Solid Organ Transplant

Lee R. Goldberg, MD, MPH, FACC
Associate Professor of Medicine
Medical Director, Heart Failure and Cardiac Transplant Program
University of Pennsylvania
Disclosures

- Thoratec – Consulting
- Medtronic – Consulting and research grants
- Novartis – Consulting
- Respircardia – Consulting and research grants
Introduction

- Apheresis (plasmapheresis) uses
  - Desensitization therapy – to expand donor pool or allow for use of “incompatible” donors
  - Intra-operatively – to prevent hyperacute rejection
  - Treat antibody mediated rejection post-transplant
  - Treat organ specific complications that are antibody mediated
Phases of Care

Plasmapheresis

Pre Transplant
- Desensitization
  - Expand Donor Pool
  - Reduce Wait Times
  - Decrease Wait List
  - Mortality

Transplant
- Desensitization
  - Avoid hyperacute rejection
- Intra-operative

Post Transplant
- Antibody Mediated Rejection
  - Treat Acute Rejection
  - ?Reduce Vasculopathy

Mortality
Techniques for detecting antibodies has changed significantly
More detection but unclear clinical significance
Desensitization

- Heart transplant recipients are most commonly sensitized through pregnancy, blood products and previous transplant
- Many heart transplant candidates have had prior cardiothoracic surgery and have received blood products
- The use of ventricular assist devices is increasing and VADs appear to increase sensitization directly as well as indirectly
Why are we “seeing” more sensitization?

• New techniques in the HLA lab have significantly increased the sensitivity of antibody testing

• More ventricular assist device placements
  – More blood products
  – VAD itself

• Number of sensitized patients listed has increased from 7.8% to 9% over the past decade
Fig. 2. PRA levels in VAD-supported vs unsupported cardiac transplant candidates. Patients who underwent VAD support before transplantation demonstrate an increase in 90th percentile (taller bar) and mean (the horizontal line within each bar) PRA levels when compared with non-VAD controls ($P < .0001$). Reprinted from J Heart Lung Transplant, volume 25, Joyce et al, Impact of left ventricular assist device (LVAD)-mediated humoral sensitization on post-transplant outcomes, pages 2054-9, copyright 2005, with permission from Elsevier.
## Distribution of PRA in VAD

### Table 1. Distribution of panel reactive antibody levels by class

<table>
<thead>
<tr>
<th>Class</th>
<th>0%</th>
<th>1%–10%</th>
<th>11%–25%</th>
<th>&gt;25%</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (N = 1544)</td>
<td>1038 (67.2%)</td>
<td>194 (12.6%)</td>
<td>94 (6.1%)</td>
<td>218 (14.1%)</td>
</tr>
<tr>
<td>II (N = 1324)</td>
<td>1078 (81.5%)</td>
<td>105 (7.9%)</td>
<td>48 (3.6%)</td>
<td>93 (7.0%)</td>
</tr>
<tr>
<td>Composite PRA</td>
<td>976 (63.3%)</td>
<td>212 (13.8%)</td>
<td>114 (7.4%)</td>
<td>240 (15.6%)</td>
</tr>
<tr>
<td>XVE (N = 673)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>437 (64.9%)</td>
<td>91 (13.5%)</td>
<td>46 (6.8%)</td>
<td>99 (14.7%)</td>
</tr>
<tr>
<td>II</td>
<td>424 (77.5%)</td>
<td>47 (8.6%)</td>
<td>25 (4.6%)</td>
<td>51 (9.3%)*</td>
</tr>
<tr>
<td>Composite PRA</td>
<td>410 (60.9%)</td>
<td>93 (13.8%)</td>
<td>57 (8.5%)</td>
<td>113 (16.8%)</td>
</tr>
<tr>
<td>HMII (N = 871)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>601 (69.0%)</td>
<td>103 (11.8%)</td>
<td>48 (5.5%)</td>
<td>119 (13.7%)</td>
</tr>
<tr>
<td>II</td>
<td>654 (84.2%)</td>
<td>58 (7.5%)</td>
<td>23 (3.0%)</td>
<td>42 (5.4%)*</td>
</tr>
<tr>
<td>Composite PRA</td>
<td>566 (65.1%)</td>
<td>119 (13.7%)</td>
<td>57 (6.6%)</td>
<td>127 (14.6%)</td>
</tr>
</tbody>
</table>

*By chi-square analysis, more patients with the XVE device were highly sensitized to PRA class II.

