Immunosuppression Minimization in Pediatric Kidney Transplantation

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William Harmon Disclosures

• I currently receive research support from:
  – National Institutes of Health (NIH)
  – Bristol Myers Squibb
  – Genzyme/Sanofi

• I receive honoraria from:
  – Springer
  – Up-To-Date

• I am an unpaid consultant to
  – Genzyme/Sanofi
  – Bristol Myers Squibb
ESRD in Children

• What are the options for treatment?
  – Conservative management
    • Too late
  – Regeneration
    • Too early
  – Chronic Dialysis
  – Kidney Transplantation
Chronic Dialysis

• Pro:
  – Technical problems have been alleviated
  – Rehabilitation has been enhanced with EPO and rhGH
  – Recurrent disease is irrelevant
  – Some progress is being made with nightly HD, making treatments less onerous on daily schedules
Chronic Dialysis

• **Con:**
  – Treatments do not correct uremia
    • Growth and development are inhibited
  – Treatments are always dependent on access
  – Treatments interfere with daily schedule
  – Recurrent treatments lead to shortened life-span and decreased graft survival
  – There has been no true technical break-through in over a decade
Kidney Transplantation

• Pro
  – Restores normal renal function
  – Provides best setting for growth and development
  – Has had multiple continuous improvements in past 3 decades
  – Has very low mortality rate
  – Children can have the best outcomes
Kidney Transplantation

• Cons
  – Is not a “cure”, requires continuous treatment and eventually fails
  – Chronic immunosuppressive medications have serious side effects
    • Infection, Cancer and Cardiovascular disease
  – Recurrent disease is possible
  – Success requires substantial adherence
How Do Children and Adults Differ?

• Children are generally smaller than adults
• Children will, on average, live longer than adults
• Children are constantly maturing: ie they are supposed to grow and develop
• Children’s immune response is diminished early in life, but then becomes “average”
How Do Children and Adults Differ?

• Children are biologically naïve:
  – They are less likely previously to be sensitized
  – They are less likely previously to have been exposed to infections

• Children frequently have inherited or congenital causes for organ failure that won’t recur in a transplanted organ

• Children are vulnerable and protected by society
Outline

• Demographics of Chronic Kidney Disease and Transplantation in Children
• Recent experimental studies
• Current practices of renal transplantation in children
• Unresolved problems
Waiting List by Age

# waiting

0 to 18
18 to 34
35 to 49
50 to 64
> 65

0 5,000 10,000 15,000 20,000 25,000 30,000 35,000

Deceased Donor Transplants by Age

# Tx

- 0 to 18
- 18 to 34
- 35 to 49
- 50 to 64
- > 65
Pediatric Living and Deceased Donor Kidney Transplants by Year
Annual renal transplants by recipient age

- 1 to 4 years: 13%
- 5 to 9 years: 12%
- 10 to 14 years: 22%
- 15 to 19 years: 53%
## Demographics of pediatric renal transplant recipients by age

<table>
<thead>
<tr>
<th>Age Range</th>
<th>0-1</th>
<th>2-5</th>
<th>6-12</th>
<th>13-17</th>
<th>&gt;17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>68%</td>
<td>68%</td>
<td>60%</td>
<td>56%</td>
<td>54%</td>
</tr>
<tr>
<td>Female</td>
<td>32%</td>
<td>32%</td>
<td>40%</td>
<td>44%</td>
<td>46%</td>
</tr>
<tr>
<td>White</td>
<td>79%</td>
<td>65%</td>
<td>64%</td>
<td>60%</td>
<td>55%</td>
</tr>
<tr>
<td>AA</td>
<td>7%</td>
<td>14%</td>
<td>13%</td>
<td>18%</td>
<td>25%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>10%</td>
<td>14%</td>
<td>16%</td>
<td>16%</td>
<td>13%</td>
</tr>
<tr>
<td>Other</td>
<td>4%</td>
<td>6%</td>
<td>6%</td>
<td>6%</td>
<td>6%</td>
</tr>
</tbody>
</table>
## Etiology of E.S.R.D. in Children and Adults

