Management of the Highly Sensitized Patient

Clinical, Logistical, and Financial Considerations

Jointly Sponsored by CTI Clinical Trial and Consulting Services and the University of Kentucky College of Medicine

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Faculty

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The Johns Hopkins Hospital

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Program Objectives

1. Describe the potential benefits and challenges of treatment with immune globulin preparations, in combination with other modalities, in highly sensitized kidney transplant candidates and recipients

2. List considerations for the implementation of immune globulin-based protocols

3. Discuss logistic and reimbursement considerations for initiating programs for highly sensitized kidney transplant recipients
## Agenda

<table>
<thead>
<tr>
<th>Topic</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplantation of the Highly Sensitized Patient: Unmet Challenges</td>
<td>Robert Montgomery, MD, DPhil</td>
</tr>
<tr>
<td>Strategies to Manage the Highly Sensitized Patient</td>
<td>Stanley Jordan, MD</td>
</tr>
<tr>
<td>Pharmacy Considerations in the Selection and Implementation of Desensitization Protocols</td>
<td>Ashley Vo, PharmD</td>
</tr>
<tr>
<td>Investment &amp; Reimbursement Issues</td>
<td>Brigitte Reeb, MBA</td>
</tr>
<tr>
<td>Clinical Logistics</td>
<td>Janet Hiller, RN, MSN</td>
</tr>
</tbody>
</table>
Transplantation of the Highly Sensitized Patient: Unmet Challenges

Robert A. Montgomery, MD, D.Phil
Chief, Division of Transplantation
Director, Incompatible Kidney Transplant Program
Director, The Johns Hopkins Comprehensive Transplant Center
Financial Disclosure

Dr. Montgomery provides contract research support for Astellas Pharma, Inc. and Genzyme Corporation.
• 30% of the patients on the list are sensitized to allo-HLA antibody
• 7000 patients are considered highly sensitized
• Anti-HLA Abs develop as a result of previous transplants, pregnancies, or transfusions
• Transplantation across a positive crossmatch can result in hyperacute or acute antibody mediated rejection (AMR)
• Approximately 2500 patients/year present with a willing, but incompatible live donor
Immunologic Risk

Old Paradigm
Risk is static

New Paradigm
Risk can be modified
Conflicting Pressures

Take Care of Vulnerable group
Take Risks

Improve Results
Limit Risk

HRSA
Unmet Need

CMS
UNOS
Sensitized Patients Are Not Normative

- SRTR algorithm has 2 categories for adjusting for PRA; 0-9 and ≥10
- SRTR algorithm weighs a PRA of 10 at the same level as a PRA 100
  - Median PRA for InKTP Patients: 88.1
  - National Median PRA: 0.0

- SRTR algorithm has 3 categories for adjusting for time on dialysis: 0, 1, or > 2 years
- SRTR algorithm weighs equally patients who has been dialysis for 2 years and 20 years
  - Mean years on dialysis for InKTP Patients: 8.7 year
  - 34% have been on dialysis for > 10 years

- SRTR algorithm has 2 categories for previous Tx: Yes or No
  - 53% of InKTP patients have had a previous transplant
  - 1/3 have had multiple previous transplants
Managing Risk

Given the current regulatory pressures, matching donor/recipient phenotype to transplant modality becomes increasingly important to provide the best outcomes.
Options For Patients with Incompatible Donors

Wait for a deceased donor organ

Avoid the incompatibility
Kidney or domino paired donation (KPD or DPD)

Lessen the incompatibility
KPD or DPD followed by desensitization

Confront the incompatibility directly
KPD or DPD followed by desensitization
Projected Years of Life on Dialysis vs Tx

- **Overall**
- **White**
- **Black**
- **0-19**
- **20-39**
- **40-59**
- **60-74**
- **Diabetes**

Projected Years of Life

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Management of the Highly Sensitized Patient:
Clinical, Logistical, and Financial Considerations

13
Management of the Highly Sensitized Patient: Clinical, Logistical, and Financial Considerations

Highly Sensitized

No Live Donor Available
- Desensitization
  - High Dose IVIg
- Wait for (-) XM
  - DD kidney

Live Donor Available
- Desensitization
  - PP/CMV-IGIV or IVIg
  - KPD

Kidney Paired Donation (KPD)
- Desensitization
  - With KPD
  - Tx

Tx = transplant; XM = crossmatch; IVIg = intravenous immunoglobulin; PP = plasmapheresis; DD = deceased donor

CMV-IGIV (CytoGam®, CSL Behring, King of Prussia, PA)
Highly Sensitized

No Live Donor Available

Desensitization
High Dose IVIg

Wait for (-) XM
DD kidney

Live Donor Available

Desensitization
PP/CMV-IGIV or IVIg

Kidney Paired Donation (KPD)

Tx if (-) XM

Desensitization
With KPD

Tx

CMV-IGIV (CytoGam®, CSL Behring, King of Prussia, PA)
Tx=transplant; XM=crossmatch; IVIg=intravenous immunoglobulin;
PP=plasmapheresis; DD=deceased donor
Which Option is Best for an Individual Incompatible Pair?

Defining the Immunologic Phenotype

- How difficult will they be to match?
- How difficult will they be to desensitize?
### How Difficult Will They Be to Match? Who Matches in a KPD Pool?

<table>
<thead>
<tr>
<th>D</th>
<th>R</th>
<th>PRA &lt; 80 100 pairs</th>
<th>PRA ≥ 80 100 pairs</th>
<th>PRA &lt; 80 1000 pairs</th>
<th>PRA ≥ 80 1000 pairs</th>
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<tr>
<td>O</td>
<td>O</td>
<td>53%</td>
<td>3%</td>
<td>56%</td>
<td>14%</td>
<td>19%</td>
</tr>
<tr>
<td>A</td>
<td>O</td>
<td>13%</td>
<td>1%</td>
<td>17%</td>
<td>2%</td>
<td>30%</td>
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<tr>
<td>B</td>
<td>A</td>
<td>70%</td>
<td>1%</td>
<td>83%</td>
<td>8%</td>
<td>5%</td>
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</table>

How Difficult Will They Be To Desensitize?

