Antibody Mediated Rejection in Heart Transplantation

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Medical Director, Heart Transplantation
Disclosures

• I will discuss off label use and/or investigational use of the following drugs in my presentation: Rituximab, Bortezomib, Everolimus

• I have no relevant relationships to disclose
Rejection
CARDIAC TRANSPLANTATION

Rejection

- 0.5 to 1 episode per patient in year one

*Adapted from Miller LW. Efficacy of induction and non-induction immunosuppression in cardiac transplantation. A report of the Working Group of Transplant Cardiologists. Presented at the Tenth Annual Meeting of the International Society for Heart Transplantation, April 1990.
PERCENTAGE OF ADULT HEART TRANSPLANT RECIPIENTS EXPERIENCING REJECTION BETWEEN TRANSPLANT DISCHARGE AND 1-YEAR FOLLOW-UP 
Stratified by Maintenance Immunosuppression (Follow-ups: July 1, 2004 - June 30, 2008)

Cyclosporine + MMF: N = 2,360 
Tacrolimus + MMF: N = 3,065

Overall: p < 0.0001 
18-44: p < 0.0001 
45-62: p < 0.0001 
Female: p = 0.007 
Male: p < 0.0001

NOTE: There were 149 patients with cyclosporine+AZA and 41 with tacrolimus+AZA. These groups were excluded due to small numbers.

Treated rejection = Recipient was reported to (1) have at least one acute rejection episode that was treated with an anti-rejection agent; or (2) have been hospitalized for rejection. 
No rejection = Recipient had (i) no acute rejection episodes and (ii) was reported either as not hospitalized for rejection or did not receive anti-rejection agents.

Analysis is limited to patients who were alive at the time of the follow-up.
Types of Rejection

- **Hyperacute rejection**
  - Preformed alloantibodies vs. HLA class 1 antigens

- **Acute rejection**
  - Most common
  - Cell mediated
  - Antibody mediated - rare <10%

- **Chronic rejection**
  - Slow progressive loss of graft function
  - Occurs months to years post-transplantation
Basic Transplant Immunology

Two forms of acute rejection

- **Cellular rejection (CR)**
  - CD4 and CD8 T cells target donor human leukocyte antigens (HLA) → cytotoxic T cells → cell damage

- **Antibody-mediated rejection (AMR)**
  - B cells activate → plasma cells → antibodies against HLA* → complement-dependent cytotoxicity
Antithymocyte/antilymphocyte globulin  OKT3 monoclonal antibody

? multiple surface antigens  CD3 surface antigen

antigen + IL-1  T Lymphocytes

opsonization

activation and proliferation

antigenic modulation with loss of antigen recognition receptor

clearance of T lymphocytes from the circulation by the reticuloendothelial system

loss of T lymphocyte function
Clinical signs of allograft rejection

- None/asymptomatic/subclinical (surveillance RV bx and DSA monitoring)
- Non-specific
- Fever
- Elevated central venous pressure
- New S3 gallop
- New dysrrhythmias
- Unexpected relative hypotension
- Abnormal ventricular function
- Cardiogenic shock
Right Ventricular Endomyocardial Biopsy

3 specimen:
False (-) 5%

5 specimen:
False (-) 3%

Complications
Mortality: 0.05%
Cardiac perforation: 0.3-0.5%
PTX: 1%
Thromboembolism, air embolism, arrhythmia, BBB
# Grades of Acute Cellular Rejection

<table>
<thead>
<tr>
<th>Grade</th>
<th>Nomenclature</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No rejection</td>
</tr>
<tr>
<td>1A</td>
<td>Focal (perivascular or interstitial) infiltrate without necrosis</td>
</tr>
<tr>
<td>1B</td>
<td>Diffuse but sparse infiltrate without necrosis</td>
</tr>
<tr>
<td>2</td>
<td>One focus with aggressive infiltration and/or focal myocyte damage</td>
</tr>
<tr>
<td>3A</td>
<td>Multifocal aggressive infiltrates and/or myocyte damage</td>
</tr>
<tr>
<td>3B</td>
<td>Diffuse inflammatory process with necrosis</td>
</tr>
<tr>
<td>4</td>
<td>Diffuse aggressive polymorphous infiltrate + edema, + hemorrhage, + vasculitis, with necrosis</td>
</tr>
</tbody>
</table>

1 = mild cellular rejection; 2 = moderate CR; 3 = severe CR
Grade 2R = MODERATE CR
RX!
IV steroid pulse or oral prednisone pulse

- multifocal/diffuse lymphocytic infiltrate with myocyte necrosis
Challenges of Antibody-Mediated Rejection

• **Diagnosis**
  – Are symptoms required?
  – Clinical versus pathological?

