Desensitization in Kidney Transplant

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Organ Shortage

• Currently there are >90,000 patients on the kidney transplant waiting list

• July 2009-June 2010:
  – 16,679 transplants in the US
  – 34,762 patients added to waiting list
Number of sensitized patients on the waiting list is increasing

• Sensitized patients wait twice as long for kidneys:
  – Transplant rate for PRA > 10: 18%, and for PRA > 80: 5%.
  – Mean waiting time PRA < 10: 4yrs vs. PRA > 10: 8yrs.
Can we help?

Important questions in today’s era of sensitive detection methods and potent desensitization tools:
- Who needs to be desensitized?
- How should they be desensitized?
- Does it work?

The ongoing development of increasingly sensitive assays for HLA-Abs has made defining “sensitization” more complicated.
Who should be desensitized?

- Different antibody screening techniques are associated with varying degrees on sensitivity and specificity
  - CDC XM +: Highest risk for rejection
    Contraindicated without desensitization
    High risk without desensitization
  - DSA detected by SAB: ??
Solid Phase Assays: Too Sensitive?

• As crossmatch techniques have evolved from CDC -> FCXM -> SAB, sensitivity for detecting anti-HLA Abs has increased.

• As sensitivity increases, so does the risk of denying transplant due to clinically insignificant antibodies.

• Significance of pre-transplant DSA detected by SAB is unclear, recent reports show conflicting data.
Clinical Relevance of Pretransplant Donor-Directed Antibodies Detected by Single Antigen Beads in Highly Sensitized Renal Transplant Patients

Transplantation 2008;85: 1086–1090

- 34 highly sensitized (PRA >85%) transplant recipients 1989-2006, CDC(-), no FCXM done.
  - DSA by SAB detected retrospectively (historic or current sera) in 13/34. MFI cutoff not provided.
  - No induction. All immunosuppression CNI-based.

![Graphs showing rejection-free and graft survival](image-url)

DSA(-) 83%

DSA(+) 54%
Clinical Relevance of Pretransplant Donor-Specific HLA Antibodies Detected by Single-Antigen Flow-Beads

Amico et al. Transplantation 2009; 87: 1681–1688

- 334 consecutive low risk (PRA <20%) kidney recipients 1999-2004 tested retrospectively for pre-transplant DSA
  - CDC (-), no FCXM done.
  - No thymoglobulin induction. CNI-based immunosuppression in 80%, SRL-based in 20%.
  - MFI > 500 considered positive.

AMR and ACR

AMR
Clinical Relevance of Pretransplant Donor-Specific HLA Antibodies Detected by Single-Antigen Flow-Beads

![Graph showing death-censored allograft survival percentages over years post-transplant for different groups.

Table 2: Correlation of HLA-DSA characteristics and immunosuppression with the occurrence of AMR

<table>
<thead>
<tr>
<th>Variable</th>
<th>HLA-DSA and AMR (n=37)</th>
<th>HLA-DSA without AMR (n=30)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of DSA, median (range)</td>
<td>2 (1–5)</td>
<td>1 (1–5)</td>
<td>0.08</td>
</tr>
<tr>
<td>Cumulative strength of DSA (MFI)(^a), median (range)</td>
<td>7021 (524–34,929)</td>
<td>5890 (991–36,715)</td>
<td>0.58</td>
</tr>
<tr>
<td>Cumulative strength of DSA (SFI)(^a), median (range)</td>
<td>164,103 (15,426–746,127)</td>
<td>131,856 (27,699–772,320)</td>
<td>0.58</td>
</tr>
<tr>
<td>Class of DSA</td>
<td></td>
<td></td>
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<tr>
<td>Class I, n (%)</td>
<td>11 (30)</td>
<td>10 (33)</td>
<td>0.59</td>
</tr>
<tr>
<td>Class II, n (%)</td>
<td>16 (43)</td>
<td>14 (47)</td>
<td></td>
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<tr>
<td>Class I+II, n (%)</td>
<td>10 (27)</td>
<td>6 (20)</td>
<td></td>
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</table>
Pre-transplant DSA when CDC and FCXM are negative

- 121 kidney recipients (low-moderate risk?) 1999-2001 retrospectively tested for DSA by SAB
  - CDC (-), FCXM (-). SAB(+) if 1.5 x background.
  - DSA(+) 16, NDSA(+) 23, DSA(-) 83.

