Heart Transplantation Update 2012

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HF Population by NYHA Class

Class I: 1.68 M (35%)
Class II: 1.68 M (35%)
Class III: 1.20 M (25%)
Class IV: 240 K (5%)
NOTE: This figure includes only the heart transplants that are reported to the ISHLT Transplant Registry. As such, the presented data may not mirror the changes in the number of heart transplants performed worldwide.
AVERAGE CENTER VOLUME
Heart Transplants: January 2006 – June 2011

Number of centers

Average number of heart transplants per year

- 1-4
- 5-9
- 10-19
- 20-29
- 30-39
- 40-49
- 50-74
- 75+

Number of centers
Percentage of transplants

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2012
ADULT HEART TRANSPLANTS
Diagnosis by Location
(Transplants: January 2006 – June 2011)
ADULT HEART TRANSPLANTS

% of Patients Bridged with Mechanical Circulatory Support* by Year and Device Type

<20%, 2000

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* LVAD, RVAD, TAH
ADULT HEART TRANSPLANTS

Number of Combined Organ Transplants Reported By Year and Type of Transplant

[Graph showing the number of combined organ transplants reported by year, with different categories such as Other Combined Organ Transplants, Heart-Kidney-Pancreas, Heart-Kidney-Liver, Heart-Liver, and Heart-Kidney.]

ISHLT


2012
## Survival Combined Heart-Kidney Tx Compared to OHT Alone: UCSF & ISHLT

<table>
<thead>
<tr>
<th>Transplant years</th>
<th>HKTx 1-yr</th>
<th>HKTx 5-yr</th>
<th>OHT 1-yr</th>
<th>OHT 5-yr</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UCSF</strong> 1991-2005</td>
<td>100% N=10</td>
<td>74.3% N=4</td>
<td>90% N=85</td>
<td>70.9% N=59</td>
</tr>
<tr>
<td><strong>ISHLT</strong> 1998-2004</td>
<td>87.3% N=118</td>
<td>74.3% N=118</td>
<td>86.2% N=6196</td>
<td>70.9% N=6196</td>
</tr>
</tbody>
</table>

Since 2005: 13 heart-kidney tx Total simultaneous: 23
HEART TRANSPLANTS
Kaplan-Meier Survival
(Transplants: January 1982 - June 2010)

Survival is based on adult and pediatric transplant recipients

Half-life = 10 years
Conditional half-life = 13 years

N = 96,273
N at risk at 25 years = 112

1-yr: 80%
5-yr: 70%
10-yr: 50%
15-yr: 30%
Recipient Selection Criteria

Late-stage cardiac disease with limited life expectancy and/or poor quality of life in whom all conventional treatment options have either failed or are inappropriate:

• Severe functional limitation NYHA class III or IV on optimal medical therapy irrespective of EF
• Severe or recurrent myocardial ischemia not amenable to revascularization
• Recurrent/refractory dysrhythmias
  – High risk of sudden death
  – Unacceptable quality of life due to frequent ICD discharges
• Other conditions that place the patient at risk of sudden death or decompensation
Recipient Selection Criteria

Severe functional limitation NYHA class III or IV on optimal medical therapy

- **Cardiopulmonary Stress Testing (ambulatory pts)**
  - **Maximal CPX:** RER > 1.05 and achievement of anaerobic threshold on optimal pharmacotherapy
    - *On β-blocker:* peak VO$_2$ ≤ 12 ml/kg/min; Young (<50 yrs) or women- peak VO$_2$ ≤ 50% predicted
    - *Intolerant of β-blocker:* peak VO$_2$ ≤ 14 ml/kg/min
  - **Submaximal CPX (RER<1.05):**
    - Ventilation equivalent of CO$_2$ (VE/VCO$_2$) slope > 35
    - Obese BMI>30 kg/m$^2$: adjust VO$_2$ to lean body mass; lean body mass-adjusted peak VO$_2$ <19 ml/kg/min can serve as threshold to guide prognosis.