J Thorac Cardiovasc Surg 2011;142:1236-45
## Proposed Mechanisms of VAD Sensitization

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Elements with presumed involvement in the immune system dysfunction seen in LVAD recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cells</strong></td>
<td></td>
</tr>
<tr>
<td>Activated macrophages/monocytes (CD14&lt;sup&gt;+&lt;/sup&gt;, CD68&lt;sup&gt;+&lt;/sup&gt;, NFκB&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>Found on LVAD surface; stimulate T-lymphocyte activation via IL-2 receptor pathways</td>
</tr>
<tr>
<td>CD95(Fas)+ T lymphocytes</td>
<td>Found in circulation, on LVAD surface; in heightened activation state, prone to apoptosis, poor response to TCR-mediated activation</td>
</tr>
<tr>
<td>Hyperreactive B lymphocytes</td>
<td>Found in circulation; release anti-HLA class I and II IgG, antiphospholipid antibody</td>
</tr>
<tr>
<td><strong>Cytokines</strong></td>
<td></td>
</tr>
<tr>
<td>IL-2</td>
<td>Promotes T-cell activation, down-regulated by selective loss of T&lt;sub&gt;H1&lt;/sub&gt; T-cells</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>Promotes T-cell activation, down-regulated by selective loss of T&lt;sub&gt;H1&lt;/sub&gt; T-cells</td>
</tr>
<tr>
<td>IL-10</td>
<td>Stimulates B-cell hyperreactivity</td>
</tr>
<tr>
<td>sCD40L</td>
<td>Stimulates B-cell hyperreactivity</td>
</tr>
</tbody>
</table>

IFN indicates interferon; sCD40L, soluble CD40 ligand; TCR, T-cell receptor.
Impact

• Sensitization increases wait times and significantly increases risk of dying on the transplant list
  – Sensitized patients are transplanted at half the rate of non-sensitized patients
  – For Sensitized VAD – 205 days vs 124 days (non-sensitized) waiting time

• Sensitization increases risk of antibody mediated rejection, graft vasculopathy and decreases graft and recipient survival
Fig. 4. Effect of IgG anti-HLA class I antibodies on waiting time to cardiac transplantation. In 37 allosensitized VAD recipients (Δ), the presence of anti-HLA class I IgG increased waiting time to cardiac transplantation compared with 18 nonsensitized VAD recipients (□) ($P < .001$). Reprinted with permission from John et al [45].
Goals of Desensitization

- Maintain equitable access to organs
- Maximize short term outcomes
- Maximize long term outcomes
- Avoid exposure to additional antigens
Protocols

• Plasmapheresis is typically used and combined with immunomodulatory therapy to reduce antibody production by B-cells
  – IVIG
  – Rituximab
  – Cyclophosphamide
  – Bortezomib
## Desensitization Protocols