• **Prevention**
  – How do we identify patients at high risk for AMR?
  – Can high-risk patients be treated prior to transplant?

• **Treatment**
  – How should AMR be treated?
  – If the initial therapy fails, what next?
Clinical Characteristics of Antibody-Mediated Rejection

- 44 patients with AMR
- More often female
  - 52% female (compared with 26% overall transplant population)
- Hemodynamic compromise common
  - 47% of all cases
  - 68% of early cases

Older Diagnostic Criteria: Antibody-Mediated Rejection

- **Histologic evidence of acute capillary injury**: A and B required
  - A. Endothelial swelling or denudation
  - B. Macrophages in capillaries
  - C. Neutrophils in capillaries
  - D. Interstitial edema, congestion, or hemorrhage

- **Immunopathologic evidence for antibody action**
  - A. Ig (G,M, and/or A) + C3d and/or C4d or C1q
  - B. Fibrin in vessels (optional)

- **Serologic evidence of donor-specific anti-HLA Ab**

- **Cardiac dysfunction** **required**

**ACUTE CELLULAR REJECTION**
- Grade 1 R, mild: Interstitial and/or perivascular infiltrate with up to 1 focus of myocyte injury.

**ANTIBODY-MEDIATED REJECTION (AMR/HUMORAL REJECTION)**
- AMR 1: Positive for antibody-mediated rejection

Edema grade (0–3) 1+
Hemorrhage grade (0–3) 1+
Capillary swelling (0–3) 2+

**GENERAL IMMUNOHISTOCHEMISTRY REPORT**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4d</td>
<td>Positive</td>
</tr>
<tr>
<td>CD20</td>
<td>Negative</td>
</tr>
<tr>
<td>CD3</td>
<td>Negative</td>
</tr>
<tr>
<td>CD31</td>
<td>Positive, highlights dilated vessels</td>
</tr>
<tr>
<td>CD68</td>
<td>Positive, highlights numerous intracapillary macrophages</td>
</tr>
</tbody>
</table>

Asymptomatic/Subclinical AMR: Increased risk of Cardiac Allograft Vasculopathy (CAV)

Wu et al, J Heart and Lung Transplant 2009; 28:417-22

1997 - 2001
246 transplants

43 with AMR
86 controls
matched for age, sex, time from tx

21 asymptomatic and untreated (AsAMR)
22 symptomatic (EF \leq 40%) (TxAMR)

9 hemodynamic compromise

Endothelial cell injury!

Wu et al, J Heart and Lung Transplant 2009; 28:417-22
Asymptomatic/Subclinical AMR: Increases Mortality

Kfoury et al, J Heart and Lung Transplant 2009; 28:781-4

1985 - 2004
869 transplants

Excluded patients with hemodynamic compromise rejection

Predominant pattern of rejection in first 3m post transplant

118 AMR
(≥ 3 AMR episodes)
All asymptomatic and untreated

490 CR
(< 3 AMR episodes)
All treated

193 mixed
(≥ 3 mixed episodes)
All treated

Mortality over 7 yr avg f/u:
CR: 12 %
MR: 18 %
AMR: 21 %

CR vs MR, p = 0.001
CR vs AMR, p = 0.009
MR vs AMR, p = 0.9

Kfoury et al, J Heart and Lung Transplant 2009; 28:781-4
Asymptomatic AMR: Lessons Learned

- **Asymptomatic AMR if untreated:**
  - Increased incidence of CAV compared to patients with no AMR and patients with treated, symptomatic AMR
  - Increased mortality compared to patients with treated cellular or mixed rejection

- **Conclusion**
  - The diagnosis of AMR should be pathological, not clinical
  - Asymptomatic AMR should be treated
New Diagnostic Criteria: AMR

**Histology**
- Endothelial “activation”: intravascular macrophages, capillary destruction
- Edema/hemorrhage less specific; not required