(+) XM

Major Factors

- DSA titer or strength
- Repeat mismatches
- Sensitized from previous transplant(s)
Matching Donor/Recipient Pair to Transplant Modality

KPD

**Easy-to-match pair**
- O Donor
- Low PRA

**Difficult-to-match pair**
- AB Donor
- Broad Sensitization

**Difficult-to-desensitize**
- High Titer DSA
- High Immunologic Risk

**Easy-to-desensitize**
- Low Titer DSA
- Low Immunologic Risk
Matching Donor/Recipient Pair to Transplant Modality

KPD followed by Desensitization

**Difficult-to-match pair**
- A/O ABOi
- Broad Sensitization

**Difficult-to-desensitize**
- High immunologic risk
- High titer DSA (CDC > 1:128)

DSA=donor-specific antibodies
CDC=complement-dependent cytotoxicity
Triple Exchange with (+) XM Only

Domino Paired Donation

Donor 1: NDD

Donor 2

Recipient 1

Recipient 2

Incompatible

1st eligible recipient
From UNOS match run

NEAD Chains

Donor 1: NDD

Donor 2

Bridge Donor

Recipient 1

Recipient X

Starts new chain

NEAD= Never Ending Altruistic Donor

Management of the Highly Sensitized Patient:
Clinical, Logistical, and Financial Considerations
First NEAD Chain

<table>
<thead>
<tr>
<th>Transplant Date</th>
<th>Recipient's State</th>
<th>Recipient's Sex and ABO type</th>
<th>Donor's Sex and ABO type</th>
<th>Recipient's PRA</th>
<th>Recipient's Ethnicity</th>
<th>Recipient-to-Donor Relationship</th>
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</thead>
<tbody>
<tr>
<td>Jul 2007</td>
<td>AZ</td>
<td>O 1</td>
<td>O</td>
<td>62%</td>
<td>Cauc</td>
<td>Wife Husband</td>
</tr>
<tr>
<td>Jul 2007</td>
<td>OH</td>
<td>O 1</td>
<td>A</td>
<td>0%</td>
<td>Cauc</td>
<td>Daughter Mother</td>
</tr>
<tr>
<td>Sep 2007</td>
<td>OH</td>
<td>A 2</td>
<td>A</td>
<td>23%</td>
<td>Cauc</td>
<td>Mother Daughter</td>
</tr>
<tr>
<td>Sep 2007</td>
<td>OH</td>
<td>B 3</td>
<td>A</td>
<td>0%</td>
<td>Cauc</td>
<td>Brother Sister</td>
</tr>
<tr>
<td>Feb 2008</td>
<td>MD</td>
<td>A 2</td>
<td>A</td>
<td>82%</td>
<td>Hispanic</td>
<td>Husband Wife</td>
</tr>
<tr>
<td>Feb 2008</td>
<td>MD</td>
<td>A 2</td>
<td>A</td>
<td>78%</td>
<td>Cauc</td>
<td>Daughter Father</td>
</tr>
<tr>
<td>Feb 2008</td>
<td>MD</td>
<td>A 2</td>
<td>A</td>
<td>64%</td>
<td>Cauc</td>
<td>Wife Husband</td>
</tr>
<tr>
<td>Feb 2008</td>
<td>NC</td>
<td>A 2</td>
<td>A</td>
<td>3%</td>
<td>Cauc</td>
<td>Friend</td>
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<tr>
<td>Mar 2008</td>
<td>MD</td>
<td>A 2</td>
<td>A</td>
<td>100%</td>
<td>AA</td>
<td>Brother</td>
</tr>
<tr>
<td>Mar 2008</td>
<td>OH</td>
<td>A 2</td>
<td>A</td>
<td>46%</td>
<td></td>
<td>Mother Daughter</td>
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</tbody>
</table>

1 The initiating donor was an unpaired altruistic donor from Michigan.
2 The recipient of Transplant 6 required desensitization to HLA DSA by T and B cell flow cytometry.
3 The recipient of Transplant 9 required desensitization to blood group (AHG titer of 1:8).

Rees NEJM (In Press)
PP/CMV-IGIV Desensitization Protocol

Tacrolimus
MMF

Anti-CD20

Steroids
Daclizumab

Rescue
Splenectomy

PP/CMV-IGIV
PP/CMV-IGIV
PP/CMV-IGIV
PP/CMV-IGIV
PP/CMV-IGIV
PP/CMV-IGIV
PP/CMV-IGIV
PP/CMV-IGIV
PP/CMV-IGIV

CMV-IGIV (CytoGam®, CSL Behring, King of Prussia, PA)
Summary and Conclusions

- Highly sensitized patients have prolonged waiting times and this increases costs.
- If there is no potential live donor, then high dose IVIG appears to increase the likelihood of receiving a (-) XM DD kidney.
- If there is a XM (+) or ABOi live donor, KPD is the most effective method of achieving a good result, but not all patients will benefit.
- Desensitization provides excellent long-term function but early losses due to antibody-mediated rejection (AMR) do occur.
- Rescue splenectomy appears to be effective in salvaging most of these organs.
- Phenotype correlations with risk and long-term outcome will be the next major breakthrough in this field.
Removing the Barriers to Successful Transplantation: Desensitization 2009

Stanley C. Jordan, MD
Director, Kidney Transplantation and Immunology
Kidney and Pancreas Transplant Program
Director, Division of Pediatric and Adult Nephrology

CEDARS-SINAI MEDICAL CENTER
Comprehensive Transplant Center
Dr. Jordan provides contract research support for Pfizer, Genentech, and Bristol-Myers Squibb.
Sensitization to HLA: An Emerging Problem in Kidney Transplantation

• Sensitization to HLA results from exposure to other human tissues (i.e., blood transfusions, previous transplants, pregnancies)

• Anti-HLA antibodies may persist for years and are of little consequence unless the patient requires a transplant

• Approximately 30% of the kidney transplant patients on the waiting list have anti-HLA antibodies

• These antibodies represent a major barrier to transplantation with more than 80% of transplanted patients experiencing graft loss at 1 year