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP</td>
<td>(A, F) 1.5 volume exchanges</td>
<td>(A) 5 consecutive days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(B) 5 times, every other day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(C) 2–3 times/week until transplant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(D) 5 times, every other day, every 2–4 weeks</td>
</tr>
<tr>
<td>IVIG</td>
<td>(A, B) 2 g/kg IV divided over 2 days</td>
<td>(A) every 2–4 weeks</td>
</tr>
<tr>
<td></td>
<td>(C) 2–3 g/kg IV divided over 4 days</td>
<td>(D) every 2–4 weeks</td>
</tr>
<tr>
<td></td>
<td>(D) 0.1 mg/kg IV</td>
<td>(G) every 4 weeks</td>
</tr>
<tr>
<td></td>
<td>(E) 100 mg/kg IV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(F) 20 g (of 10% IVIG)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(G) 150 g (of 10% IVIG) divided over 3 rounds</td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td>(A) 1 g IV</td>
<td>(A) weekly × 4</td>
</tr>
<tr>
<td></td>
<td>(C) 375 mg/m²</td>
<td>(C) × 2 doses</td>
</tr>
<tr>
<td></td>
<td>(G) 500 mg</td>
<td>(G) every 2 weeks</td>
</tr>
<tr>
<td>Cyclophosphamide (used in the past)</td>
<td>(A) 1 mg/kg orally</td>
<td>(A) daily</td>
</tr>
<tr>
<td></td>
<td>(C) 0.5 μg/m²</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(D) 1 mg/kg orally</td>
<td></td>
</tr>
</tbody>
</table>

A = UCLA; B = Stanford University; C = University of Maryland; D = University of Toronto; E = University of Wisconsin; F = Loyola University Chicago; G = University of Berlin.

*Choices to consider as desensitization therapies include IVIG infusion, PP, either alone or combined, Rituximab, and in very selected cases, splenectomy.*
Protocol - CCF

- Plasmapheresis three times/week as a status 1A and continued until a significant drop in PRA is noted
- Plasmapheresis once weekly until transplant
- IVIG at 0.4–2 g/kg every 21 days infused after plasmapheresis.
- Plasmapheresis continued for 1 week or more post transplant depending on cross-match status.
Impact of IVIG and Plasmapheresis Alone

IVIG Alone

Plasmapheresis Alone

UCLA Study

Fig. 1. Individual reductions in mean panel reactive antibody levels of all 21 treated sensitized patients.

Treated with plasmapheresis, +/- IVIG, +/- Rituximab

Survival – Positive or Negative Crossmatch

1 Year Survival

VAD Patient Outcomes

**FIGURE 1.** Kaplan–Meier estimates of 1-year survival of patients with high versus low PRA class I activity (A) and patients with high versus low PRA class II activity (B). *PRA,* Panel reactive antibody.

*J Thorac Cardiovasc Surg* 2011;142:1236-45
Modern Outcomes

• All desensitized pre-transplant PRA >50%
  – Plasmapheresis alone – 12 patients
  – Plasmapheresis with IVIG – 4 patients
  – Plasmapheresis with IVIG and Rituximab – 5 patients

• Two control groups
  – Untreated with PRA < 10%
  – Untreated with PRA 11 to 48%

• All with negative prospective crossmatch
The long-term outcome of treated sensitized patients who undergo heart transplantation


Fig. 2. There were no significant differences in five-yr survival among the three study groups (p = 0.523).

No Difference in 5 Year Survival
No Difference in vasculopathy at 5 years
The long-term outcome of treated sensitized patients who undergo heart transplantation


Fig. 5. There were no significant differences in five-yr freedom from any treated infection among the three groups (p = 0.752).

No Difference in infections at 5 years
Fewer Rejections at 1 year

Fig. 6. First-yr freedom from any treated rejection was significantly lower in the treated group vs. the untreated group (p = 0.013) and the treated group vs. the control group (p < 0.001). Hemodynamic compromise rejection (HDC) was not significantly different among the three groups.
Special Considerations

- Bleeding
- Infection
- Worsening heart failure
- VAD patients – bleeding and clotting risks
  - Continuous flow devices
  - Blood pressure monitoring
  - Right ventricular failure
CTOT-13

- NIH Sponsored Network Clinical Trial
  - Evaluate the efficacy of desensitization with plasmapheresis and bortezomib
  - 80 patients status 1A or 1B (PRA 40 to 70%) randomized 1:1 to no desensitization versus desensitization
  - First multi-center randomized trial for desensitization in heart transplant candidates
CTOT 13 – End Points

