Optimizing Long-Term Outcomes with Kidney Anti-rejection Therapies
Acute and Chronic Rejection

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Absent Tolerance or Twins:

All Transplants Reject...........

What matters to recipients is how fast......
Prevalence of Allograft Failure/Rejection
Causes of Renal Graft Loss After First Year (130,000 transplants - 16,000 failures)

- Death: 31%
- Chronic Allograft Nephropathy IF/TA: 39%
- Other: 18%
- Acute Rejection: 7%
- Non-Compliance: 3%
- Recurrence: 2%
Chronic Allograft Nephropathy
...the persistent inexorable decline in transplant renal function with time...

**Antigen Dependent**
- Acute Rejection
- Re-Transplants
- HLA antibodies
- Non-HLA antibodies

**Antigen Independent**
- Ischemia/Reperfusion
- Nephrons: age, gender, size
- Nephrotoxic Drugs
- Hypertension
- Hyperlipidemia
- CMV/other infections
- Hyperfiltration?
Clinical Manifestations of Acute Renal Allograft Rejection

- **Local**
  - Pain and swelling over graft, redness

- **Systemic**
  - Fever and Chills
  - Lethargy
  - Decreased urine output
  - Edema and SOB
  - Hypertension

- **Metabolic**
  - Increased serum creatinine, BUN, potassium
  - Acidosis
  - Proteinuria
<table>
<thead>
<tr>
<th>Agents</th>
<th>No Ab</th>
<th>Induction Ab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aza+Pred</td>
<td>80</td>
<td>50-60</td>
</tr>
<tr>
<td>CsA+Pred</td>
<td>50-60</td>
<td></td>
</tr>
<tr>
<td>FK+Pred</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>MMF+Pred</td>
<td></td>
<td>53</td>
</tr>
<tr>
<td>CsA+Aza+Pred</td>
<td>50</td>
<td>45</td>
</tr>
<tr>
<td>CsA+MMF+Pred</td>
<td>40</td>
<td>10-20</td>
</tr>
<tr>
<td>FK+MMF+Pred</td>
<td>35</td>
<td>10-20</td>
</tr>
</tbody>
</table>
Causes of Failure/Rejection
# Types of Renal Allograft Rejection

<table>
<thead>
<tr>
<th></th>
<th><strong>Hyperacute</strong></th>
<th><strong>Acute</strong></th>
<th><strong>Chronic</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time after transplant</strong></td>
<td>Minutes to Hours</td>
<td>Days to Years</td>
<td>Months to Years</td>
</tr>
<tr>
<td><strong>Mediating Factors</strong></td>
<td>Preformed anti-HLA or ABO antibodies: Class I or II</td>
<td>Cellular and humoral Immunity</td>
<td>Antigen dependent Antigen independent</td>
</tr>
<tr>
<td><strong>Sequelae</strong></td>
<td>Intravascular Coagulation</td>
<td>Tissue Destruction Tubular injury</td>
<td>Obliterative Graft Fibrosis</td>
</tr>
<tr>
<td><strong>Prevention/Therapy</strong></td>
<td>ABO typing and lymphocyte crossmatching</td>
<td>Immunosuppression Induction therapy Maintenance therapy</td>
<td>Prevent AcR Control Secondary Risk Factors</td>
</tr>
</tbody>
</table>
Normal Kidney
Hyperacute Rejection
Hyperacute Rejection: hemorrhagic necrosis
Hyperacute Rejection: platelet thrombi
HLA Antibodies Predict Kidney Graft Failure
2278 patients in 23 centers

Acute Cellular Rejection
Resolved Acute Rejection: Post Steroids
T cell Depletion Alone Does Not Produce Tolerance

- Seven unsensitized LD recipients: No maintenance therapy
- C-1-H .3mg/kg plus iv MP 250-500mg- 3 doses pretransplant
- All seven with clinical rejection (↑SCr) day 14-28 (4/6 Banff I-II)
- CD3,4,or 8 Pos T cells absent in periphery during these AcR
- Diminished expression of T cell transcripts during AcR