• HLA directed antibodies are a major cause of late allograft failure
Patients tested once post transplantation in 2002, and followed for 3 years

Anti-HLA Class II Negative (n = 141)

Anti-HLA Class II Positive (n = 28)

SCr ≥2.0 mg/dl

P = 0.003


Management of the Highly Sensitized Patient:
Clinical, Logistical, and Financial Considerations
Traditional Guidelines for Crossmatch Analysis Prior to Transplantation

No Transplant:
CDC/AHG+, FCMX (B-&T-cell) + >250CS, B-cell CFC >20

Transplant:
CDC (-), FCMX (-)

No Transplant

Transplant
No Transplant: CDC/AHG+, FCMX (B-&T-cell +) >250CS, B-cell CFC >20

Transplant: CDC (-), FCMX (-), FCMX <225CS CDC + @1:2

Guidelines for Crossmatch Analysis Prior to Transplantation: Effect of Desensitization
Mechanisms of Action of IVIG Relevant to Prevention & Treatment of Allograft Rejection

- Regulation of B-cell repertoire & antibody production
- Induction of B-cell apoptosis through FCγR-mediated signals
- Inhibition of dendritic cell maturation and function through FCγR-mediated signals
- Induction of anti-inflammatory cytokines (IL-10, TGF-β)
- Inhibition of complement-mediated inflammation
- Induction of CD4+/CD25+/Fox P3 cells
- Inhibition of macrophage maturation and function through FCγR-mediated inhibition of IFN-γ Receptor
- Neutralization of Anti-HLA Antibodies by Antiidiotypic Antibodies
- Inhibition of Cytokines IL-1β, IFN-γ, IL-2, IL-6
- Inhibition of C5b-9 MAC

Management of the Highly Sensitized Patient: Clinical, Logistical, and Financial Considerations
Anti-HLA Class I & II Antibody Levels Post-IVIG: Correlation With Transplant Status

Anti-HLA Class I-IgG

Anti-HLA Class II-IgG

PRA-IgG

Management of the Highly Sensitized Patient:
Clinical, Logistical, and Financial Considerations
IG02 Study: IVIG Improves Transplantability and Reduces Time on Dialysis

Mean time to transplantation:
Placebo: 10.3 years
IVIG: 4.8 years
P < 0.03
Transplant Immunotherapy Program (TIP) Protocol for Highly Sensitized Patients with Living Donors

- HLA Laboratory
- Kidney Transplant Program Cedars-Sinai Medical Center
- Transplant Immunology Laboratory

TIP Living Donor

- IVIG 2gm/kg-Day1
- Rituximab 1gm-Day14
- IVIG 2gm/kg-Day 30

- CDC+/FCMX+ With DSA OR
  CDC(-)/FCMX(+)

- Transplant: CDC(-)/FCMX(-) OR (CDC(-)/FCMX(+)) (CS<225)

- NO TRANSPLANT

PE QOD x 5 Rx
Then IVIG 2gm/kg
Management of the Highly Sensitized Patient: Clinical, Logistical, and Financial Considerations

HLA Laboratory

Kidney Transplant Program Cedars-Sinai Medical Center

Transplant Immunology Laboratory

IVIG 2g/kg Day1
Rituximab 1g Day14
IVIG 2g/kg Day 30
Repeat IVIG 2g/kg at Transplant

CDC+/FCMX+
With DSA OR
CDC(-)/FCMX(+)

Transplant:
CDC(-)/FCMX(-)
Or (CDC(-)/FCMX(+)) (CS<225)

TIP DD HS Candidate

PRA>30%
Wait List: >5 years
Frequent DD Offers with (+)CMX
Hx Previous Transplants/BT
Historic PRA (+)/+ B-cell CFC

NO TRANSPLANT

Transplant Immunotherapy Program (TIP) Protocol for Highly Sensitized Patients Awaiting Deceased Donation
Rituximab and Intravenous Immune Globulin for Desensitization during Renal Transplantation

Ashley A. Vo, Pharm.D., Marina Lukovsky, Pharm.D., Mieko Toyoda, Ph.D., Jennifer Wang, M.D., Nancy L. Reinsmoen, Ph.D., Chih-Hung Lai, Ph.D., Alice Peng, M.D., Rafael Villicana, M.D., and Stanley C. Jordan, M.D.

This open-label, phase 1-2, single-center study examined the use of intravenous immune globulin and rituximab to reduce anti-HLA antibodies and improve transplantation rates in 20 highly sensitized patients.

Sixteen patients (80%) subsequently received a transplant, and the 1-year survival rates for patients and allografts were 100% and 94%, respectively.

Larger and longer trials are needed to assess the safety of this approach.

A Phase I/II Trial of IVIG + Rituximab for Desensitization of Highly-HLA Sensitized Patients: Treatment Protocol

IVIG 2g/kg

Rituximab 1g IV

IVIG 2g/kg

Time: Weeks

Labs: DSA, CMX, PRAs

Panel Reactive Antibody Titers Pre- and Post-IVIG+Rituximab Therapy


Management of the Highly Sensitized Patient:
Clinical, Logistical, and Financial Considerations
Management of the Highly Sensitized Patient:
Clinical, Logistical, and Financial Considerations

T-cell Flow Cytometric Crossmatch Results Before Treatment, After Treatment, and Before Transplant

Serum Creatinine Values in the 16 Patients Who Received a Kidney Transplant after Desensitization


Management of the Highly Sensitized Patient:
Clinical, Logistical, and Financial Considerations
When Do We Transplant?