### Etiology of ESRD in Children and Adults

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>Children (&lt;18)</th>
<th>Adults (20-64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Dysplasia</td>
<td>17%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Urologic</td>
<td>26%</td>
<td>4%</td>
</tr>
<tr>
<td>Other Congenital</td>
<td>15%</td>
<td>5%</td>
</tr>
<tr>
<td>FSGS</td>
<td>11%</td>
<td>2%</td>
</tr>
<tr>
<td>Other GN/Immunologic</td>
<td>14%</td>
<td>17%</td>
</tr>
<tr>
<td>Hypertensive Nephropathy</td>
<td>0%</td>
<td>22%</td>
</tr>
<tr>
<td>Diabetic Nephropathy</td>
<td>0.1%</td>
<td>40%</td>
</tr>
</tbody>
</table>

*Source: NAPRTCS  *Source: USRDS
Pediatric Living Donor Kidney Transplant Immunosuppression @ Day 30
Pediatric Kidney Transplant
Immunosuppression Follow-Up
Acute Rejection Rates by Era

NAPRTCS 2007
5-Year Graft Survival by Recipient Age

% Graft Survival

Age at Transplant

1-5
6-10
11-17
18-34
35-49
50-64
65+

LD
CAD

OPTN/SRTR 2002 Report, Table 5.8
Kidney Graft Survival by Age

Young children have the best long-term graft survival of all age groups.
Pediatric Kidney Transplant Survival

![Graph showing graft survival rates over years from transplant for different donor types. The graph includes lines for living donor transplantation from 1987-1995 and 1996-2006, as well as deceased donor transplantation from 1987-1995 and 1996-2006. The survival rates are represented as percentage graft survival against years from transplant.]
Graft Function and Survival at Annual Follow-up
Pediatric Kidney Transplant Outcomes

- As with adults, short-term outcomes of pediatric kidney transplants have improved and are excellent.
- Young children are low risk and have the best outcomes of all age groups.
- Adolescents are a high-risk age group.
- Long term outcomes have not improved and are particularly important for children because their mortality rates are low.
- GFR (graft function) deteriorates constantly.
Why do Pediatric Studies Require Multi-Center Study Groups?
Two USA Pediatric Organizations

- CCTPT?
- CTOT-C?
What is CCTPT?

- Cooperative Clinical Trials in Pediatric Transplantation
  - Funded through NIAID
  - U-01 mechanism
    - Clinical trial
    - Mechanistic or other basic studies
  - Total funding $2.5M/year for 4-5 years for 2 centers
  - Began 1994  Ended 2008
NAPRTCS/CCTPT Transplant Studies
What is CTOT-C

• Clinical Trials in Organ Transplantation in Children
• U-01 to replace CCTPT, begin 3/08
• 4 Consortia Funded
  – 2 Kidney:
    • Harmon: 6 Center
    • Kirk: 3 Centers
  – 1 Lung: Sweet, 6 Centers
  – 1 Heart: Webber, 6 Centers
Pediatric Kidney Transplant Controlled Trials

Table 1. Recent randomized prospective multicenter trials in pediatric kidney transplantation.

