IMMUNOLOGIC RISK ASSESSMENT IN KIDNEY TRANSPLANTATION

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İstanbul Memorial Hospital
Department of Organ Transplantation
In the beginning there were ESRD patients. There were nephrologists. There were transplant surgeons. Eventually there were transplants. And, almost immediately there were rejections!

How to deal with predicting and preventing rejections?
Table 1. Direction of acceptable organ transfer when the donor and recipient have different ABO red blood cell types.

<table>
<thead>
<tr>
<th>Transfer*</th>
<th>Acceptability</th>
<th>Rej+</th>
<th>Rej-</th>
</tr>
</thead>
<tbody>
<tr>
<td>O to non-O</td>
<td>Safe</td>
<td>24</td>
<td>6</td>
</tr>
<tr>
<td>Rh- to Rh+</td>
<td>Safe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rh+ to Rh-</td>
<td>Relatively safe</td>
<td></td>
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</tr>
<tr>
<td>A to non-A</td>
<td>Dangerous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B to non-B</td>
<td>Dangerous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AB to non-AB</td>
<td>Dangerous</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

From Starzl [54].

Patel ve Terasaki, 1969, NEJM
• CDC CXM

↓

• Preformed Anti-HLA Antibodies

↓

X

• AMR and rapid graft loss
Therefore, a positive crossmatch became a strict contraindication to transplant!
The Cell Surface Is a Jungle
• to detect

CLINICALLY RELEVANT HLA-reactive donor specific IgG antibodies.
Goals in Antibody Detection

1. Is HLA antibody present?  
   **Sensitivity**

2. Is the antibody clinically relevant?  
   **Specificity**

   *HLA vs Non-HLA*  
   *Which HLA – Class, antigen, allele*  
   *Antibody Type – IgG, IgM*

   **Quantitative assessment**
TRANSPLANTABILITY INDEX

To predict the results of incompatibility between the donor and the recipient
WHAT ARE THE TOOLS?
1969. CDC XM
1970. Amos CDC CM
1972. AHG CDC XM T
1984. AHG CDC XM B
1984. Flow Cytometric XM
2011. IDENTIFY RELEVANT AB
Methods to Assess Sensitization

Cell based
- CDC crossmatch
- Flow Cytometry

Solid phase
- Luminex

Functional Assays
- Detection and quantitation Assay

Always donor tissue (lymphocytes) + recipient Abx (serum)
Sensitivity of Antibody Detection Methods

CDC  CDC-AHG  ELISA  FLOW  Luminex SAB
Histocompatibility Techniques: Role in Risk Assessment

α-HLA-Antibody Titers

Cell-C’ based assays

Solid-phase assays

Specificity

NIH-Crossmatch

AHG-CDC

ELISA

Cell-based Flow Cytometry

Microbeads Luminex®

Sensitivity
Hierarchy of sensitization evaluation

Clinical

Luminex

FXM

CDC crossmatch
Complement Dependent Cytotoxic Crossmatch (CDC CM)

CDC CXM (+): Anti-HLA Class I Ig G (+)
Anti-human Globulin (ENHANCED) LCM

1. Target Cell + serum + IgG → cell surface binding

2. Target Cell + C (vital dye) → No Ab - Few Ab?
   - Etidium bromid
   - Acridin oranj

3. Target Cell + goat anti-human IgG + vital dye →
T or B cell Flow cytometric crossmatch

Increase in fluorescence intensity seen in "channel shift" and relates to Increased Ab activity
AHG T cell CXM and FXM
Single Antigen Screening
New Technology for HLA Antibody Screening
HLA Antibody Screening by Luminex

1. Mix beads coupled to purified HLA antigens with patient sera in a membrane filter plate. Incubate for 30 minutes.

3. Add antihuman IgG with PE to membrane filter plate. Incubate 30 minutes.
Luminex Testing

- Red laser ID’s which bead
- Green laser detects intensity of reaction on the bead
# Screening for HLA Antigens

<table>
<thead>
<tr>
<th>DR</th>
<th>DQ</th>
<th>DP</th>
<th>B</th>
<th>C</th>
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<td>DQw1</td>
<td>DPw1</td>
<td>Bw4</td>
<td>Cw1</td>
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</table>
SINGLE ANTIGEN DSA ANALYSIS
Luminex-based determination of donor-HLA-specific Ab before kidney transplantation

DONOR HLA A11, A24, B7, B15, DR9, DR15

DR9, 15, 53, 51
Luminex and FXM at the UWHC

35 patients with B or T cell + FXM

R² = 0.33
P=0.002
• **Mayo:**

• B FCXM $< 200$ MCS (MFI $\approx 5000$)

• T FCXM (200 MCS) $\approx 7000$ MFI
Virtual CXM: To predict FCXM results.