Analysis of Crossmatch And Donor Specific Antibody (DSA) Testing
Monitoring SFI-DSA in Highly-Sensitized Patients Pre- and Post-Desensitization: Response to Desensitization

SFI= Standard Fluorescence Intensity

Management of the Highly Sensitized Patient:
Clinical, Logistical, and Financial Considerations
Correlation Between FCMX and SFI-DSA Units

SFI = Standard Fluorescence Intensity

Management of the Highly Sensitized Patient: Clinical, Logistical, and Financial Considerations

\[ y = 8154.7e^{0.0111x} \]

\[ R^2 = 0.4835 \]
Anti-Allo Reactivity to Various PBMCs in HS Patients and Normal Individuals

Management of the Highly Sensitized Patient: Clinical, Logistical, and Financial Considerations
Anti-Allo Reactivity to Donor PBMCs in HS Patients Can Predict AMR

Anti-Allo Reactivity to Donor PBMCs in HS Patients Can Predict AMR

IFNγ Cell% Inc. (ratio)

Months Post-Transplant

---

Graft Loss at 20mo post-Tx

AMR

---

No AMR

---

Graft Loss

---

AMR

---

HS+Donor

---

HS+3rd N-ABOcom

---

HS+3rd N-ABOincom
IVIG + Single Dose Rituximab for Desensitization

• Between July 2006-October 2008, 135 HS patients were treated with IVIG + single dose rituximab

• All were highly-HLA sensitized (PRAs >30 or with antibody specificities)

• Patients awaiting DD had at least 5 years wait time on UNOS list
IVIG + Single Dose Rituximab for Desensitization

109/135 (81%) of patients treated were transplanted

- 50DD/59LD, 43M/66M
- Patient & graft survival at 24 months 98%/93%
- 21 patients experienced AMR (19%) post-transplant
- 7 graft losses to AMR (33%) at 18 months; two were late AMRs secondary to medication non-adherence
- 6 patients needed additional PE to be desensitized, all LD
Serum Creatinine Values
IVIG + Single Dose Rituximab for Desensitization

- Plot showing changes in serum creatinine values over time (months).
- Y-axis: Serum Creatinine (mg/dl)
- X-axis: Time (Months)
- Pre-Tx to 18 M months are displayed.

Management of the Highly Sensitized Patient:
Clinical, Logistical, and Financial Considerations
Time to Transplant for DD Recipients After Desensitization with IVIG + Rituximab (2 Dose vs. Single Dose)

- G1: 4.9±5.9M
- G2: 0.8±1.1M
- G1: 144±89.5M
- G2: 89.1±43M

Time (Months)
UNOS Rates of Kidney Transplantation by PRA Status (2001-2008)

- PRA 0-10%: 51% LD, 71% DD
- PRA 10-80%: 8.5% LD, 16% DD
- PRA >80%: 2% LD, 8% DD
- Desensitized (PRA >70%): 92% LD, 72% DD
SRTR Data for Kidney Transplant Outcomes: 1/05-6/07

- **% Waitlist Transplanted**
- **Patient Survival**
- **Graft Survival**

* = Statistically Higher
** = Statistically Lower

- PRA 0-10%
  - Time Tx: 100%
  - DD (1YR): 90%
  - DD (3YR): 79%

- PRA 10-80%
  - Time Tx: 100%
  - DD (1YR): 89%
  - DD (3YR): 78%

- PRA >80%
  - Time Tx: 100%
  - DD (1YR): 88%
  - DD (3YR): 76%

- Desensitized >70%
  - Time Tx: 100%
  - DD (1YR): 92%
  - DD (3YR): 90%
Pharmacy Considerations of Desensitization Protocols

Ashley A. Vo, Pharm.D.
Assistant Professor of Pediatrics
David Geffen School of Medicine at UCLA
Director, Transplant Immunotherapy Program
Comprehensive Transplant Center

Cedars-Sinai Medical Center
Comprehensive Transplant Center
Financial Disclosure

Dr. Vo reports no disclosures
Objectives

• Discuss economic impact of desensitization protocol vs. maintenance on dialysis
• Pharmacy considerations in the selection and implementation of desensitization protocols
• Explanation of common adverse events as well as safety profile associated with the use of IVIG/rituximab in HS patients
Cost Analysis of Transplantation in Highly Sensitized Recipients vs. Dialysis

Cost per year

- Chronic Dialysis: $69,000
- Chronic Transplant: $17,000
- Desensitization: $23,760
- Transplant Desensitization: $126,000

http://www.usrds.org/adr.htm

Management of the Highly Sensitized Patient:
Clinical, Logistical, and Financial Considerations
Cedars-Sinai first to develop and apply high dose IVIG for desensitization therapy in HS patients

State-of-the-Art HLA and Immunogenetics Laboratory and Transplant Immunology Laboratory

Insurance coverage for IVIG, rituximab, and plasmapheresis

Addressing the needs of highly HLA-sensitized patients
Outpatient Administration for IVIG & Hemodialysis

• Medicare approval/licensure for in-patient hemodialysis unit to serve as out-patient hemodialysis

• Support from hospital administrators, dialysis unit, finance, billing

• Onsite pre- and post-infusion blood draw to HLA for crossmatch and Transplant Immunology Lab for immunologic monitoring

• Home infusion company as alternative for patients not on hemodialysis (pre-emptive or CAPD)
Complications of IVIG Therapy

Relationship to Product Composition
Product Features Affecting Tolerability

- Not all IVIGs are the same
- Finding the right product for the patient is a critical clinical concern
- Product features affecting tolerability include:
  - Volume load (rate of infusion)
  - Osmolality
  - Sodium content
  - Sugar content
- Side effects usually correlate with excipients (sucrose/sodium) and osmolality
IVIG Product Characteristics Affecting Tolerability

<table>
<thead>
<tr>
<th></th>
<th>Carimune® NF</th>
<th>Gamunex®</th>
<th>Gammagard® Liquid</th>
<th>Privigen®</th>
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<tbody>
<tr>
<td><strong>Form</strong></td>
<td>Lyophilized</td>
<td>Liquid</td>
<td>Liquid</td>
<td>Liquid</td>
</tr>
<tr>
<td><strong>Concentrations</strong></td>
<td>3%, 6%, 9%, 12%</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Sugar Content</strong></td>
<td>Sucrose, (1.67g per g of protein) (stabilized with glycine)</td>
<td>None (stabilized with glycine)</td>
<td>None (stabilized with glycine)</td>
<td>None (stabilized with L-proline)</td>
</tr>
<tr>
<td><strong>Sodium Content</strong></td>
<td>&lt;20mg per g of protein</td>
<td>Trace</td>
<td>None</td>
<td>&lt;0.05 mmol/L (&lt;1 mmol/L @ 10% IgG)</td>
</tr>
<tr>
<td><strong>Osmolarity/Osmolality</strong></td>
<td>mOsm/kg: In sterile water: 192 (3%), 384 (6%), 576 (9%), 768 (12%)</td>
<td>258 mOsm/kg</td>
<td>240-300 mOsm/kg</td>
<td>240-440 mOsm/kg</td>
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<tr>
<td></td>
<td>In 0.9% NaCl: 498 (3%), 690 (6%), 882 (9%), 1074 (12%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>In 5% dextrose: 444 (3%), 636 (6%), 828 (9%), 1020 (12%)</td>
<td></td>
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Reference: Product Package Inserts
### IVIG Product Characteristics Affecting Tolerability