<table>
<thead>
<tr>
<th>TABLE 3. One- and 5-year outcomes</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>1-yr graft survival</td>
</tr>
<tr>
<td>DSA 86%</td>
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<tr>
<td>NDSA 91%</td>
</tr>
<tr>
<td>NAB 92%</td>
</tr>
<tr>
<td>P NS</td>
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<tr>
<td>1-yr median creatinine, µmol/L</td>
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<tr>
<td>(censored) 137</td>
</tr>
<tr>
<td>1-yr median creatinine, µmol/L</td>
</tr>
<tr>
<td>(censored) 164</td>
</tr>
<tr>
<td>5-yr graft survival (105 patients)</td>
</tr>
<tr>
<td>62%</td>
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<tr>
<td>79%</td>
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<tr>
<td>77%</td>
</tr>
<tr>
<td>5-yr median creatinine, µmol/L</td>
</tr>
<tr>
<td>(censored) 156</td>
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<tr>
<td>174</td>
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<tr>
<td>179</td>
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<tr>
<td>Acute Rejection</td>
</tr>
<tr>
<td>23%</td>
</tr>
<tr>
<td>25%</td>
</tr>
<tr>
<td>32%</td>
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<tr>
<td>NS</td>
</tr>
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Gupta et al. Transplantation 2008;85: 1200–1204
Why so much variability?

• Multiple factors account for the frustrating degree of variability in the literature:
  – Patient populations
  – Use and type of induction and maintenance immunosuppression
  – Differing histocompatibility lab techniques
    • Variable MFI cutoffs for calling DSA “present”
    • DP and DQ antibodies
    • Interpretation of multiple allele beads
  – Use of FCXM in decision process
• 45 patients transplanted with a historic B or T cell FCXM ‘04-’08 compared to 45 matched controls with negative historic FCXM. All with negative T-CDC XM.

• For study, all peak and current sera retested using SAB, MFI >500 (A, B, Cw, DR, DP, DQ). FCXM(+): MFI ratio between patient and control sera ≥ 1.2 for T cell, ≥ 2 for B cell.

• Induction with ILR-RA or Thymoglobulin, maintenance with CNI/MPA/pred. Current FCXM(+) patients received IVIG 2g/kg 3 times over first 6 weeks post-transplant.
Worse outcomes only when current FCXM and SAB assay are both positive

More rejection in FCXM+, DSA+

Lower eGFR in FCXM+, DSA+
How much is too much?

• Pre-transplant DSA appears to result in higher immunologic risk post-transplant, especially when the FCXM is positive as well.

• Strength of DSA resulting in poor outcomes has yet to be determined.
Living donor recipients: MFI=900

- Reithmuller et al., Transplantation 2010

  - 155 recipients of living donor kidneys with negative T-CDC XM retrospectively screened (current sera) with SAB. 34 identified with DSA at transplant (normalized MFI >500).
  - AB induction in 50%, IS= CNI/MPA/pred
  - AMR 35% in DSA(+) vs. 6% in DSA(-)
  - ROC curve analysis shows only class I DSA by SAB to be predictive of AMR

<table>
<thead>
<tr>
<th>DSA class I (MFI)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Accuracy (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥500</td>
<td>75</td>
<td>76</td>
<td>46</td>
<td>92</td>
<td>76</td>
<td>0.013</td>
</tr>
<tr>
<td>≥900</td>
<td>75</td>
<td>90</td>
<td>67</td>
<td>93</td>
<td>86</td>
<td>0.001</td>
</tr>
<tr>
<td>≥5200</td>
<td>50</td>
<td>100</td>
<td>100</td>
<td>88</td>
<td>89</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Deceased donor recipients: MFI=465

- Lefaucheur et al., JASN 2010
  - 402 consecutive deceased donor transplant recipients with negative T and B CDC XM. No FCXM. SAB on peak and current sera (MFI ≥ 300).
  - Induction = thymoglobulin. IS = CNI/MPA/steroids. Remote + CDC XM = IVIG at time of transplant.
  - 31% with DSA on historic sera, 19% with DSA on current sera.
  - AMR in 29/83 with historic DSA(+) vs. 3/319 with historic DSA(-).