Mehra MR et al. JHLT 2006;25:1024
Recipient Selection Criteria

• **Age**
  - \( \leq 70 \) years
  - Carefully selected patients \( > 70 \) years on a case by case basis; use of alternate donors should be considered

• **Body habitus (controversial)**
  - Case by case basis, usually a BMI \( < 30-35 \) Kg/m\(^2\) or percent ideal body weight \( < 140\% \)

Mehra MR et al. JHLT 2006;25:1024
ADULT HEART TRANSPLANTS
Kaplan-Meier Survival by Age Group
(Transplants: January 1982 - June 2010)

All pair-wise comparisons are statistically significant at p < 0.01 except 18-29 vs. 30-39 (p=0.8452)

HALF-LIFE

18-29: 12.2 yrs  30-39: 12.0 yrs
40-49: 11.1 yrs  50-59: 10.0 yrs
60-69:  8.9 yrs  70+:  7.4 yrs
Recipient Selection Criteria

Relative Contraindications

- **Pulmonary hypertension**
  - PVR > 5 $W_u$ or, PVRI > 6 $W_u/m^2$ or, TPG > 16 mmHg
  - PAsP > 60 mmHg + 1 of above
  - Risk of RH failure and early death is increased (30-40% at 90 days)

- **Vasoreactivity trial performed with:**
  - Nitroprusside - Nitric oxide - VAD*
  - Milrinone* - Nesiritide - VAD* + sildenafil
  - Prostacyclin - Sildenafil

- **Hemodynamic goals:**
  - PAs < 50 mmHg
  - PVR ≤ 3.0 $W_u$ with SBP > 85 mmHg
  - TPG gradient < 15 $W_u$

Adapted from Mehra et al. *J Heart Lung Transplant* 2006; 25:1024

*Chronic strategies*
Recipient Selection Criteria
Specific Contraindications

- Coexistent systemic illness with poor prognosis
- Irreversible **pulmonary** disease
- Irreversible **renal** dysfunction (eGFR<40 ml/min)
- Irreversible **hepatic** dysfunction
- Severe peripheral or cerebrovascular obstructive disease
- Insulin-dependent diabetes with end organ damage
- Active: infection, diverticulitis, PUD, PE/infarct
- Coexisting neoplasm
  - Highly variable
Recipient Selection Criteria
Specific Contraindications

• **High risk of life-threatening noncompliance**
  - Inability to make strong consistent commitment to transplant
  - Cognitive impairment severe enough to limit compliance
  - Psychiatric instability severe enough to jeopardize incentive for compliance
  - Recent history of alcohol or drug abuse
  - Cigarette smoking
  - Failure to establish stable address
  - Previous demonstration of repeated noncompliance with medication or follow-up
Listing Priorities
Severity of Disease

• Status 1A
  – Mechanical circulatory support for acute decompensation
    • LVAD and/or RVAD implanted ≤ 30 days
    • Total artificial heart
    • IABP
    • ECMO
  – Mechanical circulatory support > 30 days with device-related complications
  – Mechanical ventilation
  – High dose intravenous inotrope (dobutamine ≥ 7.5 ug/kg/min or milrinone ≥ 0.5 ug/kg/min); multiple intropes/vasodilators with continuous hemodynamic monitoring
  – Life expectancy < 7 days
Listing Priorities
Severity of Disease

• **Status 1B**
  – LVAD and/or RVAD > 30 days
  – Continuous infusion of intravenous inotropes
    • Inpatient
    • Outpatient

• **Status 2**
  – Patient does not meet criteria for either Status 1A or 1B
Surgical Techniques

Bi-atrial
Bi-caval
Biatrial Technique
Biatrial Technique

H. LEFT SIDE OF EXTENDED INTERATRIAL SEPTUM OF DONOR HEART SUTURED TO SEPTAL STUMP OF RECIPIENT, SUTURE WILL THEN BE CONTINUED TO UNITE THE LEFT ATRIAL WALLS AS INDICATED BY ARROWS.

I. RIGHT SIDE OF EXTENDED INTERATRIAL SEPTUM OF DONOR HEART SUTURED TO SEPTAL STUMP OF RECIPIENT; SUTURE WILL THEN BE CONTINUED TO UNITE THE RIGHT ATRIAL WALLS AS INDICATED BY ARROWS.