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Purpose</th>
<th>Reference group immunosuppression (n)</th>
<th>Study group immunosuppression (n)</th>
<th>Conclusion/ comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>IN01 95</td>
<td>Efficacy of OKT3 induction and double blind comparison of Neoral to Sandimmune</td>
<td>Cyclosporine A induction, oral cyclosporine, anti-metabolite, steroids (n=140)</td>
<td>OKT3 induction, oral cyclosporine, anti-metabolite, steroids (n=147)</td>
<td>No differences between groups in any parameters</td>
</tr>
<tr>
<td>SW01 96</td>
<td>Late steroid withdrawal</td>
<td>Basiliximab, tacrolimus, sirolimus, steroids (n=73)</td>
<td>Withdrawal of steroids after 6 months post-transplant (n=59)</td>
<td>Significantly better height velocity and graft survival in study group but study stopped early due to excessive PTLD in both arms</td>
</tr>
<tr>
<td>Late steroid withdrawal study 97</td>
<td>Safety of late steroid withdrawal</td>
<td>Cyclosporine A, mycophenolate, steroids (n=21)</td>
<td>Withdrawal of steroids after 1-year post-transplant (n=21)</td>
<td>Significantly better catch up growth, less hypertension and less frequent dyslipidemia in the steroid withdrawal group</td>
</tr>
<tr>
<td>FDCC 98</td>
<td>Basiliximab induction efficacy in children</td>
<td>Cyclosporine A, mycophenolate, steroids and placebo (n=92)</td>
<td>Basiliximab, cyclosporine A, mycophenolate, steroids (n=100)</td>
<td>No significant difference in acute rejection rates between the groups</td>
</tr>
<tr>
<td>TWIST 68</td>
<td>Efficacy and safety of early steroid withdrawal</td>
<td>Tacrolimus, mycophenolate, steroids (n=98)</td>
<td>Tacrolimus, mycophenolate, steroids till day 4 only, 2 doses only daclizumab (n=98)</td>
<td>Significantly improved height growth in study group, more so in pre-pubertal.</td>
</tr>
<tr>
<td>SNS01</td>
<td>Efficacy and safety of steroid avoidance</td>
<td>Daclizumab 5 doses, tacrolimus, mycophenolate, steroids (n=65)</td>
<td>Daclizumab 9 doses, tacrolimus, mycophenolate (based on Stanford protocol; (n=65) 65, 69</td>
<td>Study results not yet published</td>
</tr>
<tr>
<td>Trial</td>
<td>Purpose</td>
<td>Immunosuppression (n)</td>
<td>Comments</td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------------------------------------------------</td>
<td>-------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Tricontinental study</td>
<td>Efficacy and safety of mycophenolate mofetil suspension</td>
<td>Cyclosporine A, mycophenolate, steroids (n=100)</td>
<td>Drug well tolerated, low rate of withdrawal</td>
<td></td>
</tr>
<tr>
<td>CN01 study</td>
<td>Pilot trial of calcineurin avoidance</td>
<td>Anti-IL2RmAb, sirolimus, mycophenolate, steroids (n=34)</td>
<td>Rates of graft survival and acute rejection similar to other protocols</td>
<td></td>
</tr>
<tr>
<td>FDCC subgroup study</td>
<td>Compare fixed dose versus concentration controlled mycophenolate dosing</td>
<td>Cyclosporine A, mycophenolate, steroids (n=62)</td>
<td>Younger children (&lt; 6) had numerically higher rates of leucopenia and diarrhea, but overall well tolerated</td>
<td></td>
</tr>
<tr>
<td>PC01?</td>
<td>Steroid Avoidance and CNI withdrawal</td>
<td>Campath Mycophenolate Tacrolimus to Sirolimus (n=35)</td>
<td>Generally successful with excellent function and histology</td>
<td></td>
</tr>
<tr>
<td>CTOTC-01</td>
<td>Monotherapy</td>
<td>Mycophenolate withdrawal to Sirolimus Monotherapy</td>
<td>In progress (4/7)</td>
<td></td>
</tr>
<tr>
<td>CCTPT-02?</td>
<td>Long-term impact of donor specific anti-HLA antibody development</td>
<td>Any</td>
<td>In progress (5/118)</td>
<td></td>
</tr>
</tbody>
</table>
Pediatric Renal Transplantation Induction Antibody Use

NAPRTCS, 2006
CCTPT IN-01 STUDY

- Randomized, controlled trial
- 287 subjects enrolled
- OKT3 Induction vs IV Cyclosporine
- Maintenance Immunosuppression
  - Cyclosporine
  - Azathioprine/MMF
  - Corticosteroids
CCTPT IN-01 STUDY

TIME TO FIRST ARE

GRAFT SURVIVAL

Percent

Years

Percent

Years

CSA Induction
OKT3 Induction

CSA Induction
OKT3 Induction
Pediatric Renal Transplant
Immunosuppression @ 30 Days

NAPRTCS, 2006
Research proposals

• Decrease or eliminate toxic medications
  – Diminish toxic effects without adversely affecting outcome

• Immunologic monitoring

• Mechanistic studies

• Is there something we can do for adolescents?
Which immunosuppressives should we eliminate?