<table>
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<tr>
<th>Table 2. RR for acute AMR according to the MFI of highest pregraft ranked DSA detected by Luminex (logistic regression)</th>
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<tbody>
<tr>
<td>DSA MFI(_{max}) class</td>
</tr>
<tr>
<td>--------------------------------</td>
</tr>
<tr>
<td>≤465</td>
</tr>
<tr>
<td>465 to 1500</td>
</tr>
<tr>
<td>1500 to 3000</td>
</tr>
<tr>
<td>3000 to 6000</td>
</tr>
<tr>
<td>&gt;6000</td>
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</tbody>
</table>
Summary

• Pre-transplant DSA without FCXM info appears to increase AMR risk (30-50%).
• Clinical importance of DSA in setting of negative FCXM is less clear.
• DSA MFI that correlates with poor outcomes is dependent on multiple variables and is yet to be defined.
Proposed algorithm for sensitized patients

Couzi et al., Transplantation 2011;91: 527–535

- Thymo induction
- IVIG if strong DSA (>6000?) and high risk
Which desensitization protocol should I use?

• How risky is the transplant? i.e. positive T cell CDC XM vs. low level DSA and negative FCXM
• Do patients get transplanted at a higher rate?
• Do patients experience rejection after kidney transplantation?
• Is the rejection treatable? What are the consequences for longer term graft survival?
Desensitization Options: common

- **Antibody Removal:**
  - Plasmapheresis (TPE) or immunoabsorption
  - TPE x 5 should remove ~90% of antibody
  - Invasive (vascular access needed)
  - Antibody levels return to baseline within weeks

- **Antibody Inhibition: IVIG**
  - FDA approved for post-transplant use
  - Numerous proposed pathways
    - HLA-Ab neutralization
    - Enhanced HLA-Ab clearance
    - Complement inhibition
    - B-cell apoptosis
    - EXPENSIVE: $8700 for 120g
Desensitization Options: Experimental

- Decrease Antibody Production
  - Rituximab: Anti-CD20. FDA approved for B-cell lymphoma: 375mg/m² weekly x 4 weeks. $4000/dose
  - Bortezomib: Velcade, proteosome inhibition (plasma cell inhibitor). FDA approved for multiple myeloma. 1.3mg/m² twice weekly for 2-8 weeks. $5500/cycle

- Complement Inhibition: Eculizumab
  - Humanized monoclonal Ab, anti-C5, prevents terminal complement activation. 900mg IV weekly for ? weeks
  - FDA approved for PNH, also good results in treatment of aHUS.
  - $$$$$! $10,000-$15,000 per dose.

- Lymphocyte Removal
  - Splenectomy. Reported use in ABO-incompatible transplant and treatment of acute refractory AMR. Last resort, permanent risk of encapsulating bacterial sepsis.
Hopkins protocol: TPE and low dose IVIG for living donor transplants

• Montgomery et al. described 4 patients with positive CDC XM treated with 2-10 sessions of TPE/IVIG (100mg/kg).
• All achieved negative CDC and FCXM prior to living donor transplant.

All 4 experienced AMR within 1 mo, all were successfully treated (TPE/IVIG) with functioning grafts at 1 yr.
• Used only for living donation.
Other attempts at Hopkins Protocol

• Schweitzer et al. (2000): 15 patients with living donors and +CDC XM.
  – TPE/IVIG (500mg/kg/week) qod for 2 weeks + tac/MPA/pred: 11/15 with neg CDC XM and transplanted. OKT3 induction x 10 days.
  – 4/11 (36%) with AMR, all with surviving grafts at 1 year (mean creatinine 1.6mg/dL).