J. AORTAS ALMOST COMPLETELY ANASTOMOSED; LEFT HEART FLUSHED OUT WITH SALINE VIA CATHETER IN LEFT ATRIUM TO REMOVE ALL AIR BEFORE FINAL CLOSURE; HEART IS THEN LIFTED FROM ITS BED AND ALL SUTURE LINES INSPECTED PRIOR TO REMOVAL OF AORTIC CLAMP AND ANASTOMOSIS OF PULMONARY TRUNKS; HEART IS IMMERSED IN COLD SALINE FOR ENTIRE PERIOD OF HYPOXIA.
Physiologic Aspects of Biatrial Technique

• Two sinus nodes: 2 p-waves marching independent of each other on surface ECG
  – Donor atrial activity is conducted to ventricles generating QRS
  – Native atrial activity does not cross suture line
Bicaval Anastomosis

- Higher CO
- Less bradycardia
- Less TR

FIGURE 1  Bicaval technique: note small single left atrial cuff for pulmonary veins anastomosis and long cavoatrial cuffs.
Complications
ADULT HEART TRANSPLANT RECIPIENTS
Cumulative Incidence of Leading Causes of Death
(Transplants: January 1994 - June 2010)

- CAV
- Acute Rejection
- Malignancy (non-Lymph/PTLD)
- Graft Failure
- Infection

Years
2012

Principle Challenge in Patient Management

- Too High
  - Rejection
  - Graft Dysfunction
  - Cancer
  - Infection
  - Toxicity

- Too Low
  - Quiescence

IMMUNOSUPPRESSIVE THERAPY
CARDIAC TRANSPLANTATION
Complications

- Allograft dysfunction/failure (early, late)
- Infection (50% in first year; 33% blood, 31% lung, 16% GI, 9% UTI, 9% wound, 2% heart/CNS; high index of suspicion/early & empiric treatment mandated)
- **Rejection***
- Immunosuppression-related:
  - Nephrotoxicity: 30% RI and 2.5 % dialysis by 5 yrs
  - Hypertension: 93% by 5 yrs
  - Metabolic abnormalities: 88% with hyperlipidemia, 36% with diabetes by 5 yrs
  - Hepatic, hematologic, & CNS toxicities, drug interactions
- **Cardiac allograft vasculopathy***
- Malignancy (14% at 5 yrs; skin, perineum, lymphoproliferative disorder/lymphoma)
Rejection
PERCENTAGE OF ADULT HEART TRANSPLANT RECIPIENTS EXPERIENCING REJECTION BETWEEN TRANSPLANT DISCHARGE AND 1-YEAR FOLLOW-UP Stratified by Maintenance Immunosuppression (Follow-ups: July 1, 2004 - June 30, 2008)

Despite tac/MMF maintenance rx: 20 - 25% pts experience a rejection episode in the 1st yr. post-tx

Risk for rejection is highest in younger pts and women
Types of Rejection

• Hyperacute rejection
  – Preformed alloantibodies vs. Human Leukocyte Antigens (HLA)

• Acute rejection
  – Most common
  – Cell mediated
  – Antibody mediated - rare <10%

• Chronic rejection
  – Slow progressive loss of graft function
  – Occurs months to years post-transplantation
Clinical signs of allograft rejection

- None (surveillance RV bx)
- Non-specific
- Fever
- Elevated central venous pressure
- New S3 gallop
- New dysrhythmias
- Unexpected relative hypotension
Right Ventricular Endomyocardial Biopsy

3 specimen: False (-) 5%
5 specimen: False (-) 3%

Complications
Mortality: 0.05%
Cardiac perforation: 0.3-0.5%
PTX: 1%
Thromboembolism, air embolism, arrhythmia, BBB
# Grades of Acute Cellular Rejection

<table>
<thead>
<tr>
<th>Grade</th>
<th>Nomenclature</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No rejection</td>
</tr>
<tr>
<td>1A</td>
<td>Focal (perivascular or interstitial) infiltrate without necrosis</td>
</tr>
<tr>
<td>1B</td>
<td>Diffuse but sparse infiltrate without necrosis</td>
</tr>
<tr>
<td>2</td>
<td>One focus with aggressive infiltration and/or focal myocyte damage</td>
</tr>
<tr>
<td>3A</td>
<td>Multifocal aggressive infiltrates and/or myocyte damage</td>
</tr>
<tr>
<td>3B</td>
<td>Diffuse inflammatory process with necrosis</td>
</tr>
<tr>
<td>4</td>
<td>Diffuse aggressive polymorphous infiltrate + edema, + hemorrhage, + vasculitis, with necrosis</td>
</tr>
</tbody>
</table>