Mean fluorescent intensity (MFI) >2000
Unacceptable antigens

MFI 1000-2000
Should be followed

MFI <1000
Acceptable Ag
Strategy of Minimizing Immunologic Risk

Mean fluorescent intensity (MFI) >3000
Unacceptable antigens

MFI <1000
Acceptable Ag

<table>
<thead>
<tr>
<th>Risk</th>
<th>MFI</th>
<th>CDC-CXM</th>
<th>FCXM</th>
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<tr>
<td>High</td>
<td>&gt;8500</td>
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<td>Moderate</td>
<td>2000-8499</td>
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<td>+</td>
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<td>Low</td>
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<tr>
<td>Negligible</td>
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>2000 MFI Unacceptable antigens
Baseline Donor-Specific Antibody Levels and Outcomes in Positive Crossmatch Kidney Transplantation

<table>
<thead>
<tr>
<th>DSA Activity</th>
<th>DSA Titer (MFI)</th>
<th>T-AHG CDC</th>
<th>T/B FCXM &gt; 300 CS</th>
<th>T/B FCXM &lt; 300 CS</th>
<th>T/B FCXM</th>
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<td>+</td>
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<td>+</td>
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<tr>
<td>None</td>
<td>None</td>
<td></td>
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<td>--</td>
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</tbody>
</table>

Baseline Donor-Specific Antibody Levels and Outcomes in Positive Crossmatch Kidney Transplantation

Baseline DSA level analyzed using Luminex single antigen flow beads vs. cell-based crossmatch transplant group.

(A) Sum of HLA class I and II DSA combined MFI (mean ± SD):
(B) (T-AHG-CDC+: 24 649 ± 14 252; FXMCS >300: 13 722 ± 10 578;
(C) FXMCS <300: 4392 ± 4250; −XM: 2266 ± 2750).
(D) (T-AHG-CDC+ vs. FXM CS>300 vs. FXM CS <300; p < 0.0001).

Baseline Donor-Specific Antibody Levels and Outcomes in Positive Crossmatch Kidney Transplantation (B FCXM>200 CS)

<table>
<thead>
<tr>
<th>DSA Activity</th>
<th>B FCXM &lt; 300 CS</th>
<th>B FCXM ≥ 300 CS</th>
<th>B FCXM &gt; 450 CS</th>
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<tr>
<td>Very High</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>High</td>
<td></td>
<td>+</td>
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<tr>
<td>Low</td>
<td>+</td>
<td></td>
<td></td>
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<tr>
<td>None</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do Tx</td>
<td></td>
<td>PE</td>
<td>No Tx</td>
</tr>
</tbody>
</table>

Pre-existing or De Novo DSA are Associated with Worse Graft Survival

The presence of HLA-DSAs on the highest rank pregraft serum associates with a significantly decreased graft survival (A), regardless of whether HLA-DSAs were class I or II (B).

Lefaucheur C et al. JASN 2010;21:1398-1406
The graft survival in patients with preexisting HLA-DSA MFIs >3000 is significantly lower than in patients with HLA-DSA MFIs ≤3000.

Lefaucheur C et al. JASN 2010;21:1398-1406

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FIGURE 3. A Kaplan–Meier estimate of death-censored graft survival associated with three pre-desensitization donor-specific antibody strength thresholds: a positive CDC cytotoxic crossmatch, producing inferior outcomes, and equivalent outcomes for either a positive flow cytometric cross-match (negative CDC cytotoxic cross-match), or donor-specific antibody detectable by a luminex platform with a negative flow cytometric cross-match.
FIGURE 1. Donor T-cell flow cytometric crossmatch (FXM) results expressed as MCS vs. corresponding SFI value for the highest DSA single antigen bead. (□, patients who experienced AMR; ◊, patients with no AMR.)