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<tr>
<th></th>
<th>Gammagard® SD</th>
<th>Polygam® S/D</th>
<th>Flebogamma®</th>
<th>Octagam®</th>
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<td><strong>Form</strong></td>
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<td>Lyophilized</td>
<td>Liquid</td>
<td>Liquid</td>
</tr>
<tr>
<td><strong>Concentrations</strong></td>
<td>5% or 10%</td>
<td>5% or 10%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Sugar Content</strong></td>
<td>Glucose, 20 mg/mL (5% concentration)</td>
<td>Glucose, 20 mg/mL (5% solution)</td>
<td>D-Sorbitol, 50 mg/mL</td>
<td>Maltose, 100 mg/mL</td>
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<tr>
<td><strong>Sodium Content</strong></td>
<td>~8.5 mg/mL</td>
<td>8.5 mg/mL (5% solution)</td>
<td>&lt;3.2 mEq/L (&lt;0.02%)</td>
<td>≤30 mmol/L</td>
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<td><strong>Osmolarity/Osmolality</strong></td>
<td>5% 636 mOsm/L 10% 1250 mOsm/L</td>
<td>5% 636 mOsm/L 10% 1250 mOsm/L</td>
<td>240-350 mOsm/L</td>
<td>310-380 mOsm/kg</td>
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</table>

Reference: Product Package Inserts

Management of the Highly Sensitized Patient:
Clinical, Logistical, and Financial Considerations
Safety and Adverse Events Profiles of Intravenous Gammaglobulin Products Used for Immunomodulation: A Single-Center Experience


* Comprehensive Transplant Center, Transplant Immunology Laboratory, and Department of Medical Genetics, Cedars-Sinai Medical Center, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, California

### Results: Demographics

<table>
<thead>
<tr>
<th></th>
<th>Carimune® (N=98)</th>
<th>Gamimune® N (N=76)</th>
<th>Polygam® (N=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% AE or SAE</td>
<td>n=8 (SAE)</td>
<td>N/A</td>
<td>n=5 (SAE)</td>
</tr>
<tr>
<td>Gender</td>
<td>3M / 5F</td>
<td>N/A</td>
<td>2M / 3F</td>
</tr>
<tr>
<td>Age Range</td>
<td>39 y – 79 y</td>
<td>15 y – 75 y</td>
<td>34 y – 77 y</td>
</tr>
<tr>
<td>Type of AE/SAE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombotic</td>
<td>0</td>
<td>0</td>
<td>5 (4.7%) (P&lt;0.01)</td>
</tr>
<tr>
<td>ARF</td>
<td>8 (8.2%) (P&lt;0.001)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Others (HA)</td>
<td>49 (50%)</td>
<td>39 (52%)</td>
<td>52 (50%)</td>
</tr>
<tr>
<td>Doses</td>
<td>2g/kg = 7pts</td>
<td>2g/kg</td>
<td>2g/kg = 4pts</td>
</tr>
<tr>
<td></td>
<td>1g/kg = 1pt</td>
<td></td>
<td>1g/kg = 1pt</td>
</tr>
</tbody>
</table>
• 8 reports of ARF in patients receiving IVIG (February 2002 – July 2003)

• All occurred with Carimune® 9% ($P<0.0001$)

• Most patients recovered; however, 1 patient lost kidney allograft and returned to hemodialysis

90% of IVIG-induced acute renal failure episodes were associated with sucrose in sugar-containing preparations

<table>
<thead>
<tr>
<th>Stabilizer</th>
<th>Adverse events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sucrose</td>
<td>90</td>
</tr>
<tr>
<td>Glucose/maltose</td>
<td>8</td>
</tr>
<tr>
<td>Not defined</td>
<td>2</td>
</tr>
</tbody>
</table>

• Renal biopsy from a patient with osmotic nephropathy induced by sucrose-containing IVIG

• Patient received 9% solution. Shortly thereafter, her serum creatinine level rose to 7.4 mg/dL, and she required dialysis
5 reports of myocardial infarction in patients receiving IVIG
- Occurred from April 2001 – February 2002
- All associated with Polygam® 10% ($P<0.01$)
- Different lot numbers

Naranjo algorithm
- Moderate probability

Incidences reported to FDA MedWatch

Issue of Dear Doctor Letter from American Red Cross (March 2002)
Possible Mechanisms for IVIG-Related Thrombotic Events

- **Increased serum viscosity**
  - Impairs microcirculatory blood flow

- **Increased serum osmolality**
  - Erythrocyte shrinking and aggregation

- **Procoagulant activity in IVIG preparations**
  - Variations in IVIG manufacturing may affect level of Factor Xla in IVIG preparation
  - Factor Xla may lead to significant thrombin production

Stangel M. *ClinNeuropharmacol* 1997;20:385-393.
A 34 year-old man, blood type AB+, with ESRD secondary to FSGS received Gamunex® 10% (2g/kg) for desensitization 6 days prior to receiving transplant from a living related donor.

His hematocrit dropped significantly over 3 days (from 39% to > 16.9%) and he experienced fatigue and shortness of breath. He was admitted to hospital.