• Corticosteroids:
  – Cushingoid appearance, obesity
  – Hypertension, Hyperlipidemia
  – Steroid diabetes
  – Aseptic necrosis, Osteoporosis
  – Growth failure
Which immunosuppressives should we eliminate?

• Calcineurin inhibitors
  – NEPHROTOXICITY
  – Neurotoxicity, hepatotoxicity
  – Hypertension, hyperlipidemia
  – Cosmetic issues
  – Steroid diabetes
  – ?PTLD risk
Recent Studies

• NAPRTCS/CCTPT Steroid Withdrawal (SW-01)
• NAPRTCS/CCTPT Calcineurin Inhibitor Avoidance (CN-01)
• CCTPT Steroid Avoidance Protocol (SNS-01)
• NAPRTCS/CCTPT Campath Induction (PC-01)
Randomized, controlled, double-blind trial of steroid withdrawal

Primary LD or CD recipients

Initial Immunosuppression: αIL-2r, Pred, Rapa, FK/CyA for 6 months

Biopsy at 6 months: Randomize if no rejection

Randomize to Taper to 0 vs Daily Low Dose
• 274 of 300 Patients enrolled by August, 2004

• Enrollment closed August, 2004 for PTLD rate
SW-01 Results

• 274 Subjects enrolled
• Acute rejection rate 13.8%
• Subjects who had steroids withdrawn had:
  – *Lower* rate of late acute rejection
  – *Same* 3-year patient and graft survival
  – *Possibly better* growth rate

Than the control group
PTLD in SW-01

- Rate was:
  - 12% in 0-5 year olds
  - 7% in 6-10 year olds
  - 3% in 11-17 year olds
  - 0% in >17 year olds

- Prophylaxis and enhanced observation were not prescribed by original protocol

- Most patients treated by decreasing immunosuppression alone
Our conclusions from SW-01

- This was first controlled trials demonstrating that steroid withdrawal is possible in children
- We have left withdrawal group on CNI + Rapa and have weaned control group off of steroids
- IL2r antibody, steroids, CNI and Rapamycin are too immunosuppressive in at-risk population
- Pediatric immunosuppression trials must include strategies for PTLD avoidance
CN-01 Study Design

- Single-arm pilot trial of calcineurin inhibitor avoidance
- 35 pediatric living donor kidney transplants
- 4 Centers
- CCTPT oversight
- Primary objective: To determine if rejection risk is sufficiently low to permit use of this protocol in children: Acute rejection rate at 6 months
CN-01 Clinical Protocol

- Eligibility: 1st or 2nd Living donor transplant
- Immunosuppression
  - Daclizumab 5 doses
  - Sirolimus to target levels (25 -> 15 ng/ml), dosage bid
  - MMF at 1,200 mg/M^2/day, divided bid
  - Prednisone tapered to QOD dose
- Biopsies at 0, 3, 6, 12 months
- Mechanistic studies
Acute Rejections

- 11/33 subjects had 14 ARE
  - 11 acute cellular
  - 2 acute/chronic
  - 1 acute cellular/vascular

- 14 treated with pulse steroids
  - 3 received antibody Rx
  - 2 converted to FK

---

**Time to First Rejection**

- Percent: 0.00, 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00
- Years: 0.00, 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00
Many of the infiltrates were not associated with tubulitis or vasculitis and resolved spontaneously.
Measured GFR

Gross (ml/min)

Normalized (ml/min/1.73m²)
CN-01 Summary

- This calcineurin inhibitor avoidance protocol resulted in excellent short-term patient and graft survival and GFR.
- The acute rejection rate was high
  - More robust induction might be beneficial.
- Complications included some cases of lymphocele and poor wound healing. Also, GI disturbance was frequent.
Steroid No Steroid (SNS): Controlled trial to test Stanford Steroid Avoidance Pilot

- 120 Primary LD and CD primary transplants
- Randomized at entry
- Group 1: αIL-2r x 6 months, FK, MMF
- Group 2: αIL-2r x 2 months, FK, MMF, low dose Pred
- Outcomes: Rejection, growth, etc
- 1-2 year
CCTPT: SNS-01

