Is it Rejection?
Work Up and Initial Management of AKI in the Transplant Patient

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Outline

• Defining AKI in the kidney transplant recipient

• Betting the odds: is it rejection?

• If not rejection, then what is it?

• Evaluation of AKI in kidney transplant recipients

• Treatment
## Defining AKI

### In Native Kidneys:

<table>
<thead>
<tr>
<th>Risk</th>
<th>GFR criteria</th>
<th>Urine output criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injury</td>
<td>Increased SCreat x1.5 or GFR decrease &gt;25 percent</td>
<td>UO &lt;.5 mL/kg/h x 6 hr</td>
</tr>
<tr>
<td>Injury</td>
<td>Increased SCreat x2 or GFR decrease &gt;50 percent</td>
<td>UO &lt;.5 mL/kg/h x 12 hr</td>
</tr>
<tr>
<td>Failure</td>
<td>Increase SCreat x3 GFR decrease 75 percent OR SCreat ≥4 mg/dL Acute rise ≥0.5 mg/dL</td>
<td>UO &lt;.3 mL/kg/h x 24 hr or Anuria x 12 hrs</td>
</tr>
</tbody>
</table>

**Loss**
- Persistent ARF = complete loss of kidney function >4 weeks

**ESKD**
- End stage kidney disease (>3 months)

Typically an INPATIENT disease

### In Kidney Transplant:

**Immediate post-transplant:**
- The lack of increased urine output, or fall in serum creatinine, or the persistent need for dialysis following transplant (DGF)
  - Multitudes of definitions

**After a period of sustained function:**
- “a plasma creatinine that is stable at an elevated level above the previous baseline or is increasing”
  - General consensus: 20-30% decline in renal function (SCr)

Bellomo R et al, Crit Care 2004; 8: B204
## Acute Rejection: Definitions
(Adapted from Banff ‘07 Update)

<table>
<thead>
<tr>
<th>Antibody-Mediated:</th>
<th>T cell-Mediated:</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Rule of Three”</td>
<td>“Is it in the tubules/interstitum, or in the vessels?”</td>
</tr>
<tr>
<td>PMNs &gt;&gt; monocytes</td>
<td>Monocytes &gt;&gt; PMNs</td>
</tr>
<tr>
<td>• 1. C4d+</td>
<td>IA: &gt;25% interstitial infiltration, (4\text{-}10) mononuclear cells/tubular cross-section</td>
</tr>
<tr>
<td>• 2. Presence of antidonor antibodies (DSA)</td>
<td>IB: &gt;25% interstitial infiltration, (&gt;10) mononuclear cells/tubular cross-section</td>
</tr>
<tr>
<td>• 3. Acute tissue injury:</td>
<td>IIA: Intimal arteritis -mild-to-moderate (0-25% of lumenal area)</td>
</tr>
<tr>
<td>I. ATN-like (minimal inflammation)</td>
<td>IIB. Intimal arteritis -severe (&gt;25% of lumenal area)</td>
</tr>
<tr>
<td>II. Capillary and/or glomerular inflammation and/or thromboses</td>
<td>III. Transmural arteritis and/or fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocyte inflammation</td>
</tr>
<tr>
<td>III. Arterial inflammation</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>“Suspicious”</th>
<th>Borderline</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 of 3 above (C4d, DSA or injury)</td>
<td>10-25% interstitial infiltration, &lt;4 mononuclear cells/tubular cross-section</td>
</tr>
</tbody>
</table>
Prevalence of acute rejection - 2 eras

**SRTR 1995-2000:**
- Rate of AR fell from >40% to <20%
- After 1y, AR rates <3%

**SRTR 2000-2008:**
- 28,686 patients, 1st kidney transplant, on TAC/MMF/Pred +/- IL2ra
- 1y Acute rejection:
  - Overall: 12.3%
  - +IL2ra: 11.6%
  - No induction: 13.0%

Gralla and Wiseman, Transplantation 2010; 90: 639
Why do kidneys fail?

- Mayo Clinic: 1317 consecutive kidney transplants 1996-2006, 330 with graft loss at mean 50.3 mo f/u
  - 138 (43.4%) due to death
  - 39 (11.8%) due to 1° nonfunction
  - 153 (46.3%) due to graft failure:

- Conclusion: glomerular pathology most common cause of graft loss other than death, not acute rejection (or CNI toxicity)

Why do kidneys fail?

- Of “IF/TA”
  - 1/4 history of acute rejection

- Of “glomerular disease”
  - 40% “transplant glomerulopathy” (~HLA Ab?)