**Immunopathology**
- Immunofluorescence: C3d, C4d, HLA deposition
- Immunoperoxidase: C4d, CD68 deposition

**IMMUNOFLUORESCENCE RESULTS:**
- IgG: 1+ interstitial
- IgM: Negative
- IgA: Negative
- C3: Negative
- C1q: Negative
- *HLA-Dr: 1+ vascular
- C4D: 3+ vascular
- C3D: Negative
- Fibrinogen: 1+ interstitial

**IMMUNOPEROXIDASE RESULTS:**
- CD68: Stromal macrophages present
- CD31: Vascular endothelial cells highlighted
- C4D: Diffuse capillary staining
- C3D: Diffuse capillary staining

**RESULTS SUMMARY:**
- X Immunologic positive
- Histology positive
- Findings of severe rejection

**ANTIBODY-MEDIATED REJECTION CLASSIFICATION:**
- AMR 0: None. Negative immunologic stain(s) and negative histology.
- X AMR 1: Suspicious. Positive immunologic stain(s) or histology (but not both).
- AMR 2: Definite. Positive immunologic stain(s) and positive histology.
- AMR 3: Severe. Positive immunologic stain(s) and positive histology with hemorrhage, edema, neutrophils, vasculitis.

Kobashigawa et al, J Heart and Lung Transplant 2011;30(3):252-269
Diagnostic Criteria: Antibody Mediated Rejection

- **New pathologic diagnostic criteria**
  - **pAMR 0:** both histological and immunopathological studies are negative
  - **pAMR 1(H+):** suspicious for pathologic AMR histopathological alone
  - **pAMR 1 (I+):** suspicious for pathologic AMR immunopathological alone
  - **pAMR 2:** both histological and immunopathological studies are positive
  - **pAMR 3:** severe AMR; interstitial hemorrhage, capillary fragmentation, mixed inflammatory infiltrates, endothelial cell pyknosis, and/or karyorrhexis, marked edema

- **Serologic evidence of donor specific anti-HLA Ab and non-HLA antibodies**

Antibody-Mediated Rejection

A. Intravascular cells; no lymphocytes

B. Intravascular cells; no lymphocytes

C. Prominent macrophages

D. Rare T lymphocytes

E. EC; Intravascular macrophages

F. Complement in capillaries

Courtesy Michelle Kittleston from Wu, G et al J Heart Lung Transpl 2009;28:417-22
EC swelling; Macrophages

C4D stain Surrounds EC

Gonzales-Stawinski GV et al J Heart Lung Transplant 2008;27:375-61
C4D labeling with cardiac dysfunction

Focal C4D labeling without cardiac dysfunction

Positive DSA
MFI = 8,000

Bruneval, P ISHLT Newsletter
Recommended Frequency for Routine Monitoring

Endomyocardial Biopsy

• Histologic evaluation of every protocol biopsy for AMR
• Immunoperoxidase/immunofluorescent staining (C4d):
  – Post-transplant: 2 weeks and 1, 3, 6, 12 months, and
  – AMR suspected
• Interval testing for C4d
  – AMR suspected on histologic, serologic, or clinical findings
• Routine C4d staining on subsequent biopsy specimens after a positive result until clearance

Kobashigawa et al, J Heart and Lung Transplant 2011;30(3):252-269
Recommended Frequency for Routine Monitoring

Circulating Antibody

• Use of solid-phase assay and/or cell-based assays to:
  – Assess for DSA (& quantification if Ab present)
  – Post-transplant: 2 weeks and 1, 3, 6, 12 months, and annually, and
  – AMR clinically suspected

Kobashigawa et al, J Heart and Lung Transplant 2011;30(3):252-269
Challenges of Antibody-Mediated Rejection

• Diagnosis
  – Are symptoms required? *No*
  – Clinical versus pathological? *Pathological*

• Prevention
  – How do we identify patients at high risk for AMR?
  – Can high-risk patients be treated prior to transplant?