• Haririan et al. (2009): 41 patients with positive FCXM to living donor
  – TPE/IVIG (100mg/kg) 3x/wk x 2wks. Tac/MPA started 2 weeks before transplant, pred added after. Induction with OKT3 or thymoglobulin x 7 days.
  – All achieved reduced FCXM channel shift, 20/41 remained positive at transplant
  – AMR in only 12% of patients. 5 yr graft survival 69% vs. 80% in matched controls. Actuarial graft ½ life 6.8 yrs.
Cedars-Sinai protocol: high dose IVIG for living or deceased donor transplant

- 97 patients with either +CDC XM to living donor (n=54), or PRA>50% on waiting list >5 yrs (n=43), underwent transplant after desensitization.
  - IVIG 2g/kg monthly until CDC XM negative, FCXM <200 channel shift. Recipients of deceased donor kidneys received extra 2g/kg IVIG at transplant.
  - Induction with IL2-RA (‘99-’03, n=58) or thymoglobulin (‘03-’05, n=39). Maintenance tac/MMF/pred
  - AMR = 22%. 10/20 AMR resulted in graft loss. 2yr graft survival 84% (ILR-RA) and 90% (thymo).
  - Transplant rates of 87% (67/77 sensitized patients successfully transplanted, 42 living donor, 25 cadaveric) described in other reports

Vo et al., AJT 2006; 6: 2384–2390
IVIG vs. Placebo for sensitized patients: NIH-IG02 trial


- 98 sensitized (PRA>50% x 3mo) patients from 12 centers randomized to receive IVIG or placebo, 2g/kg monthly x 4mo, again at 12 and 24 mo if not transplanted.
  - Overall transplant rate 35% IVIG, 20% control (p=ns)
  - Cadaveric transplant rate 31% IVIG vs. 12% control (p=.01)
  - Rejection in 9/17 IVIG transplants vs. 1/10 placebo
  - 2 yr graft survival similar (75-80%)
IVIG and Rituximab

- 20 patients with either high PRA (mean 77%) or DSA to living donor received IVIG 2g/kg (day 0 and 30) and rituximab 1g (day 7 and 22).
- Transplanted if T-CDC XM negative at 1:2 and/or FCXM with channel shift < 250. Campath induction, tac/MPA/pred maintenance.
- Results:
  - 16/20 (80%) transplanted (6/9 cadaveric donor, mean time to transplant 5 mo). 11/16 still with +FCXM at transplant.
  - Rejection in 50% (3/16 with AMR), 1 graft loss from rejection at 1yr.


Mean Channel Shift: 212 249 149
High DSA levels after desensitization increase AMR risk
Single dose IVIG alone: not enough for positive CDC crossmatch

- 61 patients with + T-CDC XM to living donor underwent 1 of 3 protocols, transplanted when T-CDC XM negative.

<table>
<thead>
<tr>
<th>Protocol</th>
<th>N = 61</th>
<th>Pre-conditioning therapy</th>
<th>Desensitization success</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP/IVIG/anti-CD20 from April 2000 to July 2003</td>
<td>32</td>
<td>PP/IVIG (100 mg/kg) daily, Rituximab 375 mg/m², Splenectomy 19/32 patients</td>
<td>27/32 (84%)</td>
</tr>
<tr>
<td>High-dose IVIG from August 2003 to July 2004</td>
<td>13</td>
<td>IVIG 2 gm/kg × 1 prior to Tx (3 gm/kg in 2 patients)</td>
<td>5/13 (36%)</td>
</tr>
<tr>
<td>PP/IVIG/anti-CD20/monitoring from August 2004 to May 2005</td>
<td>16 (2*)</td>
<td>PP/IVIG (100 mg/kg) daily, Rituximab 375 mg/m² × 1, Intensive post-transplant DSA monitoring</td>
<td>14/16 (88%)</td>
</tr>
</tbody>
</table>

*2 patients resistant to desensitization protocol, not transplanted.

Table 4: Humoral rejection rates

<table>
<thead>
<tr>
<th>Negative crossmatch at transplant</th>
<th>N</th>
<th>Humoral rejection</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-dose IVIG responders</td>
<td>5</td>
<td>4/5 (80%)</td>
</tr>
<tr>
<td>PP/IVIG/anti-CD20 (includes 3 IVIG nonresponders)</td>
<td>30</td>
<td>11/30 (37%)</td>
</tr>
<tr>
<td>PP/IVIG/monitoring</td>
<td>14</td>
<td>4/14 (29%)</td>
</tr>
</tbody>
</table>