- ~1/3 of graft loss is linked to alloimmune/rejection response

Risk Factors for Acute Rejection

• Recipient Factors: sensitization, prior transplant, ethnicity, HLA mismatching

• Donor Factors: ECD (age, donor disease, cause of death), DCD

• Transplant Factors: immunosuppressive regimen
The Symphony Trial:
Acute rejection with various immunosuppressive regimens and the impact on outcomes

- 12-month randomized open-label multicenter trial of 1645 KTX
- 4 Treatment arms (IL2ra induction in “low” arms, MMF/Prednisone for all)
  - Standard: CSA 150-300 ng/ml x 3 months, then 100-200 ng/ml

At 12 months:

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Acute Rejection (%)</th>
<th>Graft Survival (%)</th>
<th>GFR (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSA “standard”</td>
<td>25.8</td>
<td>89.3</td>
<td>57.1</td>
</tr>
<tr>
<td>CSA (50-100 ng/ml)</td>
<td>24.0</td>
<td>93.1</td>
<td>59.4</td>
</tr>
<tr>
<td>TAC (3-7 ng/ml)</td>
<td>12.3*</td>
<td>94.2*</td>
<td>65.4*</td>
</tr>
<tr>
<td>SRL (4-8 ng/ml)</td>
<td>37.2</td>
<td>89.3</td>
<td>56.7</td>
</tr>
</tbody>
</table>

NEJM 2007; 357: 2562-75
Impact of Early Steroid Withdrawal on Incidence of Acute Rejection

- 5 year, randomized double blind trial
- Steroid withdrawal after 7 days vs steroid taper to 5 mg at 6 months
- 274 pts, TAC/MMF, induction agent determined by center practice

**Biopsy Proven Acute Rejection: KM Analysis**

- Acute rejection rate 5y:
  - Maintenance: 10.8%
  - Withdrawal: 17.8%
  - \( p = 0.042 \) (log rank)

**Bx Proven Acute Rejection: Induction Effect**

- Thymoglobulin:
  - CCS: 10.3%
  - CSWD: 14.4%
- IL-2R:
  - CCS: 11.9%
  - CSWD: 24.2%

- Steroid Withdrawal: Higher acute rejection rate, particularly with IL-2ra induction (24.2% vs 14.4%)
- Control group: similar acute rejection rates (10.3% vs 11.9%) with either induction agent

For “high risk” patients: IL2ra or Thymoglobulin to prevent acute rejection?

- 278 patients at elevated risk (PRA>20%, retransplant, high risk for DGF)
  - rATG x 4 vs. basiliximab x 2 and triple immunosuppression (CSA)

<table>
<thead>
<tr>
<th>Status @1 year:</th>
<th>rATG (n=141)</th>
<th>Basiliximab (n=137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute rejection</td>
<td>15.6%</td>
<td>25.5% (p=0.02)</td>
</tr>
<tr>
<td>AR requiring Ab therapy</td>
<td>1.4%</td>
<td>8.0% (P=0.005)</td>
</tr>
</tbody>
</table>

- 227 patients at elevated risk (PRA>30%, retransplant)
  - rATG x 8 vs. daclizumab x 5 and triple immunosuppression (TAC)

<table>
<thead>
<tr>
<th>Status @1 year:</th>
<th>rATG (n=113)</th>
<th>Daclizumab (n=114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute rejection</td>
<td>15.0%</td>
<td>27.2% (p=0.016)</td>
</tr>
<tr>
<td>AR requiring Ab therapy</td>
<td>2.7%</td>
<td>14.9% (P=0.002)</td>
</tr>
</tbody>
</table>

- Thymoglobulin more effective in preventing acute rejection in “high risk” patients

Brennan DC et al, NEJM 2006; 355: 1967
Noel C et al, JASN 2009; 20: 1385
Incidence of acute antibody-mediated rejection: pretransplant DSA vs no DSA

- 334 patients (CDC negative crossmatch)
- 67 were retrospectively determined to have preformed donor-specific antibody by flow cytometry
- **No desensitization or depleting Ab induction**