• Treatment
  – How should AMR be treated?
  – If the initial therapy fails, what next?
Antibody-Mediated Rejection: Prevention

• Targets of the antibody response
  – Human leukocyte antigens (HLA)
  – Endothelial cell antigens

• Risk factors: sensitization
  – Blood transfusions
  – Pregnancy
  – Previous transplant
  – VAD

• Goal: identify sensitized patients
  – Anti-HLA Ab *aka* Panel Reactive Antibodies (PRA)
  – Non-HLA Ab (experimental)
Assessing Panel Reactive Antibodies: Screening for the Presence of Antibodies

- **Screening**
  - Low Risk: PRA < 10%
  - Moderate Risk: PRA 10-25%
  - High Risk: PRA > 25%

- **Specification**
  - Identification of anti-HLA Ab

- **Quantification**
  - Are they cytotoxic?
Antibody Detection Methods

Membrane-Based Peripheral Leukocytes or Cell Lines

- Lacks sensitivity for all HLAs
- Cannot detect HLA Class II reliably
- Cannot distinguish IgM from IgG

Complement Dependent Cytotoxicity (CDC)

Solid Phase

- ELISA

Fluorescent Bead Assays
- Luminex
- Flow PRA

- Specification of single HLA Class I and II IgG Ab
  - Quantification of HLA Ab (indication of cytotoxicity)
  - Rapid turn-around time
Assessing Panel Reactive Antibodies: Identification by Fluorescent Bead Assays

• Screening
  – Low = PRA < 10%
  – Moderate = PRA 10-25%
  – High = PRA > 25%

• Specification
  – Identification of anti-HLA Ab

• Quantification
  – Are they cytotoxic?
Assessing Panel Reactive Antibodies: Quantification by Fluorescent Bead Assays

- **Screening**
  - Low = PRA < 10%
  - Moderate = PRA 10-25%
  - High = PRA > 25%

- **Specification**
  - Identity of anti-HLA Ab

- **Quantification**
  - Are they cytotoxic?

<table>
<thead>
<tr>
<th></th>
<th>Mean Fluorescent Intensity (MFI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weak</strong></td>
<td>&lt; 5,000</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>5,000 - 10,000</td>
</tr>
<tr>
<td><strong>Strong</strong> (Cytotoxic)</td>
<td>&gt; 10,000</td>
</tr>
</tbody>
</table>
What matters clinically: Calculated PRA

- How easy will it be to find a donor for my patient awaiting transplant?

- cPRA defines the frequency of the unacceptable HLA in the donor population

- **Step 1: Define unacceptable HLA**
  - Potentially cytotoxic: MFI > 5000
  - Patient has anti-HLA Ab with MFI > 5000 → unacceptable HLA

- **PANEL REACTIVE ANTIBODY SCREEN**
  - ANTIBODY CLASS II % PRA 75
  - ANTIBODY CLASS I % PRA 78
  - SINGLE ANTIBODY ID CLASS I
    - MFI
      - B78: 6829
      - B51: 6537
      - B37: 5717
      - B75: 3996
      - B35: 3190
      - B53: 2748
      - B76: 2521
      - B52: 2455
      - A66: 2397
      - A26: 2164
      - A25: 2125
  - SINGLE ANTIBODY ID CLASS II
    - MFI
      - DR7: 14135
      - DQ7: 7789
      - DQ9: 6256
      - DQ8: 4472
      - DR12: 4403
      - DR103: 4111
      - DR53: 3268
What matters clinically: Calculated PRA

- How easy will it be to find a donor for my patient awaiting transplant?

- cPRA defines the frequency of the unacceptable HLA in the donor population

- Step 2: Determine frequency of those HLA in the population
  - Link on UNOS website

http://optn.transplant.hrsa.gov/resources/professionalResources.asp?index=78
What matters clinically: The Calculated PRA

- How easy will it be to find a donor for my patient awaiting transplant?
- cPRA defines the frequency of the unacceptable HLA in the donor population
- Step 3: Assess cPRA
  - cPRA 10% = 90% of donors would be a match
  - cPRA 80% = only 20% of donors would be a match

http://optn.transplant.hrsa.gov/resources/professionalResources.asp?index=78
Pre-transplant Protocol: Management of Sensitized Patients

Check PRA

< 10%
- Recheck
  - Q 6 m
  - 2w post sensitizing event
    - Infection
    - Transfusion

> 10%
- Specification (anti-HLA Ab)
- Quantification (MFI)
- Calculated PRA
- Prospective vs Virtual Xmatch
- Desensitization if cPRA > 50%

Kobashigawa JA J Heart and Lung Transplant 2009; 28:213-25
Desensitization Protocols