Assessment of Rejection Risk
Based on preformed DSA on Luminex and FXM Channel Shifts.
One size does not fit all!

Recipients with HLA Ab, but (-) FCXMs are at risk for rejection. (30-50%)

The greater the % of HLA Ab, the earlier the rejection.
• Luminex is highly sensitive and specific for the target antigen but less clinically predictive, with successful transplants despite MODERATELY strong pretransplant DSA as measured by MFI and (-) FXM.
• Not all IgG Ab are a contraindication to transplant, nor do all appear to be immediately detrimental peri- or posttransplant.
Methods

C1q Assay Based on the Single Ag Bead Technology

Dolly Tyan (Stanford University)
High Specificity of C1q Assay

Dolly Tyan (Stanford University)
Clinical usefulness of a novel C1q assay to detect immunoglobulin G antibodies capable of fixing complement in sensitized pediatric heart transplant patients

Clifford Chin, MD, Ge Chen, MD, Flavia Sequeria, MD, Gerald Berry, MD, Stephanie Siehr, MD, Daniel Bernstein, MD, David Rosenthal, MD, Olaf Reinhartz, MD, and Dolly Tyan, PhD

From the "Department of Pediatrics, Division of Pediatric Cardiology, the "Department of Pathology, and the "Department of Surgery, Division of Pediatric Cardiothoracic Surgery, Stanford University, Stanford, California.

CONCLUSIONS: The C1q assay can detect a sub-set of antibodies capable of fixing complement and predicts AMR early after transplant. Avoiding only the donor antigens that would be recognized by the C1q assay may accelerate time to transplant by expansion of the donor pool and potentially allows transplantation of previously “incompatible” organs.
C1q Binding Anti-HLA-DSA

% Graft Survival

Years Post-transplant

n= 700 691 668 613 504 338 164 38

n= 316 237 297 251 179 102 58 19

P<0.0001

Loupy A, Lefaucheur C, in submission
C1q Binding Anti-HLA-DSA

% Graft Survival

Years Post-transplant

DSA neg (n=700)

DSA pos C1q neg (n=239)

DSA pos C1q pos (n=77)

P<0.0001

n= 700 691 668 613 504 338 164 38

n= 316 237 297 251 179 102 58 19

n= 77 75 69 49 38 21 13 5

Loupy A, Lefaucheur C, in submission
• 53% of HLA-Ab specificities identified by Luminex could not bind C1q, suggesting that about half of the IgG antibodies may not have an immediate (or even late?) adverse effect on the graft.
Fig. 5  Comparison of human leukocyte antigen class I and II results by immunoglobulin G (IgG) and C1q. Patient sera ($n = 23$) were tested by IgG and C1q single antigen beads for class I and II. Sera are represented in the class I an...

G. Chen, F. Sequeira, D.B. Tyan

**Novel C1q assay reveals a clinically relevant subset of human leukocyte antigen antibodies independent of immunoglobulin G strength on single antigen beads**

Human Immunology Volume 72, Issue 10 2011 849 - 858

http://dx.doi.org/10.1016/j.humimm.2011.07.001
CASE–1

- 20-year-old male patient
- LRDK-Tx (1st transplant) (Donor: Mother)
- History of blood transfusions: 1 Unit PRBC (2011)
- History of peritonitis ×2
CASE-1

• Before Tx:

• HLA DQ B1*02:01 (DSA) (MFI:13561) (LUMINEX SINGLE BEAD)
CXM

- FCXM T: 0.74 %  
- B: 2.38 %

- No channel shift

---

- C1q NEGATIVE for DQ
- (LUMINEX SINGLE BEAD)
CASE–2

• 48-year-old female patient
• LRDK-Tx (1st transplant) (Donor: Husband)
• History of blood transfusions: 2 Unit PRBC (2010)
• History of pregnancy ×3
CASE-2

• Before Tx:

• HLA C 07 (DSA) (MFI:17000)
• HLA C 12 (DSA) (MFI:15252)  
  (LUMINEX SINGLE BEAD)
• FCXM T: 1.01 %    B: 12.36 %

• C1q POSITIVE for C 07
  (LUMINEX SINGLE BEAD)
CASE – 3

• 48-year-old, female patient
• 8 Pregnancies
• Positive history for blood transfusions
• Donor: Husband
CASE-3