• Enrollment closed 8/2006
  – 130 recipients from 12 sites
• Results
• Acute rejection rate is ~20% in experimental and control groups
  – Patient and graft survival is excellent
  – Growth rate not yet improved in experimental group
CCTPT: Campath Induction PC-01

- 35 patients in a pilot trial from 4 sites
- Campath 1-H induction (2 doses)
- MMF and FK for 2-3 months
- Convert FK to Rapa after 2-3 months
- Steroid Avoidance and CNI withdrawal
- Protocol biopsies and mechanistic studies
PC-01 Results

- 35 Subjects enrolled
  - 1-year follow-up
    - 6 Acute Rejections (17%)
      - 4 with Clinical Acute Rejection
      - 2 with Sub-clinical Acute Rejection
    - 2 Graft losses: Recurrent FSGS and non-adherence
    - No deaths, no serious infections
    - No PTLD
    - Most important complication is leukopenia
CCTPT: Campath Induction
PC-01
T Cell Recovery After Alemtuzumab in Children

Figure 2.

CD4+ cells
- 35% recovery

CD8+ cells
- 60% recovery

CD4+ naive vs. memory cells
- 45% recovery
- 33% recovery

CD8+ naive vs. memory cells
- 64% recovery
- 78% recovery

CD4+ effector vs. central memory cells
- 44% recovery
- 24% recovery

CD8+ effector vs. central memory cells
- 73% recovery
- 69% recovery
Percent of circulating Tregs in peripheral blood

![Graph showing percent of circulating Tregs over months for CD4+ and CD25+FOXP3+ cells.](image)
## Comparison between Pediatric and Adult Data

<table>
<thead>
<tr>
<th>Pediatric</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Profound depletion of both CD4+/CD8+ T cells.</td>
<td>• Profound depletion of both CD4+/CD8+ T cells.</td>
</tr>
<tr>
<td>• CD4+ T cells recovered at ~18 months post-tx.</td>
<td>• CD4+ T cells still reduced at 15 months post-tx.</td>
</tr>
<tr>
<td>• CD8+ T cells return to baseline at 6 months.</td>
<td>• CD8+ T cells return to baseline at 6 months.</td>
</tr>
<tr>
<td>* Depletion of both memory and naïve T cells with quicker recovery of naïve T cells.</td>
<td>* CD4+ Memory T cell (mostly Tcm) spared in comparison to naïve counterpart.</td>
</tr>
<tr>
<td>* Memory T cells spared were mostly effector (Tem) in comparison to central memory (Tcm).</td>
<td></td>
</tr>
</tbody>
</table>

Wood, K. *Transplantation* 2006  
Extension of PC-01: CTOTC-01

• 10 subjects from PC-01
  – Stable at 2 years post transplant
  – No ARE
  – < 5% anti-HLA antibody
  – Normal GFR
  – No CAN

• Taper MMF gradually to monotherapy with Sirolimus
CTOT/CCTPT-02

- Combined adult/pediatric study to measure incidence of anti-HLA antibody production in unsensitized kidney transplant recipients
- 18 centers involved
- 694 subjects enrolled, 653 evaluated
- 79 subjects developed anti-HLA antibodies
Pediatric Subjects in CTOT/CCTPT-02

Pediatric 98

Adult 555
De Novo anti-HLA Antibody
HLA Conversion by Class

n = 98

Negative (n = 74)

Class I only (n = 4) 17%

Both (n = 4) 17%

Class II only (n = 16) 66%
Induction Agent and HLA Ab Production

Conversion-free Survival

Log-Rank p = 0.001

Subjects at Risk

<table>
<thead>
<tr>
<th></th>
<th>ATG</th>
<th>Campath</th>
<th>IL-2RI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td>28</td>
<td>3</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>3</td>
<td>51</td>
</tr>
<tr>
<td>12</td>
<td>23</td>
<td>3</td>
<td>50</td>
</tr>
<tr>
<td>18</td>
<td>15</td>
<td>3</td>
<td>41</td>
</tr>
<tr>
<td>24</td>
<td>11</td>
<td>3</td>
<td>34</td>
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<td>30</td>
<td>7</td>
<td>2</td>
<td>28</td>
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<td>36</td>
<td>2</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>42</td>
<td>0</td>
<td>0</td>
<td>2</td>
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</table>
## Induction and Anti-HLA Antibody Production