Positive crossmatch at transplant

| High-dose IVIG, PP/IVIG/anti-CD20 nonresponders | 10 | 7/10 (70%) 5/10 allograft loss (50%) |

Stegall et al., AJT 2006; 6: 346–351
Single dose IVIG: also not enough for T-CDC(-), FCXM(+) crossmatch

- 35 patients with negative T-CDC and positive B-CDC and/or B or T-FCXM treated with IVIG (2g/kg at surgery) and thymoglobulin induction.
  - 4/12 early AMR episodes -> retrospective SAB analysis shows AMR only with strong DSA (MFI>6000)
  - Protocol changed to add TPE to those with strong DSA: 4-8 sessions pre-tx until MFI < 6000 (living donor) or 3-6 sessions post-tx (deceased donor).
  - AMR dropped from 44% to 7% in next 14 patients

New agents: Eculizumab

• Stegall et al. has reported (abstract) results of 16 patients with +B-FCXM with living donor and post-tx eculizumab weekly x 4, extended to 9 if DSA remained high, to 51 historic controls.
• Pre- and post-transplant TPE if FCXM channel shift >300. Thymoglobulin induction, tac/MPA/pred maintenance.
• AMR in 6% of eculizumab group vs. 40% of controls.
• However, 6/16 showed evidence of chronic AMR on protocol biopsy within 4 months, 4 of which had persistently elevated DSA.

Stegall et al., AJT 2010:10, pg 125 (abstract)
New agents: Bortezomib

• Ragavaiah et al. reported (abstract) the effect on donor specific plasma cells and sensitization in 18 patients treated either with TPE alone (n=9) or bortezomib + TPE (n=9).

• All had + B-FCXM, treatment success = <300 channel shift.

<table>
<thead>
<tr>
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<th>Reduced AlloPC</th>
<th>Desensitization Success</th>
<th>Transplanted</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE alone n=9</td>
<td>0% (0/5)</td>
<td>11% (1/9)</td>
<td>11% (1/9)</td>
</tr>
<tr>
<td>Bortezomib. Overall n=9</td>
<td>66% (6/9)*</td>
<td>66% (4/6)*</td>
<td>50% (3/6)</td>
</tr>
<tr>
<td>4 doses n=4</td>
<td>50% (2/4)</td>
<td>50% (2/4)</td>
<td>50% (2/4)</td>
</tr>
<tr>
<td>16 doses n=5</td>
<td>80% (4/5)</td>
<td>100% (2/2)**</td>
<td>50% (1/2)</td>
</tr>
</tbody>
</table>
Summary

• Pre-Transplant DSA: 20-50% increased risk of AMR
  – DSA strength resulting in increased risk is a moving target, reported as low as 100 MFI up to 6000 MFI
    • Until national/international standardization occurs, MFI thresholds should be evaluated by individual centers
  – For now, clinical decisions should take into account both SAB and FCXM data.
  – With negative FCXM: risk is likely small
    • Transplant with Thymoglobulin induction
  – With positive FCXM: risk is high (30-50%)
    • Desensitization
Summary

• Desensitization protocols have successfully increased transplant rates for sensitized patients, but are met with high rejection rates.
  • DSA(+), FCXM(-): Induction therapy +/- IVIG at transplant
  • DSA(+), FCXM (+): TPE/IVIG until XM(-) for living donor, high dose IVIG + post-tx TPE for deceased
  • T-CDC (+): High risk. TPE/IVIG/Rituximab for living donor
  • Long waitlist patients: Monthly high dose IVIG or IVIG/rituximab

• Long term outcomes are lacking, AMR does not necessarily lead to graft loss.
  – Expected graft survival of 6 yrs vs. 12 for low risk transplants is still 6 years without dialysis
Thank You
High risk recipients and Campath induction: MFI=100?

- 237 consecutive transplant recipients with negative T-CDC XM from deceased donors, retrospectively tested for DSA by SAB (detected in 67%). FCXM not done.

- Class II MFI ≥ 500 associated with decreased GFR at 1 year (47 vs. 54 cc/min); no association of class I DSA with GFR

- Class II MFI ≥ 1000 associated with worse graft survival up to 2 years (75% vs. 92%, p=.055) and anti-DR Abs specifically (54% vs. 87%).