Preparation

• Some small (n=4-13) single centered studies show no difference in:¹-³
  – Post-op intubation time
  – Survival

• Incidence 2.3 → 7.5% post LAS

• Cystic fibrosis most common (best outcomes)

¹Low 1992; ²Flume 1994; ³Vermeijden
Pre-Lung TXP ECMO

- ECMO first bridged to transplant in 1975
- Case reports suggested poor outcomes
- ECMO contraindicated at most centers
- LAS does not directly prioritize ECMO patients
- Use Pre-TXP is increasing
  - Pre-LAS=0.5%
  - Post-LAS=1%

¹UNOS Registry Data
Survival is worse with Pre-LTXP ECMO

- Single institution reports positive……but…
- UNOS Registry study 1987-2008
- Total n=15,883; 51 on ECMO
- Matched by propensity analysis to 49 controls

<table>
<thead>
<tr>
<th>Time since transplant (months)</th>
<th>Unsupported (% alive)</th>
<th>ECMO (% alive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>93</td>
<td>72</td>
</tr>
<tr>
<td>6</td>
<td>85</td>
<td>53</td>
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<td>12</td>
<td>79</td>
<td>50</td>
</tr>
<tr>
<td>24</td>
<td>70</td>
<td>45</td>
</tr>
</tbody>
</table>
Causes of Death

• ECMO was reported to be the **strongest** predictor of 1-year mortality\(^1\)
  – OR = 6.9 (2.4-20.1)

• Cause of Death\(^2\)
  – PGD 21%
  – Infection 20%
  – Cardiovascular: 13%
  – Multi-organ failure 11%

JTCVS 2009. 139;3: 765-773
UNOS database
Advancements in ECMO

• Major advancements in ECMO:
  – Polymethylpentene oxygenators (PMP)
  – Heparin coated circuit
  – Centrifugal pump
  – Dual lumen cannulas

• Pumpless ECMO:
  – Novalung
Pre-Transplant ECMO Support

- We can transplant off of ECMO (*sickest of the sick*)
- Post-transplant outcomes have been poor
- Impact on allocation is indirect / inappropriate
- Organ availability is limited
- Use of pre-transplant ECMO should be used cautiously

- *Prospective, multicenter trial is required*
- *UNOS is actively collecting data*
Take Home Points

• WE ARE TRANSPLANTING SICKER RECIPIENTS

• AGGRESSIVE DONOR MANAGEMENT IS MANDATORY
Take Home Points

- Volume Restriction (avoid colloid) (vasopressin)
- Actively promote alveolar fluid clearance
- Early extubation
- Aggressive / directed pulmonary toilet (bronchoscopcopy)
- Protocol driven care (antibiotics, immunosuppression)
- iNO for Rx of PGD
- Post-TXP ECMO valuable (early)
- Vigilant care of ventilated candidates
- Pre-TXP ECMO use not yet validated