**AMR in 55% of those with DSA (but 45% did not!)**

**Incidence of AMR in absence of DSA: 6%**
Defining risk of acute rejection by ethnicity: still valid?

2000-2008: Acute Rejection in 23,240 1st tx recips, 0% PRA, on TAC/MMF/Pred

<table>
<thead>
<tr>
<th>Induction type</th>
<th>AA N=5704 (25%)</th>
<th>Non-AA N=17,540 (75%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>Acute Rejection</td>
</tr>
<tr>
<td>No induction</td>
<td>2011 (35%)</td>
<td>16.1%*</td>
</tr>
<tr>
<td>IL2ra rATG</td>
<td>1754 (31%)</td>
<td>12.7%*</td>
</tr>
<tr>
<td></td>
<td>1939 (34%)</td>
<td>13.5%*</td>
</tr>
</tbody>
</table>

*p<0.001

• AA recipients still have 37% increased risk of acute rejection (adjusted analysis)

Gralla and Wiseman, ATC 2011
The risk of acute rejection increases with donor age and decreases with recipient age

• Analysis of 108,118 recipients from 1995-2008:
  • Older donors may be more immunogenic
  • Younger recipients may be more immunoresponsive:
    – 28% AR in patients age 18-29
    – 14% AR in patients >70

Tullius S et al, Ann Surgery 2010; 252: 662
Summary:
Risk of rejection

- Acute rejection is 10-12% in the first year in “low risk” patients.
- Acute rejection is 15-30% with steroid withdrawal, CNI avoidance.
- Acute rejection is 15-30% in “high risk” patients.
- Antibody-mediated rejection: 5% in de novo setting, 35-50% in setting of known DSA without pretreatment.
Differential Diagnosis of AKI: Timing (post transplant) is everything

<table>
<thead>
<tr>
<th>Immediate (0-1 week)</th>
<th>Early (1-12 weeks)</th>
<th>Late (after 12 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prerenal: hypotension, volume depletion, thrombosis (renal a or v)</td>
<td>Prerenal: hypotension, volume depletion, <strong>CNI effects</strong></td>
<td>Prerenal: hypotension, volume depletion, CNI effects, renal artery stenosis</td>
</tr>
<tr>
<td>Postrenal: bladder dysfunction, BPH &gt; ureteral obstruction (leak, hematoma, lymphocoele, stricture)</td>
<td>Postrenal: <strong>ureteral obstruction</strong> (leak, hematoma, lymphocoele, stricture &gt; bladder dysfunction, BPH)</td>
<td>Postrenal: bladder dysfunction, BPH &gt; ureteral obstruction (stricture)</td>
</tr>
</tbody>
</table>
AKI in Kidney Transplant: Questions to ask

- **THE “OTHER” RIFLE CRITERIA!**
  - **R:** Is it Rejection?  
    - Examples: CNI
  - **I:** Is it Infection?  
    - Examples: pyelonephritis, BKV
  - **F:** Is it Flow?  
    - Examples: hypovolemia, thrombosis, obstruction, leak
  - **L:** Is it their Last disease (recurrence)?  
    - Examples: HUS, FSGS
  - **E:** Is Everything else stable?  
    - Examples: new meds, new/unstable systemic disease
## Recurrent glomerulonephritis following kidney transplant

<table>
<thead>
<tr>
<th>Disease</th>
<th>Approximate recurrence rate (%)</th>
<th>Graft loss due to recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membranous</td>
<td>10-30</td>
<td>Uncommon</td>
</tr>
<tr>
<td>FSGS</td>
<td>30–60</td>
<td>Common</td>
</tr>
<tr>
<td>HUS</td>
<td>20–50</td>
<td>Common</td>
</tr>
<tr>
<td>Type I MPGN</td>
<td>20–30</td>
<td>Common</td>
</tr>
<tr>
<td>Type II MPGN</td>
<td>80–100</td>
<td>Common</td>
</tr>
<tr>
<td>HSP</td>
<td>15–50</td>
<td>Uncommon</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>30-50</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Anti-GBM</td>
<td>Rare</td>
<td>Uncommon</td>
</tr>
<tr>
<td>ANCA-Associated</td>
<td>20%</td>
<td>Common</td>
</tr>
</tbody>
</table>

Adapted from Wiseman AC et al, Diseases of the Kidney (Schrier RW, Ed)
Questions regarding initial assessment of AKI in kidney transplant recipients

- Should I order a BKV PCR? (blood? urine?)
- Should I order an HLA screen for donor-specific antibody?
- Should I order an ultrasound?
- Should I biopsy?
## Initial Evaluation of AKI

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PE:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Focus on VS/hypovolemia, graft tenderness, fever</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lab Assessment:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• CNI monitoring</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Rule out infection (UA/micro)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Rule out GN (urine dipstick)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Imaging:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Rule out vascular compromise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Rule out urinary leak or obstruction</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Expanding the DDX:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• BKV blood PCR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• HLA for DSA (usually in conjunction with biopsy, rather in lieu of a biopsy)</td>
<td></td>
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</tbody>
</table>