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio (95% CI)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.93 (0.80-1.07)</td>
<td>0.288</td>
</tr>
<tr>
<td>No IL-2 RI vs. IL-2 RI</td>
<td>5.74 (1.97-16.72)</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Acute Rejection and HLA Ab Production

Conversion-free Survival

Subjects at Risk

<table>
<thead>
<tr>
<th>No rejection</th>
<th>78</th>
<th>72</th>
<th>71</th>
<th>56</th>
<th>47</th>
<th>38</th>
<th>10</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rejection</td>
<td>20</td>
<td>19</td>
<td>16</td>
<td>12</td>
<td>8</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Log-Rank p = 0.002
## Acute Rejection and HLA antibody

<table>
<thead>
<tr>
<th></th>
<th>HLA Ab Positive (n=24)</th>
<th>HLA Ab Negative (n=74)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute rejection, n(%)</td>
<td>10 (42%)</td>
<td>10 (14%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Cellular, n(%)</td>
<td>9 (38%)</td>
<td>10 (14%)</td>
<td>0.016</td>
</tr>
<tr>
<td>Antibody-mediated, n(%)</td>
<td>4 (17%)</td>
<td>0 (0%)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

### Acute Rejection among HLA Ab positives (n=10)

<table>
<thead>
<tr>
<th></th>
<th>Acute rejection among HLA Ab positives (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rejection <strong>before</strong> Ab conversion</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Time before conversion (mo)</td>
<td>-6.3 ± 2.3</td>
</tr>
<tr>
<td>Rejection <strong>after</strong> Ab conversion</td>
<td>8 (80%)</td>
</tr>
<tr>
<td>Time after conversion (mo)</td>
<td>+4.0 ± 4.3</td>
</tr>
</tbody>
</table>
Minimization the Pediatric Organ Transplant Recipient

- Infants and young children can have the best outcome of kidney transplantation of any age group
- Infants and young children undergoing kidney transplantation have unique conditions
- Infants and young children may be the ideal candidates for minimization protocols
- Monotherapy with Tacrolimus or Sirolimus
What Have We Accomplished?

- Multiple studies have accomplished steroid avoidance or withdrawal in pediatric kidney transplantation (SW-01, SNS-01, TWIST, Pittsburgh monotherapy, PC-01)
- Some pediatric kidney transplant recipients can be withdrawn from CNIs and perhaps reach monotherapy
- Prior to CCTPT young children had the worst outcomes of all kidney transplant recipients; now they have the best
Conclusions

• Successes during past two decades
  – Overall early graft survival benefit
  – Marked improvement in success in young children
  – Reduction in ARE
  – Growth delay overall is not as severe
  – Steroid avoidance is possible
• Remaining challenges
  – Opportunistic viral infections
  – CNI/Steroid toxicities
  – CAN
  – Adherence to multi-drug protocols
  – Cost of chronic immunosuppression
  – Recurrent disease
  – Racial differences in outcome
What Are the Most Important Barriers to Successful Organ Transplantation in 2013?
What Are Current Barriers to Success of Organ Transplants

• Children are at high risk for chronic viral infections, especially EBV

• Chronic Graft Loss continues and results in need for re-transplantation
  – CAN has not been defined or treated

• Recurrent disease has not been addressed

• Adolescents currently lose transplants at accelerated rate: Biology vs Adherence?

• African Americans have unacceptably high rates of graft loss and we don’t know why
Viral Infections

• Viruses and treatments:
  – CMV: Valganciclovir prohyllaxis and treatment
  – EBV: ? Valganciclovir, surveillance, IS modulation
  – Polyomavirus: Surveillance, IS modulation, ? meds

• Pediatric-specific problem of Donor +/- Recipient -
Chronic Allograft Nephropathy (CAN) is the major limiting factor in pediatric kidney transplantation.