**Primary End Points**
- Death
- Removal from waiting list for any reason other than improvement
- Infection
- Stroke
- Acute renal failure

**Secondary End Points (Post-Transplant)**
- Death
- Re-transplant or re-listed
- Hospitalizations
- Rejections
- Vasculopathy at 1 year
- Infections
- PTLD
- LVAD
- Cardiac Dysfunction (EF <40%)
Intra-operative

• Requires coordination between Transplant team, aphresis staff, perfusion and anesthesia
  – A few hours notice

• Requires availability of sterile cannulae
  – Ability to connect to cardiopulmonary bypass circuit
Protocols

- Plasmapheresis (as soon as possible after donor availability) followed by 20 g of 5% intravenous immunoglobulin (IVIG) in sensitized patients with a PRA above 10%
Special Considerations

• Similar to pre-transplant
  – Bleeding – need to replete clotting factors
  – Infection
Hyperacute Rejection

• Plasmapheresis in conjunction with ECMO for immediate post-operative hemodynamic compromise

• Several case reports of success early but longer term outcomes clearly not as good
• Occurs in two settings
  – Pre-sensitized patients
  – De-novo production of anti-donor antibodies

• Defined by 3 components - ISHLT
  – Evidence of antibodies and complement by immunofluorescence (C4d, C3d and others)
  – Donor specific antibodies
  – Allograft dysfunction
Impact of AMR

- Associated with increased risk of coronary graft vasculopathy
- Associated with increased risk of hemodynamic compromise
- Associated with increased risk of rejection
- Associated with increased mortality
AMR with Vasculopathy

Figure 3. The 5-year freedom from cardiac allograft vasculopathy was lower in the treated antibody-mediated rejection (TxAMR) and asymptomatic antibody-mediated rejection (AsAMR) groups compared with the control group. Cardiac allograft vasculopathy is defined as ≥ 30% stenosis in any vessel on an angiogram.

J Heart Lung Transplant 2009;28:417-22
Figure 3. AMR vascular scores and risk of cardiovascular mortality. AMR, antibody-mediated rejection; V1, no AMR; V2, borderline AMR; V3, mild AMR; V4, moderate AMR; V5, severe AMR.
### Table 1: ISHLT pAMR grade (2)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Pathologic features of AMR¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>pAMR 0</td>
<td>Negative histologic and immunopathologic findings</td>
</tr>
<tr>
<td>Negative for pathologic AMR</td>
<td></td>
</tr>
<tr>
<td>pAMR 1 (H⁺):</td>
<td>Positive histologic findings alone</td>
</tr>
<tr>
<td>Histopathologic AMR</td>
<td></td>
</tr>
<tr>
<td>pAMR 1 (I⁺):</td>
<td>Positive immunopathologic findings alone</td>
</tr>
<tr>
<td>Immunopathologic AMR</td>
<td></td>
</tr>
<tr>
<td>pAMR 2</td>
<td>Both histologic and immunopathologic findings</td>
</tr>
<tr>
<td>Pathologic AMR</td>
<td></td>
</tr>
<tr>
<td>pAMR 3</td>
<td>Interstitial hemorrhage, edema, capillary fragmentation, mixed inflammatory infiltrates, endothelial cell pyknosis/karyorrhexis</td>
</tr>
<tr>
<td>Severe pathologic AMR</td>
<td></td>
</tr>
</tbody>
</table>

¹Histologic features of AMR: endothelial swelling, macrophage infiltration, interstitial hemorrhage and edema. Immunopathologic features of AMR: C4d, C3d, CD68 and Ig.

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Histology

A. No AMR
B. Borderline AMR
C. Severe AMR
D. Mild AMR
E. Moderate AMR

J Heart Lung Transplant 2009;28:51-7
Immunopathology

A: IgG
B: C4d
C: HLA-DR
D: Fibrin
E: HLA-DR
F: Fibrin

Mild AMR
Moderate AMR
Severe AMR

J Heart Lung Transplant 2009;28:51-7
When To Treat

Protocols
Data