Return of monocytes predate return of lymphocytes between weeks 2-3

Kirk, et al. Transplantation 2003; 76:120
The Process of Rejection –
T Cell Trafficking
BANFF Criteria: Revised 2005

1. Normal
2. Antibody Mediated Rejection-DSA identified
   1. I. ATN-like; C4d+ minimal inflammation
   2. II. Capillary margination and/or thrombosis, C4d+
   3. III. Arterial C4d+
   4. Chronic active antibody mediated rejection C4d+
3. Borderline changes-suspicious for acute T cell mediated rejection
4. T cell Mediated Rejection
   – Acute (i, t, v)
   – Ia inflammation >25% parenchyma (i2 or i3); moderate tubulitis t2
   – Ib inflammation >25% parenchyma (i2 or i3); severe tubulitis t3
   – IIa cases with intimal arteritis (v1)
   – IIb cases with severe intimal arteritis (v2)
   – III transmural arteritis; fibrinoid changes; necrosis smooth muscle
   – Chronic rejection (cv, cg)
   – arteriopathy-intimal fibrosis with mononuclear glomerulopathy-double contours GBM
BANFF Criteria: Revised 2005

5. Interstitial Fibrosis and Tubular Atrophy (TAIF) without evidence of specific etiology
   - Grade I: mild TAIF < 25% of cortical area
   - Grade II: moderate TAIF 26-50% of cortical area
   - Grade III: TAIF >50% or cortical area
   - May include non-specific vascular and glomerular sclerosis, graded by TAIF

6. Other changes not rejection, acute or chronic
   - drug toxicity: CNI drugs
   - recurrent disease
   - viral infection: polyoma, cmv etc.
   - bacterial infection
   - severe hypertension
Time Course of Failure/Rejection
The Fate of Renal Allografts - Immunosuppression

- Induction Treatment of Rejection
  - Steroids
  - Anti-lymphocyte Agents
- Maintenance

Scr mg/dl

Time

Chronic Rejection
Transplant Kidney: Day 0
Transplant Kidney: Chronic Allograft Nephropathy
# The Progression of Alloimmune Injury

<table>
<thead>
<tr>
<th>Week 2</th>
<th>Isografts</th>
<th>Allografts C57BL and Balb/c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>Acute inflammation with edema, vasculitis, and tubulitis</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>Progressive acute inflammation with vasculitis and tubulitis</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>Extensive fibrosis, tubular atrophy, chronic inflammatory cell infiltrates, arteriosclerosis, and glomerulosclerosis</td>
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</tbody>
</table>

Cheng et al AJT 2006; 6:2292
# Chronic Immune Injury of Renal Allografts

## T-Cell Mediated (Cellular) Rejection

<table>
<thead>
<tr>
<th>Targets</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>interstitium</td>
<td>fibrosis</td>
</tr>
<tr>
<td>tubular epithelium</td>
<td>atrophy, mesenchymal transition</td>
</tr>
<tr>
<td>arterial intima</td>
<td>fibrous intimal thickening</td>
</tr>
</tbody>
</table>

## B-Cell Mediated (Humoral) Rejection

<table>
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<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>capillary endothelium</td>
<td>complement activation</td>
</tr>
<tr>
<td>(peri-tubular)</td>
<td>C4d and PMN margination</td>
</tr>
<tr>
<td>glomeruli</td>
<td>double contours</td>
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</tbody>
</table>
Summary

• Acute and chronic rejection are the consequences of different HLA antigens on the donor and recipient.
  – the incidence of acute rejection episodes has diminished.
  – the incidence of chronic rejection may be increasing.

• The changes that occur in kidney grafts over time are due to both antigen dependent and antigen independent mechanisms.

• Histologic assessment of kidney grafts is the most accurate way to diagnose acute and/or chronic rejection, and to rule out other causes of renal dysfunction.

• Most rejection episodes are due to both cellular and humoral immune activation; detection of donor specific antibody before or after the transplant correlate with diminished graft outcome.