Transplant in Pediatric Heart Failure

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Pediatric Heart Transplants
Kaplan-Meier Survival (Transplants: January 1982 – June 2014)

- <1 Year (N = 2,944)
- 1-5 Years (N = 2,720)
- 6-10 Years (N = 1,743)
- 11-17 Years (N = 4,684)
- Overall (N = 12,091)

1-5 vs. 11-17: p = 0.0001
6-10 vs. 11-17: p = 0.0312
No other pair-wise comparisons were significant at p < 0.05.

Median survival (years): <1=20.7; 1-5=18.2; 6-10=14.0; 11-17=12.7

Pediatric Heart Transplants
Kaplan-Meier Survival by Era
Age: < 1 Year (Transplants: January 1982 – June 2014)

- 1982-1989 (N=183)
- 1990-2003 (N=1,460)
- 2004-2008 (N=558)
- 2009-6/2014 (N=743)

All pair-wise comparisons were significant at p<0.05.

Increasingly Complex Pediatric Heart Transplant Candidates

- Complex congenital heart disease
- Elevated pulmonary vascular resistance
- Multisystem organ dysfunction
- Pre-formed HLA antibodies
- Increasing wait-list with unchanged donor pool
Who Should Have a Heart Transplant?

- What is the estimated 1-2 year survival with medical and/or surgical management?
- What is the estimated post-transplant survival for that child?
- Is there a clinically important survival advantage with transplant?
Notable Advances During the Last Decade

- ABO incompatible transplant
- Transplant of highly sensitized patients – CTOT trial
- Decreasing waitlist mortality with ventricular support devices designed for children
- The prospect of DCD heart transplantation
Strategies for Improving Outcomes

- Improve waitlist survival
- Increase donor pool
- Optimize post-transplant outcomes
Improve waitlist survival
Selection of Recipients

- Transplant evaluation
  - Characterize severity of heart failure
  - Uncover co-morbid conditions
  - Identify reversible causes of heart failure

- High mortality within 12-24 months

- Longevity not impacted as much as quality of life (pediatric application?)
Assessment of Risk

- Renal- GFR
- Pulmonary- PFTS
- Hepatic, endocrine, GI
- PVR reactivity with O2, NO
- Neurocognitive/psychiatric
- PRA
- Social
Survival for children listed status 1A according to level of support

Log-rank Test $P<0.001$

Neither ECMO nor ventilator

ventilator

ECMO

Almond et al. 2008
Pediatric Heart Transplants

% of Patients Bridged with Mechanical Circulatory Support*
by Year (Transplants: January 2005 – December 2014)

- ECMO
- VAD + ECMO
- VAD or TAH

% of Patients

<table>
<thead>
<tr>
<th>Year</th>
<th>ECMO</th>
<th>VAD + ECMO</th>
<th>VAD or TAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>22.1</td>
<td>0.0</td>
<td>77.9</td>
</tr>
<tr>
<td>2006</td>
<td>21.3</td>
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<td>78.7</td>
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<tr>
<td>2007</td>
<td>22.5</td>
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<td>77.5</td>
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<td>2008</td>
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<td>77.6</td>
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<td>2010</td>
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<td>70.3</td>
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<td>2013</td>
<td>34.8</td>
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</tr>
<tr>
<td>2014</td>
<td>32.9</td>
<td>0.0</td>
<td>67.1</td>
</tr>
</tbody>
</table>

* LVAD, RVAD, TAH, ECMO
UNOS Status at transplant: changes over time
**UNOS 1 and 2 (before 1999)**
Defined by location of patient

- **UNOS status 1**
  - in ICU

- **UNOS status 2**
  - Anywhere else

**UNOS 1A, 1B and 2 (1999-2016)**
Defined by medical needs of patient

- **UNOS status 1A**
  - Less than 6 months of age with CHD and reactive pulmonary disease
  - Single high dose inotrope (Milrinone 0.5mcg/kg or more; Dopamine 7.5mcg/kg or Dobutamine 7.5mcg/kg or more
  - Multiple low dose inotropes (any combination of inotropes)
  - Intubated
  - Mechanical support (ECMO/VAD)
  - 1A by exception: life expectancy <14 days, life threatening arrhythmias