Diagnosis: Acute hemolytic anemia (Coombs [+] IgG/Polys)
- Anti-A IgG eluted from patients RBCs

Pathology: IgG Anti A and Anti B eluted from patient’s RBC due to IVIG.
IgG Anti-ABO (A) Activity in Different IVIG Products

- Carimune®
- Gamimune-N®
- Gamunex®
- Gammagard® liquid
- Privigen®
IgG Anti-ABO (B) Activity in Different IVIG Products

Titer

Dilution

- Carimune®
- Gamimune-N®
- Gamunex®
- Gammagard® liquid
- Privigen®
• To date, 10 patients (blood type A, B, AB) exhibited anemia due to hemolysis.
  - 7/10 required blood transfusions
  - 7/10 tested positive by direct antiglobulin method (DAT)

• Average pre- and post-IVIG hemoglobin values were 12.8g/dl (11.5-13.9) and 7.8 g/dl (6-11)
In patients at risk for hemolysis (i.e., those with blood type A, B or AB):
- Avoid high titer anti-A/B products
- Split IVIG dose: 1g/kg per day x2 days
- Monitor CBC within 1 week
- Use Carimune® if given on HD
IVIG is Safe to Give to Patients on Hemodialysis

<table>
<thead>
<tr>
<th>IGO2 Study Result</th>
<th>IVIG (Gamimune® N 10%)</th>
<th>Placebo (Albumin 0.1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>49</td>
<td>52</td>
</tr>
<tr>
<td>Infusions</td>
<td>300</td>
<td>318</td>
</tr>
<tr>
<td>AE (Reported)</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>SAE (Reported)</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Others (HA)</td>
<td>25 (52%)</td>
<td>12 (24%)</td>
</tr>
</tbody>
</table>


Management of the Highly Sensitized Patient:
Clinical, Logistical, and Financial Considerations
Rituximab

- Chimeric murine/human monoclonal antibody selectively depletes B cells bearing the CD20 surface marker
- Dose: 375mg/m² IVPB x1 or 1000mg x1 in 250cc NS over 6hrs
- Adverse effects: headache, nausea, vomiting, rash, hypotension, hypertension
- Pre-medications 30 minutes prior to infusion
Comparison of Two Desensitization Strategies for Highly-HLA Sensitized Patients: Viral Infections

<table>
<thead>
<tr>
<th></th>
<th>Number of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BK</td>
</tr>
<tr>
<td><strong>Group 1 (N=16)</strong></td>
<td>0</td>
</tr>
<tr>
<td><strong>Group 2 (N=109)</strong></td>
<td>5(5%)*</td>
</tr>
</tbody>
</table>

* BK viremia only no nephropathy

Group 1: IVIG x2 doses + Rituximab x2 doses
Group 2: IVIG x2 doses + Rituximab x1 dose

Vo et al. NEJM 2008;359:242-51
Vo et al. ATC 2008. Toronto, Canada (Abstract #8)

Management of the Highly Sensitized Patient:
Clinical, Logistical, and Financial Considerations
Safety Profile of Desensitization Protocols

- To date, 155 HS patients have been desensitized with IVIG (2g/kg x 2 doses) + rituximab (1-2 doses)
  - No patients have had neurologic symptoms suggestive of progressive multifocal leuko-encephalopathy
  - No infusion related side effects with pre-medication
  - Rates of ADE did not differ significantly among HS patients treated with IVIG during HD as compared with those who received placebo

To minimize risk of adverse events

- Administer pre-medications, 30 minutes before each IVIG & rituximab infusion:
  - Acetaminophen 650mg PO
  - Diphenhydramine 25-50mg PO or IVP
  - Methylprednisolone 40mg IVP or prednisone 40mg PO

- Limit maximum dose of IVIG to 140g for patients >70kg
Conclusions

• Most IVIG products are now isosmolar and come as liquid preparations, which reduces risk for thrombotic complications and ARF

• However, high titer of anti-A/B blood group antibodies may cause hemolysis in susceptible individual

• Rituximab has an acceptable safety profile in HS ESRD patients and does not increase risk for infections

• IVIG and rituximab are safe to give sequentially without reducing efficacy
Conclusions

• IVIG and rituximab protocol adds ~$24,000 to cost of transplantation

• This protocol is very robust for improving chances of transplantation for both LD and DD

• Dialysis cost for our HS patients awaiting DD transplant prior to desensitization was approximately $4.3 million for 58 patients

• 42 patients (72%) were transplanted within 2-5 months after desensitization
Financial Disclosure

Ms. Reeb reports no disclosures
Financial Considerations

- Treatment costs
- Infrastructure requirements
- Reimbursement strategies
- Return on investment
- Regulatory impact
## Components of Charges

<table>
<thead>
<tr>
<th>Type</th>
<th>Avg Inpatient Charges</th>
<th>Avg Pheresis Charges</th>
<th>Avg IGIV Charges</th>
<th>Total Charges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deceased Donor</td>
<td>$ 69,145</td>
<td>$ -</td>
<td>$ -</td>
<td>$ 69,145</td>
</tr>
<tr>
<td>Traditional Live Donor</td>
<td>$ 40,443</td>
<td>$ -</td>
<td>$ -</td>
<td>$ 40,443</td>
</tr>
<tr>
<td>Highly Sensitized Live Donor</td>
<td>$ 94,840</td>
<td>$ 14,912</td>
<td>$ 19,320</td>
<td>$ 129,072</td>
</tr>
</tbody>
</table>

*Based on JHH patients transplanted 1/1/06 – 12/31/08
Includes facility and physician fees*
## Components of Length of Stay

<table>
<thead>
<tr>
<th>Type</th>
<th>Total Inpatient Days</th>
<th>ICU Days</th>
<th>Pre-Op Days</th>
<th>Post-Op Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deceased Donor</td>
<td>13.5</td>
<td>1.3</td>
<td>0.1</td>
<td>13.4</td>
</tr>
<tr>
<td>Traditional Live Donor</td>
<td>8.0</td>
<td>1.2</td>
<td>0.1</td>
<td>7.9</td>
</tr>
<tr>
<td>Highly Sensitized Live Donor</td>
<td>20.3</td>
<td>2.2</td>
<td>4.7</td>
<td>15.6</td>
</tr>
</tbody>
</table>
## Infrastructure: Labor

