Paediatric cardiac transplantation: history

- 1967: first infant heart transplant (anencephalic donor)
- 1968: first infant heart-lung transplant
- 1984: first HLHS recipient (Yacoub)
- 1985: baboon-to-human xenograft
- 1985: successful newborn transplant
Paediatric cardiac transplantation
ethical issues

- Is it appropriate to offer solid organ transplantation to infants and young children?
- Should newborns with unfavourable cardiac malformations be palliated in anticipation of likely future transplantation?
- Should extended ICU therapy be offered to children awaiting transplantation?
- Is it justifiable to refuse transplantation to children with significant disabilities?
- Who should decide allocation of community resources?
### NACCS

**DCM: Multivariate analysis for death/transplant**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting age (&gt;5 yrs)</td>
<td>6.6</td>
<td>3.0-14.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Family history DCM</td>
<td>3.7</td>
<td>1.9-7.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Initial FS Z score*</td>
<td>0.8</td>
<td>0.7-0.9</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

* Per unit Z score
NACCS
DCM survival related to EMBx findings

Survival probability over years for patients with and without myocarditis.
NACCS
DCM survival related to 3 month FS

Survival probability

Years

Survival probability

Years

FS ≥ 20%

FS < 20%
Paediatric cardiac transplantation
indications

- End-stage heart disease (CM, CHD, anthracycline toxicity) with anticipated poor 12 month survival
- Palliated cardiac malformations with poor quality of life
- Cardiac disease with severe ventricular dysfunction and likely poor outcome (time uncertain)
Paediatric cardiac transplantation

contraindications

- Active neoplasm
- Inadequate pulmonary arteries
- Degenerative CNS/muscular disease/metabolic disease
- Severe elevation of pulmonary vascular resistance without reactivity
- Lack of a social support system
Recipient assessment: risk factors

- Multiple previous sternotomies
- Requires additional surgery at time of transplantation
- Elevated pulmonary vascular resistance
- Considerable deconditioning prior to transplantation
- On life support at time of transplantation
- Poor social circumstances
Transplant assessment

- Make a firm diagnosis; quantify ventricular function
- Let family meet team members including transplant coordinator, social worker, psychologist and ward staff
- Let family meet other transplant families
- Allow multiple visits before asking parents for a decision
- Discuss issues of publicity and extended ICU therapy in advance
- Periodically reassess the patient first-hand
- Only offer transplantation to those on the waiting list!
Recipient diagnoses

CHD - 60%

Cardiomyopathy - 40%

Two ventricles
One ventricle
HLHS

DCM
LVNC
HCM
RCM
Myoc
Anth
## Waiting list outcomes by age: all patients

<table>
<thead>
<tr>
<th>Age</th>
<th>Transplant</th>
<th>Death</th>
<th>Delist</th>
<th>Waiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 1 year</td>
<td>6 (24%)</td>
<td>15 (60%)</td>
<td>4 (16%)</td>
<td></td>
</tr>
<tr>
<td>1 – 5 years</td>
<td>12 (50%)</td>
<td>11 (46%)</td>
<td></td>
<td>1 (4%)</td>
</tr>
<tr>
<td>&gt; 5 years</td>
<td>38 (72%)</td>
<td>10 (19%)</td>
<td>2 (4%)</td>
<td>3 (5%)</td>
</tr>
</tbody>
</table>
## Donors: referral state and weight

<table>
<thead>
<tr>
<th>State</th>
<th>0 – 10kg</th>
<th>11 – 30kg</th>
<th>31 – 60kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT/NSW</td>
<td>1</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>N.T.</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>N.Z.</td>
<td>1</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Qld</td>
<td>3</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td>S.A.</td>
<td>8</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Tas</td>
<td></td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Vic</td>
<td>6</td>
<td>12</td>
<td>55</td>
</tr>
<tr>
<td>W.A.</td>
<td>1</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td>Waiting mortality</td>
<td>37%</td>
<td>31%</td>
<td></td>
</tr>
<tr>
<td>Median waiting time (25% – 75%)</td>
<td>57 days (19 – 87)</td>
<td>73 days (23 – 130)</td>
<td></td>
</tr>
</tbody>
</table>
Donor assessment

- Check donor story and clinical status with appropriate physician
- ABO and lymphocyte cross-match
- Size matching (donor:recipient weight of up to 3.5:1)
- Check donor inotrope requirements once DI and hypovolaemia corrected
- Consider potential ischaemic time in light of:
  - Recipient characteristics
  - Donor function (always get an echo & ECG on remote donors)
  - Clinical urgency
Post-transplant: perioperative considerations

- Prophylactic NO for pulmonary hypertensive recipients
- Treat chronotropic incompetence if CO low
- Titrate early CSA levels to urine output
- Set limits for BP and treat hypertension aggressively as hypertensive encephalopathy occurs at lower than expected BP
- Ganciclovir for CMV mismatches
- Prophylactic H2 antagonist
Paediatric heart transplantation

Immunosuppressive issues

- Endomyocardial biopsy vs. non-invasive surveillance
- Cyclosporine vs. FK506
- Azathioprine vs. mycophenolate mofetil
- Triple therapy with maintenance steroids
Immunosuppressive issues: endomyocardial biopsy

- Conventional echo parameters are insensitive markers for the presence of mild-moderate cellular rejection
- Biopsies are not a gold standard - they are subject to differences in observer interpretation and there may be little to see in someone with rapidly progressive rejection
- Biopsies are of low risk and often add useful information
Children older than 5 years have a biopsy based protocol with around 12 surveillance biopsies during the first year.