- **UNOS status 1B**
  - Less than 6 months and does not meet 1A criteria
  - Single low dose inotrope
  - Failure to thrive

- **UNOS status 2**
  - All others
Current 2016 UNOS Listing changes: Key points

- Reducing waitlist mortality to highest risk groups (infants, CHD, high level of support)
- Granular definitions of medical needs
- Location of patient is brought back into definitions (ie: admitted to listing center)
Current UNOS definitions

UNOS 1A:

- Definition: Patient under the age of 18 years at the time of registration and meets one of the following criteria:
  - Continuous mechanical ventilation and inpatient at the listing hospital
  - Intraortic balloon pump and inpatient at the listing hospital
  - Ductal dependent pulmonary or systemic circulation with ductal stent in place or continuous infusion to keep the duct open and inpatient at the listing hospital (no age requirement)
  - Congenital heart disease with multiple low dose inotropes or 1 high dose inotrope and inpatient at the listing hospital
  - Mechanical circulatory support (does not require hospitalization)
  - 1A Exception – hospitalized at listing hospital and MD feels that medical urgency is comparable to other 1A candidates/requirements. Valid for 14 days.
  - Valid for up to 14 days, renewal process unchanged; downgraded to 1B by system if not renewed at 14 days.
Current UNOS definitions (cont.)

UNOS 1B:
- Definition: Patient under the age of 18 years at the time of registration and meets one of the following criteria:
  - Continuous infusion of 1 or more inotropes and does not qualify for 1A (can be home; CDMY)
  - <1yr of age at initial registration with restrictive or hypertrophic cardiomyopathy

UNOS 2:
- Definition: Patient under the age of 18 years at the time of registration and does not meet status 1A or 1B criteria but is suitable for transplant.
Expand the donor pool
Heart Transplantation in Childhood

Age at transplantation

Wait-list mortality

Major Problems:
- Donor organ shortage
- Blood type (ABO)-incompatibility of recipient and donor

Almond et al. 2009, Circulation
ABO-incompatible Heart Tx

“ABO-I heart Tx can be safely performed in the infant population”

♥ 10 infants transplanted with ABO-incompatible cardiac grafts
♥ no hyperacute rejection
♥ 8/10 survivors
♥ (deaths unrelated to ABO status)
Outcomes of ABOi Htx
Clinical trials in infants in Toronto

No specific adverse event
Comparative long term survival
No increased cellular rejection
No delayed humoral rejection
Graft coronary artery disease (chronic vascular rejection): one case
No increased drug side-effects because no aggressive immunotherapy required

3. West et al. 2006 J Thor Card Surg,
4. Nishant et al. 2008 J Heart Lung Transpl,
5. Fan et al. 2004 Nat Med
Canada demonstrated a decrease in wait list mortality for infants under 6 months of age from 58% to 7% with ABO incompatible transplants.
Time Trend in Listing of U.S. Infants for an ABO-I HT 2000-2008

Percentage

2000-1 (227)
2002 (135)
2003 (103)
2004 (130)
2005 (106)
2006 (123)
2007 (121)

Year of Listing

At Any Time
At Initial Listing

N=1331
Proposed Change in 2016

- Priority ABO compatible – status 1A, 1B or 2 then ABO incompatible – status 1A or 1B then in utero compatible/incompatible

- Change the allocation priority of ABO incompatibles
With the new proposal now in effect, an organ (regardless of ABO compatibility) would be offered to the most urgent, local, recipient.
Patient survival on the heart transplant waiting list

All < 1 year of age

<table>
<thead>
<tr>
<th>Time</th>
<th>% survival</th>
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<tbody>
<tr>
<td>1 month</td>
<td>77.3 %</td>
</tr>
<tr>
<td>2 months</td>
<td>59.2 %</td>
</tr>
<tr>
<td>3 months</td>
<td>54.3 %</td>
</tr>
<tr>
<td>4 months</td>
<td>49.4 %</td>
</tr>
<tr>
<td>5 months</td>
<td>37.0 %</td>
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<tr>
<td>6 months</td>
<td>24.7 %</td>
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Pediatric Heart Transplantation after Declaration of Cardiocirculatory Death