1 = mild cellular rejection; 2 = moderate CR; 3 = severe CR
Grade 2R = MODERATE CR RX!
IV steroid pulse or oral prednisone pulse

- multifocal/diffuse lymphocytic infiltrate with myocyte necrosis
Allomap Testing: Acute Rejection vs Quiescence

- Non-invasive test for rejection using gene expression profiling of peripheral blood specimens
- Major value of Allomap is the high negative predictive value to rule out rejection
  - Allomap score <34 is associated with negligible risk of CR
- Among patients > 6 mos post-transplant and at low risk or rejection, strategy using Allomap testing as compared to EMBx:
  - Not associated with ↑ risk of adverse events
  - Resulted in performance of fewer EMBx

Starling RC et al., *J Heart Lung Transplant* 2006;25:1389-95
Mehra M et al. *J Heart Lung Transplant* 2008;27:297-301
New Diagnostic Criteria: AMR(vascular)

- **Histology**
  - Endothelial “activation”: EC swelling, intravascular macrophages, capillary destruction
  - Edema/hemorrhage less specific; not required

- **Immunopathology**
  - Immunofluorescence: C4d, C3d, HLA deposition
  - Immunoperoxidase: C4d, CD68 deposition

- **Serologic evidence DSA**

- *Prevention of AMR: screening for pre-formed allo-antibodies*

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**IMMUNOFLUORESCENCE RESULTS:**
- IgG: 1+ interstitial
- IgM: Negative
- IgA: Negative
- C'3: Negative
- C1q: Negative
- *HLA-Dr: 1+ vascular
- C4D: 3+ vascular
- C3D: Negative
- Fibrinogen: 1+ interstitial

**IMMUNOPEROXIDASE RESULTS:**
- CD68: Stromal macrophages present
- CD31: Vascular endothelial cells highlighted
- C4D: Diffuse capillary staining
- C3D: Diffuse capillary staining

**RESULTS SUMMARY:**
- Immunologic positive
- Histology positive
- Findings of severe rejection

**ANTIBODY-MEDIATED REJECTION CLASSIFICATION:**
- AMR 0: None. Negative immunologic stain(s) and negative histology.
- AMR 1: Suspicious. Positive immunologic stain(s) or histology (but not both).
- AMR 2: Definite. Positive immunologic stain(s) and positive histology.
- AMR 3: Severe. Positive immunologic stain(s) and positive histology with hemorrhage, edema, neutrophils, vasculitis.

Kobashigawa et al, J Heart and Lung Transplant 2011;30(3):252
EC swelling; Macrophages

C4D stain Surrounds EC

Gonzales-Stawinski GV et al J Heart Lung Transplant 2008;27:375-61
Immunosuppression (Maintenance)

- **Corticosteroids**
  - Anti-inflammatory with IMS effects mediated by ↓ cytokine gene activation
  - Prednisone

- **Anti-proliferative agents**
  - Inhibit purine synthesis
  - Azathioprine (Imuran)
  - Mycophenolate mofetil (Cellcept, Myfortic)

- **Calcineurin inhibitors**
  - Reduce cytokine gene activation by inhibiting calcineurin
  - Cyclosporine (Neoral, Gengraf, Sandimmune)
  - Tacrolimus (Prograf)

- **TOR inhibitors/proliferation signal inhibitors**
  - Reduce cytokine gene activation by inhibiting TOR
  - Rapimmune (Sirolimus, Everolimus)
### Treatment of Rejection

**Asymptomatic/Subclinical**
- Target higher CNI levels
- Oral steroid bolus + taper
- Sirolimus

**Reduced EF**
- Oral steroid bolus/taper
  - IV pulse steroids

**Heart Failure/Shock**
- IV pulse steroids
- Cytolytic therapy (ATG)
- Plasmapheresis (before ATG dose)

**Cellular**
- To treat or not to treat?
  - IV pulse steroids
  - Cytolytic therapy
  - Plasmapheresis (before ATG dose)
  - IV immune globulin