Etiology of CAN:
- Immunologic
- Non-Immunologic
Pediatric Kidney Transplant Graft Survival by Source and Era

EXHIBIT 5.2

<table>
<thead>
<tr>
<th>Source</th>
<th>Year 1</th>
<th>Year 3</th>
<th>Year 5</th>
<th>Year 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Living Donor (1987-1995)</td>
<td>0.59</td>
<td>0.76</td>
<td>0.89</td>
<td>1.05</td>
</tr>
<tr>
<td>Living Donor (1996-2010)</td>
<td>0.37</td>
<td>0.56</td>
<td>0.81</td>
<td>1.13</td>
</tr>
<tr>
<td>Deceased Donor (1987-1995)</td>
<td>0.81</td>
<td>0.96</td>
<td>1.06</td>
<td>1.15</td>
</tr>
<tr>
<td>Deceased Donor (1996-2010)</td>
<td>0.50</td>
<td>0.88</td>
<td>1.15</td>
<td>1.71</td>
</tr>
</tbody>
</table>

NAPRTCS 2010
Immunologic Causes of CAN

• Insufficient Immunosuppression
  – Chronic Immunosuppression is inadequate
  – Late acute rejections
  – Race
  – Immunosuppression adherence
  – ?Pubertal changes
CAN and Race

DECEASED DONOR

Race
- Black
- Non-Black

Mean Calculated Creatinine Clearance

Percent Graft Survival

50 60 70 80 90 100

NAPRTCS 2007
Pediatric Kidney Graft Survival by Recipient Race

EXHIBIT 5.4
GRAFT SURVIVAL BY SELECTED CHARACTERISTICS

Recipient Age
- 0-1 years
- 2-5 years
- 6-12 years
- >12 years

% Graft Survival
- 30
- 40
- 50
- 60
- 70
- 80
- 90
- 100

Years from Transplant
- 0
- 1
- 2
- 3
- 4
- 5
- 6
- 7

Induction Antibody
- No Induction
- Induction

% Graft Survival
- 30
- 40
- 50
- 60
- 70
- 80
- 90
- 100

Years from Transplant
- 0
- 1
- 2
- 3
- 4
- 5
- 6
- 7

Recipient Race
- White
- Black
- Hispanic
- Other

% Graft Survival
- 30
- 40
- 50
- 60
- 70
- 80
- 90
- 100

Years from Transplant
- 0
- 1
- 2
- 3
- 4
- 5
- 6
- 7

Transfusion History
- 0 Transfusions
- 1-5 Transfusions
- >5 Transfusions

% Graft Survival
- 30
- 40
- 50
- 60
- 70
- 80
- 90
- 100

Years from Transplant
- 0
- 1
- 2
- 3
- 4
- 5
- 6
- 7

NAPRTCS 2010
Pediatric Kidney Transplant Graft Survival by Recipient Age

Recipient Age

% Graft Survival

Years from Transplant

0-1 years

2-5 years

6-12 years

>12 years

0 Transfusions

1-5 Transfusions

>5 Transfusions

No Induction

Induction

White

Black

Hispanic

Other

NAPRTCS 2010
Chronic Allograft Nephropathy

- Calcineurin Inhibitor Toxicity
Medication Adherence

• Rejection is an inevitable consequence of failure of adherence to immunosuppression protocol

• Solution to failure of IS adherence
  – Change adolescent behavior
  – Change immunosuppression delivery
  – Promise of belatacept
Recurrent Disease after Kidney Transplantation

- Atypical HUS: Eculizumab or Liver/Kidney transplantation
- Oxalosis: Liver/Kidney transplantation
- FSGS: ???? Current approaches do not address pathophysiology
- Diabetes: Islet cell or Kidney/Pancreas transplantation
Conclusions

• Kidney Transplantation is currently the best treatment for children with ESRD and is likely to remain so for the foreseeable future
• Outcomes in kidney transplantation are continually improving
• Long-term consequences of kidney transplantation need increased attention
Conclusions

• Resolution of current barriers to successful transplantation require better understanding of their etiologies
• Application of new treatments requires careful pediatric trials
• Children are naïve to many viruses
• Children are more easily sensitized by transplantation than adults