Mark M. Boucek, M.D., Christine Mashburn, B.S.N., Susan M. Dunn, M.B.A., Rebecca Frizell, B.S.N., Leah Edwards, Ph.D., Biagio Pietra, M.D., and David Campbell, M.D., for the Denver Children’s Pediatric Heart Transplant Team*
Study Overview

• This report describes transplantation of hearts from three infant donors (mean age at donation, 3.7 days) who had died from cardiocirculatory causes

• The recipients (mean age, 2.2 months) all survived to 6 months with excellent left ventricular function

• This approach to transplantation has been controversial but offers the prospect of expanding the donor pool

DCD Heart transplants
University of Colorado DCD Study Protocol

1. Inclusion criteria: All status 1A recipients < 18 months

2. Advance parental consent to receive first available heart-BD or DCD donor

3. Donor interventions - large bore venous and arterial access, balloon catheter in ascending aorta, 300 u/kg heparin bolus and 20 U/kg/hour.

4. 75 second wait time for pronouncing death followed by cardioplegic flush
Proposed DCD Heart protocol (BCH)

1. Include only Status IA infants < 1 year old on the heart transplant waiting list for >2 months
2. Special study consent to transplant next available heart - whether from BD or DCD donor.
3. No invasive donor interventions
4. 2 min wait time (vs 5 min with ex-vivo perfusion)
5. On-site>>>>add local area donors
Optimize post-transplant outcomes
Pediatric Heart Transplants
Relative Incidence of Leading Causes of Death
(Deaths: January 2004 – June 2015)

- CAV
- Acute Rejection
- Infection (non-CMV)
- Graft Failure

Percentage of Deaths

- 0-30 Days (N = 256)
- 31 Days - 1 Year (N = 297)
- >1 Year - 3 Years (N = 236)
- >3 Years - 5 Years (N = 204)
- >5 Years - 10 Years (N = 366)
- >10 Years (N = 408)
Advances During the Last Decade

- Advances in Rejection Diagnosis and Treatment
  - Rejection diagnosis – Antibody mediated rejection with C4D
  - Newer maintenance immune suppression agents
  - Increased use of induction agents
  - Immune suppression agents with potential of slower progression of CAD
  - Changing protocols and individualized therapy
Reducing Immune Suppression Associated Morbidity

• New immune suppression protocol at BCH since May 2006 in non-sensitized patients

• Objectives
  • Decrease incidence of early post-transplant renal failure
  • Decrease incidence of rejection during first year post-transplant
  • Decrease long-term steroid related morbidity –hypertension, diabetes, osteopenia, decreased growth
Steroid Avoidance protocol

• Previous protocol:
  • Tacrolimus, mycophenolate, prednisone

• Current protocol: Induction for 5 days
  • Tacrolimus started at a lower dose 48-72 hours after transplant
  • Tacrolimus+Mycophenolate after 5 days

• Rejection episodes seen have been infrequent, all mild (1R) by biopsy, asymptomatic and usually associated with sub therapeutic levels.
Advances During the Last Decade

• Advances in Infection Diagnosis and Treatment
  • CMV antigen
  • EBV Quantitative PCR – ? prevention of PTLD
  • Newer drugs: Cytogam, val ganciclovir,
Opportunities for the Next Decade

Challenges

• A: High Risk Early Period
• B: Long-term Attrition
• C: Long-term patient morbidities
• D: Evidence Based practices

Opportunities

• A: Improve patient risk profile at transplant (VAD instead of ECMO)
• B: Prevention of CAD, rejection, PTLD
• C: IS Protocols with less drug-related morbidity
• D: Randomized trials
Conclusions

1. Transplant continues to be the best short and long-term option for children with end-stage heart failure
2. Donor pool expansion must be a priority
3. Advanced therapies, especially new assist device technologies, need careful pediatric trials design.
4. Survival continues to increase following heart transplant with excellent QOL but morbidity over time.
Thank you