• PRE-Tx:
  — PRA Class I: %1.8
  — PRA Class II % 13.3

• FCXM T: % 0.6  B: % 2.2

• AHG-CDC T: --  AHG-CDC B: --

• NIH-CDC: --
• DSA FOR HLA DR04 (MFI> 20000) (LUMINEX SINGLE BEAD)
CASE-3

- Preoperative desensitization:
  - Plasmapheresis
  - IVIG (500 mg/kg)

- Post desens.:
  - DSA FOR HLA-DR 04 (MFI<8000)
    (LUMINEX SINGLE BEAD)
Important Therapeutic Options for ABMR

- Therapies aimed at
  - Antibodies: Plasmapheresis/IVIG
  - B cells: Rituximab
  - Plasma cells (B-cell effectors): Bortezomib
  - Complement: Eculizumab
CASE-3

- Post-Tx: AMR-Lost the graft
- C1q HLA-DR 04: POSITIVE
• CDC (+) Ab ---------- C1q (+)
• C1q (+) Ab ---------- 19% CDC (+)
Hysterically Historical Statement

Besides confirmation of ABO, the pretransplant crossmatch is the most important assay performed in the transplant laboratory.

New Paradigm

The ability to identify the presence of IgG-HLA Abs in patient sera allows us to discriminate clinically relevant from irrelevant crossmatches.
Without knowledge of the patient’s antibody status, crossmatch results are of little or no value.
An IgG-positive crossmatch (alone) should no longer be a contraindication to transplant.
Knowing that sera contain HLA Abs contributes to the interpretation of the data and clinical decision making.
HLA Ab specificity is important.

A serum with (+) HLA Ab and (+) FCXM will result in rejection and a high percentage of graft loss, although not necessarily 100% loss.
Patients with high titer (donor-specific) HLA Abs are a serious challenge.

HLA Ab titer is important:
Patients with donor-specific HLA Abs are at high risk for rejection and graft loss.

However, patients with low titer donor-specific HLA Abs may be candidates for desensitization and/or rejection reversal protocols.

Patients with high titer (donor-specific) HLA Abs are a serious challenge.
Desensitization Improves Patient Survival in HLA-Incompatible Kidney Recipients

MPA, mycophenolic acid; ATG, anti-thymocyte globulin; IL, interleukin; IVIG, intravenous immunoglobulin; PP, plasmapheresis; Tx, transplant.

Figure 2. Survival Benefit of Desensitization According to Strength of Cross-Matching for Donor-Specific Anti-HLA Antibody.

Kaplan–Meier survival estimates are shown for kidney recipients in the treatment group, as compared with the two matched control groups of patients on a kidney waiting list who continued to receive dialysis (dialysis-only group) or who either continued to undergo dialysis or underwent HLA-compatible transplantation (dialysis-or-transplantation, or dual therapy, group), according to whether donor-specific anti-HLA antibody was detected on the multiplex bead assay (Panel A), flow-cytometric assay (Panel B), or positive complement-dependent cytotoxicity assay (Panel C).
Luminex-Based Desensitization Protocols Significantly Decreases DSA at the Time of Transplant

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Tx Type</th>
<th>MFI Maximum</th>
<th>Induction</th>
<th>PE+IVIG</th>
<th>TAC+MPA 1wk pre-Tx</th>
<th>Target TAC level (ng/mL)</th>
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<tr>
<td>No DSZ</td>
<td>LD</td>
<td>0-100</td>
<td>Basiliximab</td>
<td>-</td>
<td>-</td>
<td>8-10</td>
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<td>Basiliximab</td>
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<td>8-10</td>
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<tr>
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<tr>
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<td>LD</td>
<td>1001-3000</td>
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<td>+</td>
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<td>Thymoglobulin</td>
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<tr>
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<td>DD</td>
<td>1001-3000</td>
<td>Thymoglobulin</td>
<td>1 pretransplant, 2 posttransplant</td>
<td>-</td>
<td>9-11</td>
</tr>
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</table>

Tx, transplantation; LD, live donor; DD, deceased donor; FXM, flow cytometry crossmatch; PE-IVIG, plasmapheresis and intravenous immunoglobulins; TAC+MPA, tacrolimus and mycophenolic acid; MFI, mean fluorescence intensity; DSZ, desensitization.
### UW desensitization and induction immunosuppression protocols based on DSA