Allograft biopsy

And of course, consider acute rejection!
Screening for BKV as a cause of AKI

Unexplained kidney dysfunction >0.3 mg/dl over baseline:
- Check blood BKV PCR as part of workup

Blood BKV PCR >10,000 copies/ml:
- Kidney biopsy for BKV presence and staging

No BKV identified:
- ("Presumptive BKVAN")
  - Decrease Immunosuppression

BKV and vascular rejection +/- C4d+:
- ("BKVAN and rejection")
  - IVIg, decrease immunosuppression, consider change to leflunomide

BKV +/- tubulitis:
- ("BKVAN, with/without features of cellular rejection")
  - Decrease immunosuppression, consider corticosteroids or IVIg for tubulitis (controversial)

Continue to follow BKV PCR every 2-4 weeks until negative
- Decrease immunosuppression as needed for elevations in BKV PCR titer
- Consider ancillary therapies (cidofovir, leflunomide, IVIg, fluoroquinolones)

Adapted from Wiseman AC, AJKD 2009; 54: 131
Prospective screening for \textit{de novo} HLA Ab: \\
\textit{Can this help identify patients at risk for acute rejection?}

246 patients transplanted 9/07 to 9/09

185 without de-novo DSA (AR: 9%)

65 developed de-novo DSA

9/07 to 9/09

*De-Novo DSA detected prospectively in 26.4%

13 in the setting of clinical suspicion (AKI) (AR: 69%)

52 by protocol screening at 1, 6, 12 months (AR: 19%)

- When identified in setting of AKI, \textit{de novo} DSA associated with high probability of acute rejection
- When identified in stable patients, \textit{de novo} DSA often is clinically insignificant
- Bottom line: DSA cannot “rule in” or “rule out” current/future rejection

Cooper JE et al, Transplantation 2011; 91:1103
Indications for biopsy:

- When other causes of graft dysfunction have been ruled out
- Subtherapeutic immunosuppression or nonadherence, with renal dysfunction
- Renal dysfunction in a “high risk” patient (prior desensitization, known DSA)
- Whenever considering T cell depleting therapy (antithymocyte globulin)
Indications for empiric treatment for acute rejection?

- A trial of IV corticosteroids may be considered…

- Only after ruling out other causes of acute graft dysfunction:
  - BKV, obstruction, infection, CNI nephrotoxicity, glomerulonephritis, donor-specific antibody

- AND

- Only when biopsy is considered unsafe
  - Anticoagulation/bleeding risk, bowel overlying kidney
Acute rejection - Treatment

Steroids vs depleting Ab for acute rejection?

• Meta-analysis of 14 trials (965 patients) compared therapies for first rejection episodes:
  
  • Ab was better than steroid in reversing rejection (RR 0.57) and preventing graft loss (death-censored RR 0.74)

“Most trials were small, incompletely reported, especially for potential harms, and did not define outcome measures adequately.”

TPE/IVIg/Rituximab vs. IVIg for antibody-mediated rejection

- 24 patients with Ab-mediated rejection: all received solumedrol 500 mg x 3
- N=12: IVIg 2g/kg q 3 weeks x 4
- N=12: TPE x 4d with IVIg 100 mg/kg following TPE; then IVIg 2g/kg x 4 and RTX 375 mg/m² weekly x 2

% reduction in DSA at 3 mo

% Graft Survival at 36 mo

Treatment of Rejection
“standard practice”/ “in one’s experience”

• Patient with AKI:
  – US, UA/cx not revealing
  – Send blood HLA for DSA, BKV PCR, empiric treatment with corticosteroids while performing/awaiting biopsy (stain for SV40 and C4d)

• Treatment guided by biopsy:
  • TCMR Ia, Ib,IIa:
    – assess response to pulse IV corticosteroids, if improvement then continue for total 3-5 d; if no improvement after 1-2 (?) doses then advance to rATG 1.5 mg/kg x 4-14 doses
  • TCMR IIb:
    – rATG 4-14 doses
  • AHR:
    – Corticosteroids (rATG?), plasmapheresis, IVIg; consider rituxan or bortezomib
Conclusions

• Acute rejection remains an important consideration in the transplant patient presenting with AKI

• Risk factors and timing from transplant may improve pre-test probability, but ultimately the individual in front of you requires individual assessment

• Treatment beyond a brief course of steroids (when appropriate) will require histological assessment