• Adapted from renal transplantation experience

• Indications
  – Pre-transplant cPRA > 50% to prevent AMR
  – Post-transplant
    • Positive Xmatch (induction)
    • Refractory AMR

• Components
  – Remove preformed Ab: Plasmapheresis
  – Block Ab function: IV IgG
  – B cell destruction: Monoclonal Ab against CD20 on B cells – Rituximab
  – Plasma cell destruction: Proteasome inhibitor targeting plasma cells – Bortezomib
    • FDA approved for multiple myeloma
Desensitization Protocols

- **Indications**
  - Pre-transplant
cPRA > 50%
  - Post-transplant
    - Positive Xmatch (induction)
    - Refractory AMR

Vo AA NEJM 2008 359: 242-51
Desensitization Protocol: Managing Refractory Antibodies

- Some patients have a persistently elevated PRA despite plasmapheresis, IV Ig and rituximab.
Refractory Antibodies: Role of Bortezomib

Cedar Sinai experience

- 6 patients with cPRA ≥ 50% despite PP/IV Ig/ritux
- Side effects
  - UTI, pneumonia, catheter infection, *C difficile*
  - Neuropathy: responded to reduction in dose
- Outcomes
  - cPRA ↓ from 62% to 35%
  - 5 with fall in cPRA and successfully transplanted
  - 1 with no Δ in cPRA and died from sepsis after cycle #2
  - 1 died post-OHT from sepsis

Patel et al *J Heart and Lung Transp* 2011; 30:1320
Prospective Crossmatch

• **Purpose**
  - Avoid donors with HLA to which the recipient has cytotoxic anti-HLA antibodies
  - Prevent hyperacute rejection

• **Process**
  - Test recipient serum against donor cells
  - Geographic constraints to limit the donor pool

• **Indications**
  - **Pre-transplant**, if multiple low-level anti-HLA Ab (MFI 2000-5000)
  - **Post-transplant** surveillance

---

**T CELL FLOW CROSSMATCH**

**T CELL MCS**

<table>
<thead>
<tr>
<th>Reference range:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart: Negative &lt; 50 MCS</td>
</tr>
</tbody>
</table>

**B CELL FLOW CROSSMATCH**

**B CELL MCS**

<table>
<thead>
<tr>
<th>Reference range:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart: Negative &lt;121 MCS</td>
</tr>
</tbody>
</table>
Virtual Crossmatch

• Purpose
  – Avoid donors with HLA for which the recipient has strong anti-HLA Ab
  – Prevent hyperacute rejection

• Advantages
  – Does not require donor cells + recipient serum
  – No geographic constraints

• Process
  – Step 1: define cytotoxic HLA Ab by MFI threshold (> 5000-7000)
  – Step 2: avoid donors with these HLA

• Higher MFI threshold
  – More donor offers
  – Greater chance of rejection
  – Reserved for unstable patients with projected long wait time

- PANEL REACTIVE ANTIBODY SCREEN
  - ANTIBODY CLASS II % PRA 75
  - ANTIBODY CLASS I % PRA 78
  - SINGLE ANTIGEN ID CLASS I
    - MFI
  - B78: 6829
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  - DR103: 4111
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Prospective vs Virtual Crossmatch

257 samples from highly sensitized pts

<table>
<thead>
<tr>
<th></th>
<th>Incompatible (+)</th>
<th>Compatible (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incompatible (+)</td>
<td>89</td>
<td>23</td>
</tr>
<tr>
<td>Compatible (-)</td>
<td>12</td>
<td>133</td>
</tr>
</tbody>
</table>

89/112 PPV 79%
133/145 NPV 92%

• **PPV 79%** → 21% false-incompatible rate → yet donor pool is still expanded by lack of geographical constraints

• **NPV 92%** → 8% of patients will have incompatible matches → use retrospective Xmatch post transplant to guide therapy