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Sub-protocol</th>
<th>Donor</th>
<th>MFI&lt;sub&gt;max&lt;/sub&gt;</th>
<th>Biopsy (reperf)</th>
<th>Simulect 20mg d0,4</th>
<th>Thymo 5-10mg/kg</th>
<th>Ritux 375mg/m&lt;sup&gt;2&lt;/sup&gt;</th>
<th>PE + IVIG 100 mg/kg</th>
<th>TAC Dose/target</th>
<th>MPA 1g IV bid</th>
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<tr>
<td>P0</td>
<td>-</td>
<td>L</td>
<td>0-100</td>
<td>±</td>
<td>x</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Target 7-9</td>
<td>d0</td>
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<tr>
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<td>-</td>
<td>L</td>
<td>1000-3000</td>
<td>x</td>
<td>x</td>
<td>-</td>
<td>±</td>
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<td>x</td>
<td>x</td>
<td>-</td>
<td>±</td>
<td>-</td>
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<td>d-7 oral</td>
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<tr>
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<td>-</td>
<td>L</td>
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<td>x</td>
<td>-</td>
<td>±</td>
<td>d-3,-1,+1,+3</td>
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<td>x</td>
<td>-</td>
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<td>x</td>
<td>-</td>
<td>x</td>
<td>-</td>
<td>-</td>
<td>Target 9-11</td>
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<td>-</td>
<td>d-1,+1,+3</td>
<td>Target 9-11</td>
<td>d0</td>
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</table>

*The DSA algorithm to follow once a deceased donor becomes available
1-Obtain the UNOS runoff sheet for potential recipients
2-Determine top 4-5 patients’ Immunodominant MFI (MFI<sub>max</sub>) for *mismatched antigens* using the Luminex AB ID report in WISCR or Health Link. Exact MFI values (in addition the bar graphs) will soon be scanned in and available as well.
3-Once a patient is selected by the surgeon, the induction immunosuppressive protocol may be decided based on the MFI<sub>max</sub>

**These protocols are general guidelines and may be modified according to provider-patient criteria.**
Immune Considerations for Solid Organ Transplantation

All donors and recipients must be ABO compatible.

Patients must be tested for the presence of clinically relevant donor-specific antibody.

Donors and recipients are matched for HLA antigens to improve kidney allograft survival. Matching may be done for heart, liver, pancreas or lung transplants.
Suggested Solution

New technologies help to define “acceptable” HLA mismatches.

Instead of pairing donors and recipients by HLA matching we should look for the recipient that has no reactivity against donor.
There are Many Strategies to Prevent Antibody Mediated Rejection

- Wait for compatible donor for highly sensitized patients
- Use kidney-paired donation(s)
  - ABO
  - HLA incompatible
- KPD/Desensitization---Hybrid approach
- Acceptable mismatch program (Eurotransplant)
- Perform pretransplant desensitization: depletion of DSA
  - Plasmapheresis plus IVIG*
  - Addition of rituximab*† (anti-CD20 antibody)?
  - Addition of bortezomib*‡ (proteasome inhibitor) or eculizumab*‡ (C5 inhibitor)?
- High anti-donor antibody titer after treatment = poor long-term prognosis

IVIG, intravenous immunoglobulin.
*These drugs are used off label in solid organ transplant recipients.
‡Eculizumab has a boxed warning in the full prescribing information at http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/125166lbl.pdf.
WHAT DO WE DO?

• CDC CXM
  – DILUTIONS?
• FCXM T VE B
  – CHANNEL SHIFT?
• DSA
  – MFI?
  – C1q +/-
  – IG 1/2/3/4 -- NOT YET
WHAT DO WE DO?

• LRDK-TX: HLA A, B, Cw
  HLA DR, DQ, DP

• MFI < 5000 ----- OK
• MFI > 10000 --- Poor Prognosis
• MFI < 7000-8000 ----- OK (First kidney Tx)
• After desensitization 50% ↓ MFI ----- Significant drop
• After desensitization MFI < 5000 ----- OK
• C1q (+) (>50-100): Don’t do!
“How often have I said to you, that when you have eliminated the impossible, whatever remains, however improbable must be the truth.”

-Sherlock Holmes