<table>
<thead>
<tr>
<th>Position</th>
<th>Deceased Donor</th>
<th>Live Donor</th>
<th>HS/ Incom. Program</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Transplant Recipient Nurse Coordinators</td>
<td>2.00</td>
<td>1.50</td>
<td>2.00</td>
</tr>
<tr>
<td>Paired Donation Coordinator</td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Post-Transplant Nurse Coordinators</td>
<td>1.30</td>
<td>1.30</td>
<td>1.30</td>
</tr>
<tr>
<td>Nurse Extenders</td>
<td>2.00</td>
<td>5.00</td>
<td>3.00</td>
</tr>
<tr>
<td>Living Donor Pre &amp; Post Nurse Coordinators</td>
<td></td>
<td>1.50</td>
<td>0.70</td>
</tr>
<tr>
<td>Inpatient Nurse Practitioners</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Data Coordinators</td>
<td>1.00</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>Social Worker</td>
<td>0.75</td>
<td>0.75</td>
<td>0.50</td>
</tr>
<tr>
<td>Financial Coordinator</td>
<td>0.50</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>Organ Acquisition Billing Specialist</td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>Administrator/Regulatory Manager</td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>Total FTEs</strong></td>
<td><strong>8.95</strong></td>
<td><strong>12.45</strong></td>
<td><strong>10.90</strong></td>
</tr>
<tr>
<td><strong>Total Transplant Cost Center Labor</strong></td>
<td><strong>$ 657,771</strong></td>
<td><strong>$ 847,401</strong></td>
<td><strong>$ 811,926</strong></td>
</tr>
<tr>
<td><strong>Annual Transplant Volume</strong></td>
<td><strong>80</strong></td>
<td><strong>75</strong></td>
<td><strong>50</strong></td>
</tr>
<tr>
<td><strong>Salary &amp; Benefits Per Transplant</strong></td>
<td><strong>$ 8,222</strong></td>
<td><strong>$ 11,299</strong></td>
<td><strong>$ 16,238</strong></td>
</tr>
</tbody>
</table>
Reimbursement Strategies

• **Medicare:** Maximize cost report allowables, DRG limits, and secondary payers

• **Private:** Demonstrate savings from dialysis while waiting deceased donor (as well as likelihood of no transplant), ensure HS patients carved out of case rate contracts
## Reimbursement Strategies

<table>
<thead>
<tr>
<th>Organ Acq.</th>
<th>Reimbursement Method</th>
<th>Medicare</th>
<th>Commercial</th>
<th>Deceased Donor</th>
<th>Traditional Live Donor</th>
<th>HS Live Donor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney Donor (SAC or LD Evaluation &amp; Nephrectomy)</td>
<td></td>
<td></td>
<td></td>
<td>$ 29,500</td>
<td>$ 12,479</td>
<td>$ 12,479</td>
</tr>
<tr>
<td>Tissue Typing (pre and post)</td>
<td>Organ Acq.</td>
<td>Standard Acq. Charge</td>
<td>$ 13,160</td>
<td>$ 930</td>
<td>$ 11,000</td>
<td></td>
</tr>
<tr>
<td>Recipient Evaluation Testing</td>
<td></td>
<td>Billed at time of service</td>
<td>$ 9,425</td>
<td>$ 4,878</td>
<td>$ 8,030</td>
<td></td>
</tr>
<tr>
<td>Pre-Transplant Staffing</td>
<td></td>
<td>Include in SAC or IP Rates</td>
<td>$ 4,320</td>
<td>$ 6,474</td>
<td>$ 9,827</td>
<td></td>
</tr>
<tr>
<td>Other Hospital Overhead</td>
<td></td>
<td></td>
<td>$ 3,240</td>
<td>$ 4,856</td>
<td>$ 7,370</td>
<td></td>
</tr>
<tr>
<td>Sub-Total Organ Acquisition</td>
<td></td>
<td></td>
<td>$59,645</td>
<td>$29,617</td>
<td>$48,707</td>
<td></td>
</tr>
</tbody>
</table>
# Reimbursement Strategies

<table>
<thead>
<tr>
<th>Reimbursement Method</th>
<th>Charges Per Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deceased Donor</td>
</tr>
<tr>
<td>Medicare</td>
<td>Commercial</td>
</tr>
<tr>
<td><strong>Sub-Total Organ Acquisition</strong></td>
<td>$59,645</td>
</tr>
<tr>
<td>Transplant Inpatient Admission</td>
<td>$69,145</td>
</tr>
<tr>
<td>Inpatient Pheresis &amp; IGIV</td>
<td>Negotiated Rate</td>
</tr>
<tr>
<td>Outpatient Pre &amp; Post-Transplant Pheresis &amp; IGIV</td>
<td>Fee for Service</td>
</tr>
<tr>
<td>1 Year Post-Transplant Care (IP, OP, Immuno)</td>
<td>Fee for Service</td>
</tr>
<tr>
<td>Inpatient and Post Transplant Staffing</td>
<td>Not specifically billable</td>
</tr>
<tr>
<td><strong>Total Costs Transplant + 1 Year Per Transplant</strong></td>
<td>$166,570</td>
</tr>
</tbody>
</table>
## Cost Benefit

### 10 Year Healthcare Costs for Highly Sensitized Patient

<table>
<thead>
<tr>
<th>Estimated Wait-time to Transplant (years)</th>
<th>Per Year Cost</th>
<th>ESRD Patients PRA &gt;80</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Awaiting Compatible Transplant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.8*</td>
</tr>
<tr>
<td>Per Dialysis Patient Per Year Cost**</td>
<td>$ 85,158</td>
<td>$ 834,548</td>
</tr>
<tr>
<td>Transplant &amp; 1 Year Post*</td>
<td></td>
<td>$ 162,668</td>
</tr>
<tr>
<td>Per Transplant Patient Per Year Cost (year after transplant)**</td>
<td>$ 20,249</td>
<td>$ 4,050</td>
</tr>
<tr>
<td><strong>Total 10 Years</strong></td>
<td></td>
<td><strong>$ 1,001,266</strong></td>
</tr>
</tbody>
</table>