Children younger than 5 years have periodic but less frequent biopsies.

Try and avoid biopsies in haemodynamically unstable patients and in very young infants.
**Immunosuppressive issues**

**cytokine inhibitors**

**Cyclosporine**
- Established therapy
- Government funded
- Cosmetic side effects
- Doesn’t abolish existing rejection
- Renal dysfunction similar to Tacrolimus
- Works well with MMF

**Tacrolimus (FK506)**
- Used in 20-30% paed. transplants
- Not government funded
- No cosmetic side effects
- More potent anti-rejection
- No survival benefit
- Lower chol and less hypertension
- Works well with Azathioprine
- 4% incidence of diabetes
Immunosuppressive issues

RCH strategies

- Cyclosporine used initially for all children
- Unacceptable cosmetic side-effects: change to Tacrolimus
- Frequent or persisting cellular rejection: change to Tacrolimus or Mycophenolate Mofetil
- Renal dysfunction: change to Mycophenolate Mofetil and lower the dose of CSA
Immunosuppressive issues
antimetabolites

**Azathioprine**
- WBC and RBC effect
- 89% one year survival
- 75% incidence rejection
- Less opportunistic infections
- Works well with CSA and FK506
- Few side effects

**Mycophenolate Mofetil**
- More lymphocyte specific
- 94% one year survival
- Less rejection than Azathioprine
- More opportunistic infections
- Works better with CSA
- Can lower CSA dose if renal problems
- GI side effects
Immunosuppressive issues

***steroids***

- Triple therapy is more effective for preventing cellular rejection than dual therapy
- Steroids potentiate hypertension and obesity
- Early severe rejection attenuated by an early oral steroid taper with maintenance steroids for at least 6 months
- Depending on other medications used, up to 50% of children can have steroids withdrawn
Results:
Kaplan-Meier survival estimate

RCH: 1992-2001

ISHLTLT data
RCH transplants:
Causes of death

- Acute cellular rejection: 9 (2 hosp deaths, 4 non-compliant adolescents)
- Primary graft failure: 2 (2 hosp deaths)
- Coronary artery disease: 1 (1 non-compliant adolescent)
- Cerebral bleed: 1 (1 hosp death)
- Sepsis: 1 (1 hosp death)
- Bronchomalacia: 1 (1 hosp death)
Protocol:
late follow-up

- Regular review in a clinic setting
- Periodic endomyocardial biopsy and coronary angiography
- Pravastatin for prevention of post-transplant coronary disease in recipients >10 years
- Additional biopsies if changes in therapy, low drug levels or evidence of non-compliance
- Annual measurement of glomerular filtration rate
- Dental review
Late follow-up: renal function

- Renal function is moderately depressed at 12 months post-transplant and doesn’t change much during follow-up
- Median GFR at latest follow-up is 75/ml/min/1.73m²
- No relation between GFR and early or late CSA dose/levels, pre-existing disease, age at transplant or duration of follow-up
- 15% of recipients have a GFR of <50ml/min/1.73m²
- If GFR low with acceptable CSA levels, consider using Mycophenolate Mofetil and reducing CSA dose to sub-therapeutic levels
Late follow-up: coronary disease

- Incidence in children is around 15% at 5 years and is less frequent than in adults
- Difficult to diagnose, even with selective coronary angiography
- Stress echo not well validated as a screening tool in paediatrics
- Therapeutic options include antiplatelet and lipid lowering drugs, coronary intervention and re-transplantation
Late medical problems

- Rejection episodes: median 2 (range 0-9)/patient
- Hypertension requiring therapy: 12%
- Coronary artery disease: 12% (1 death)
- PTLD (all lymphomas): 8% (no deaths)
Adolescent non-compliance outcomes

- Non-compliance is the single biggest late hazard facing adolescents and young adults
- The mortality for those presenting with rejection is around 50%
- Other sequelae include recurrent cellular rejection and rapidly progressive coronary disease
Adolescent non-compliance warning features

- Missed appointments without explanation
- Clinic attendance without parents
- Unstable home life, single parent or changes in partners
- Low CSA levels without changes to therapy
- No routine for taking therapy
- Parents unfamiliar with drugs or doses
- Unexpected late rejection
- Previous non-compliance
Adolescent non-compliance

minimising the risk

- Regular clinical review with non-invasive cardiac assessment and CSA levels
- Patient or family to list medications at each visit
- Pill-box
- Social worker or clinical psychologist on the team sees patients separately
- Follow-up biopsies for those with late rejection
Psychosocial outcomes

- Not well quantified in cardiac transplant recipients
- Family dynamics often abnormal
- Outcomes depend on pre-existing illness, age at transplant, extent of post-transplant medical problems, cognitive function, individual motivation and family support
- All local transplant recipients have attended school, except for one family who has home teaching for all 4 children