**Antibody-Mediated**
- IV pulse steroids
  - Cytolytic therapy
  - Plasmapheresis (before ATG dose)
  - IV immune globulin
  - IV heparin
  - Inotropes, IABP or ECMO support
Cardiac Allograft Vasculopathy (CAV)
Cardiac Allograft Vasculopathy (CAV)

- **Incidence**
  - Angiographically evident in 25-45% of patients at 3 years post transplant; **32% within 5 years**
  - 5-10% per year post-transplant

- **Distinct from typical atherosclerosis**

- **Putative pathophysiology**
  - Immune-mediated or preservation injury-mediated endothelial cell damage
  - Platelet activation → ingress of mitogenic factors → myointimal cell proliferation ± lipid deposition,

- **Associated with classic risk factors + AMR, HLA-mismatch, CMV disease, etc.**

- **A major limiting factor to long-term survival**

- **Major indication for retransplantation**
**CAD: ARTERIOGRAPHY**

**Natural CAD:**
- Type A Lesion
- Discrete, tubular, or multiple stenoses

**Transplant CAD:**
- Type B₁ Lesion
  - Abrupt onset, distal diffuse concentric narrowing
- Type B₂ Lesion
  - Gradual concentric tapering
- Type C Lesion
  - Narrowed irregular distal branches, ending abruptly

![Arteriogram at 5 Years Posttransplant](image)

Transplant CAV
Clinical Presentation

• Allograft dysfunction/failure
• New dysrhythmias
• Sudden death
• Angina pectoris
  – Uncommon due to cardiac denervation
  – Atypical symptoms
Transplant CAV Diagnosis

- **High index of suspicion for atypical presentations**
- **Acute dx:**
  - CK/MB; Troponin I
  - ECG changes
  - ECHO wall motion abnormalities
- **Dobutamine ECHO**
  - If no dobutamine-induced wall motion abnormalities, significant CAV unlikely
- **Coronary angiogram**
  - Low threshold to perform with new clinical event
  - Annual surveillance exam if dobutamine ECHO abnormal
- **Intravascular ultrasound**
  - Early detection
  - More sensitive than angiogram
Transplant CAV Prevention

• Classical risk factor modification
  – Lifestyle modification (diet, smoking cessation)
  – Lipid lowering agents - any “statin”
    • Slow progression, improve survival, decrease incidence of acute rejection with hemodynamic compromise
      – Control hypertension
      – Control hyperglycemia
  
• Use of sirolimus and everolimus promising
  – Mean↑ in IVUS MIT at 12 mos. less
  – Incidence of vasculopathy lower

Transplant CAV Treatment

• Acute ischemia/myocardial infarction
  – Usual management

• Chronic, recurrent ischemia
  – Prevention strategies
  – Aggressive anti-ischemic therapy (ASA, B-blockers, nitrates, calcium channel blockers)
  – PCI / stent
  – CABG
  – Re-transplantation
    • (poor short- and long-term survival)

Less effective in transplant CAD especially in setting of distal disease
ADULT HEART TRANSPLANTS
Kaplan-Meier Survival by Diagnosis
(Transplants: January 1982 - June 2010)

All pair-wise comparisons are statistically significant at < 0.001 except cardiomyopathy vs. congenital (p=0.6340).

ISHLT
Cardiac Transplantation: Summary

- Heart transplantation is a *treatment* and not a *cure*
- Effective treatment for pts. with late-stage cardiac disease in whom all conventional treatment options have failed or are inappropriate
  - Improve survival
  - Improve quality of life
- Minority of patients will receive OHT
- Outcome is dependent on careful patient selection and close vigilance for complications (multidisciplinary team)
- Complications are manageable
- Graft failure, CAV and malignancy limit long-term survival
UCSF Advanced Heart Failure Evaluation and Therapies Program
Contact Information

- **24/7 physician-to-physician hot line:**
  (415) 514-8866

- **24/7 main program line:**
  (415) 353-4145 option 1

- **Office Fax:**
  (415) 353-4166