# Prognostic Value of Post-transplant PRA

<table>
<thead>
<tr>
<th>Study</th>
<th>Post-tx PRA</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith JD</td>
<td>Anti-HLA DSA</td>
<td>↑ 6-month rejection</td>
</tr>
<tr>
<td><em>Transplantation</em> 1992</td>
<td></td>
<td></td>
</tr>
<tr>
<td>George JF</td>
<td>Anti-HLA DSA</td>
<td>↓ 1-year survival</td>
</tr>
<tr>
<td><em>JHLT</em> 1995</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Przybylowski P</td>
<td>Anti-HLA DSA</td>
<td>↑ 1-year rejection (50% vs 16%)</td>
</tr>
<tr>
<td><em>Transplantation</em> 1999</td>
<td></td>
<td>↓ 1-year survival (86% vs 92%)</td>
</tr>
<tr>
<td>Tambur AR</td>
<td>Anti-HLA DSA</td>
<td>↑ 1-year rejection</td>
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<tr>
<td><em>Transplantation</em> 2000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ho EK</td>
<td>Anti-HLA DSA</td>
<td>↓ 10-year survival (63% vs 79%)</td>
</tr>
<tr>
<td><em>Human Immunology</em> 2009</td>
<td></td>
<td></td>
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</tbody>
</table>
Challenges of Antibody-Mediated Rejection

- **Diagnosis**
  - Are symptoms required?
  - Clinical versus pathological?

- **Prevention**
  - How do we identify patients at high risk for AMR?
  - Can high-risk patients be treated prior to transplant?

- **Treatment**
  - How should AMR be treated?
  - If the initial therapy fails, what next?
Mechanisms Underlying Treatment of AMR

Adapted from Singh et al, Transplantation Reviews, 2009;23:34-46

- Anti-thymocyte globulin
- Rituximab
- Proliferation signal inhibitors
- Bortezomib
- IV immune globulin
- Plasmapheresis
- Photopheresis
## Treatment of Rejection

### Asymptomatic/Subclinical
- **Target higher CNI levels**
- **Oral steroid bolus + taper**
- **Sirolimus**

### Reduced EF
- **Oral steroid bolus/taper**
  - or
  - **IV pulse steroids**

### Heart Failure/Shock
- **IV pulse steroids**
  - or
  - **Cytolytic therapy**
  - **Plasmapheresis (before ATG dose)**
  - **IV immune globulin**

### To treat or not to treat?
- **IV pulse steroids**
  - or
  - **Cytolytic therapy**
  - **Plasmapheresis (before ATG dose)**
  - **IV immune globulin**

### Cellular
- **Inotropes, IABP or ECMO support**
## Treatment of Rejection

<table>
<thead>
<tr>
<th>Cellular</th>
<th>Asymptomatic/Subclinical</th>
<th>Reduced EF</th>
<th>Heart Failure/Shock</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Target higher CNI levels</td>
<td>• Oral steroid bolus/taper or • IV pulse steroids</td>
<td>• IV pulse steroids</td>
</tr>
<tr>
<td></td>
<td>• Oral steroid bolus + taper</td>
<td></td>
<td>• Cytolytic therapy (ATG)</td>
</tr>
<tr>
<td></td>
<td>• Sirolimus</td>
<td></td>
<td>• Plasmapheresis (before ATG dose)</td>
</tr>
<tr>
<td>Antibody-Mediated</td>
<td>• IV pulse steroids or • Cytolytic therapy • Plasmapheresis (before ATG dose)</td>
<td>• IV immune globulin</td>
<td>• IV immune globulin</td>
</tr>
<tr>
<td>To treat or not to treat?</td>
<td>• IV pulse steroids</td>
<td>• Inotropic therapy</td>
<td>• IABP or ECMO support</td>
</tr>
<tr>
<td></td>
<td>or • IV heparin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
After the dust settles... AMR Maintenance Protocol

Acute therapy determined by clinical picture

- Normal EF/hemos, no DSA, no rejection
  - EMBx/echos per protocol
  - PRA q 6m

MMF → PSI
- Repeat echo, EMBx, PRAs 1-2w post rx

Persistent low EF, abnormal hemos, or DSA
- Photopheresis
- IV Ig, rituximab, bortezomib
## Evidence for AMR therapies