**Break-Even Point**

*JHH patients transplanted 1/1/98 - 12/31/08

### Medicare - The Biggest Financial Risk

<table>
<thead>
<tr>
<th></th>
<th>HS Transplant</th>
<th>LD Transplant</th>
<th>DD Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Avg Medicare Reimbursement for Inpatient Admission</td>
<td>$ 50,564</td>
<td>$ 50,564</td>
<td>$ 50,564</td>
</tr>
<tr>
<td>Average Hospital Charges</td>
<td>$ 117,072</td>
<td>$ 35,443</td>
<td>$ 56,145</td>
</tr>
<tr>
<td>Average Hospital Cost</td>
<td>$ 93,657</td>
<td>$ 31,899</td>
<td>$ 47,723</td>
</tr>
<tr>
<td>Uncovered Costs</td>
<td>$(43,093)</td>
<td>$ -</td>
<td>$ -</td>
</tr>
<tr>
<td>Outlier Threshold</td>
<td>$ 22,981</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outlier Payment</td>
<td>$ 17,840</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Reimbursement</td>
<td>$ 68,404</td>
<td>$ 50,564</td>
<td>$ 50,564</td>
</tr>
<tr>
<td>Margin</td>
<td>$(25,254)</td>
<td>$ 18,665</td>
<td>$ 2,841</td>
</tr>
<tr>
<td>Volume Transplants</td>
<td>50</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>Annual Profit Margin</td>
<td>$(1,262,686)</td>
<td>$ 1,399,898</td>
<td>$ 213,056</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>$350,268</strong></td>
</tr>
</tbody>
</table>
Return on Investment

- Increased “compatible” live donor volume
- Downstream/associated revenue generation
- Model appropriate payment from non-Medicare payers
Regulatory Impact

Inclusion of patients in SRTR outcomes data

Impacts Medicare, private payers and UNOS!
Conclusion

- Transplantation of highly sensitized patients is an expensive endeavor.
- What are not included in any of the cost data are physician time/effort, which is significant.
- As the option becomes more available to patients, costs are expected to decrease (as patients are being transplanted earlier in the ESRD).
Conclusion

• Careful management of the administrative aspects can assist in off-setting the expense (though not completely) and maximizing the total revenue

• Until there are changes in how CMS views these transplants (both reimbursement and outcomes), there will be significant barriers to performing them on a large scale
Desensitization Protocols: Clinical Coordination and Management

Janet Hiller, RN, MSN, CCTC
Johns Hopkins Hospital
Baltimore, MD
Ms. Hiller reports no disclosures
Factors Affecting Successful INKTP Transplant Outcomes

- Immunogenetic Profile
- Hospital Infrastructure
- Experienced Practitioners
- Co-Morbidities
- Psychosocial Stability
- Financial Means

Management of the Highly Sensitized Patient: Clinical, Logistical, and Financial Considerations

102
A PROFILE IN DETERMINATION

- Desperate
- Willing to accept greater risk
- Knowledgeable, motivated
- Multiple co-morbidities (mean 7/patient)
- Many with unrealistic expectations
Impact of an Incompatible Transplant Program on Hospital Resources

These programs have a far reaching impact on most hospital resources.

Infrastructure is crucial to successful patient outcomes.
Interdepartmental Cooperation

- Transplant Surgery, Staff and Coordinators
- Urology Surgery
- Operating Room Staff
- Anesthesia
- PACU
- Pre-operative Evaluation Center
- Transplant Outreach Department
- Ethics Committee
- Risk Management
- Hospital Laboratories
- Admissions

- Nursing Staff
- ICU Staff
- Nephrology Department
- Inpatient Dialysis
- Patient Representatives
- Transplant Business Office
- Department of Social Work
- Department of Psychiatry
- Department of Public Affairs
- Immunogenetics Lab
- Department of Surgical Pathology
- Transfusion Medicine, Plasmapheresis
Hospital Infrastructure

- Immunogenetics Lab
- Blood Bank capable of isoagglutinin titering
- Infusion Room: 10 hour/day, 5 days/week
- Inpatient dialysis: 7 day support
• **Plasmapheresis**: flexibility, 7 days/week support
  - +XM (n=150) 1522 treatments
  - ABOI (n=59) 691 treatments

• **Pathology**: clinical and protocol biopsies
  - 913 biopsies (85% in +XM group)
Experienced Practitioners

- Surgeons
- Nephrologists
- Immunogenetic technicians
- Surgical pathologists
- Transplant nurses
- Social Workers
- Psychologists
- Administrators
Preparation for Desensitization Begins at Evaluation

Assessment Parameters Prior to Desensitization Treatment

- Vascular Access
- Anemia Management
- Splenectomy Prophylaxis
- Current Medications
- Allergies
- Hypercoagulopathy Screening
- Stability on Dialysis
Patient Issues During Planning Phase

• Obtain insurance authorization
• Adequate financial plan during transplant period and recuperation
• Purchase pre-transplant immunosuppression
Patient Issues During Planning Phase

• Communicate with home nephrologist for follow-up care
• Arrange for support system; friends, family to assist
• Identify pharmacy while away from home
• Reserve local housing
• Secure transient dialysis pre-transplant
Pre-Transplant
ABO Incompatible and Highly Sensitized

8 Weeks Pre-Transplant
Procedure/Test/Event
• Confirm vaccinations have been administered
• Schedule transplant
• Schedule pre-plasmapheresis evaluation
• Schedule outpatient hemodialysis, if needed
• Create schedule of pre-transplant treatments

4 Weeks Pre-Transplant
Procedure/Test/Event
• Notify nephrologist of transplant date and need to discontinue ACE inhibitors 2 weeks pre-transplant
• Schedule plasmapheresis
• Schedule CMV-IGIV infusion
• Schedule DAVOL catheter placement
Follow-Up post Incompatible Kidney Transplant

DSA Titers and Screening (XM and solid phase)

- Before and after each pp treatment
- 72 hours after the last treatment
- Any suspected clinical change
- AMR on biopsy
- Weekly for the 1st month
- At 2, 3, 6, 12 months
Follow-Up post Incompatible Kidney Transplant

• Biopsies Triggered by:
  • Clinical change
  • Rise in titers
  • By protocol: pre and post-reperfusion at 1, 3, 6, and 12 months