<table>
<thead>
<tr>
<th>Study</th>
<th>Organ</th>
<th>Therapy</th>
<th>#pts</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crespo-Leiro MG</td>
<td>Heart</td>
<td>PP 7-19d</td>
<td>12 pts</td>
<td>11/12 had resolution of AMR</td>
</tr>
<tr>
<td><em>Am J Transplant</em> 2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jordan SC</td>
<td>Kidney</td>
<td>IV Ig +/- PP</td>
<td>20 pts</td>
<td>15/20 had resolution of AMR</td>
</tr>
<tr>
<td><em>Pediatr Transplant</em> 2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garrett HE</td>
<td>Heart</td>
<td>Rituximab</td>
<td>8 pts</td>
<td>8/8 had resolution of AMR</td>
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<td><em>JHLT</em> 2005</td>
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Proliferation signal inhibitors (PSIs)

- **Mechanism**
  - Inhibit proliferation of T, B, smooth muscle, endothelial cells

- **In clinical trials**
  - ↓ rejection, CAV
  - ↓ viral infections
  - ↑ renal insufficiency
  - Impaired wound healing

- **Indications for sirolimus/everolimus**
  - Rejection
  - CAV
  - Malignancy
  - Viral infections (CMV)
  - Renal dysfunction (i/o CNI)

Refractory Antibodies: Role of Bortezomib

Cedar Sinai experience
- 6 patients with cPRA ≥ 50% despite PP/IV Ig/ritux
- Side effects
  - UTI, pneumonia, catheter infection, *C difficile*
  - Neuropathy: responded to reduction in dose
- Outcomes
  - cPRA ↓ from 62% to 35%
  - 5 with fall in cPRA and successfully transplanted
  - 1 with no Δ in cPRA and died from sepsis after cycle #2
  - 1 died post-OHT from sepsis

Days 1, 4, 8, 11
Plasmapheresis
Bortezomib 1.3 mg/m²
Day 25
Check PRA
Repeat 2-wk cycle if cPRA ≥ 50%

Patel et al *J Heart and Lung Transp* 2011; 30:1320
Photopheresis

- **Principle**
  - “Immunomodulation”
  - Promote destruction of cytotoxic T cells against the donor heart

- **Procedure**
  - Leukapheresis: remove white cells
  - Photoactivation: mix cells with psoralen and expose to UV light → apoptosis
  - Reinfusion

- **Role in rejection**
  - Tested in primary prevention and recurrent rejection
  - Reduction in rejection and coronary intimal medial thickness (marker for CAV)
Photopheresis

- 60 pts, standard therapy vs photopheresis q wk for 6 months post- OHT
  - Decrease in acute rejection
  - Did not look at humoral rejection

- 36 pts with recurrent rejection
- 3-12 mon photopheresis
- Risk of rejection or death reduced after 3 months


Kirklin JK JHLT 2006; 25: 283-288
Clinical Characteristics of Antibody-Mediated Rejection

- 44 patients with AMR
- Higher incidence of CAV (stenosis > 30%)
  - 1 year: 16% vs 5%
  - 3 years: 36% vs 17%
  - 5 years: 64% vs 30%

CASE STUDY

25 yr M  3 yrs S/P OHT non-compliant with IMS

• Admitted in cardiogenic shock  
  EF <20%; Bx: Severe AMR; + DSA 

• Treatment: Inotropes, IABP, 
  cytolytic rx, plasmapheresis, 
  IVIgG, augmented 3 drug rx 

• Subsequent bx: neg; 
  DSA low MFI 

• Clinically improved with 
  EF 50%; 

• Pre-discharge coronary 
  angiogram: no luminal abn 

• 4 mon after successful rx of 
  AMR pt died suddenly 

Autopsy: 
Severe CAV
Challenges of Antibody-Mediated Rejection

- **Diagnosis**
  - Are symptoms required?
  - Clinical versus pathological?

- **Prevention**
  - How do we identify patients at high risk for AMR?
  - Can high-risk patients be treated prior to transplant?

- **Treatment**
  - How should AMR be treated?
  - If the initial therapy fails, what next?
Antibody-Mediated Rejection: Summary

- **Diagnosis**
  - Pathological findings only

- **Prevention**
  - Assays for specification and quantification of HLA Ab
  - cPRA and virtual crossmatch
  - Desensitization targeting B cells, plasma cells, and antibodies

- **Treatment**
  - Subclinical AMR should be treated
  - Long-term therapy: photopheresis vs desensitization

- Close monitoring for complications
AMR: Conclusion

• Difficult problem in heart transplantation - requires high index of suspicion
• Associated with increased morbidity and mortality
• Evidence based therapeutic strategies are limited