Acute and Chronic ABMR Outcomes
in the Context of Memory or Naïve Alloimmunity

FDA Workshop, ABMR in Kidney Transplantation
12 April 2017

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Flynn Family Chair in Renal Transplantation
Professor of Internal Medicine and Immunology
Relevant Financial Relationship Disclosure Statement

Peter Nickerson, University of Manitoba, Winnipeg, Canada

Consultant for Astellas, GSK, Novartis and Vitaeris

AND

My presentation does include discussion of off-label or investigational use of drugs
Preformed DSA and Kidney Graft Outcomes

NATURAL HISTORY
Unrecognized Immunologic Memory
Clinical & Subclinical ABMR prevalent with Pre-transplant DSA

55% of patients with HLA-DSA developed clinical/subclinical AMR
if not desensitized pre-transplant

CDC CXM negative pre-transplant

Pre-Tx SAB DSA +ve (MFI >500)

Pre-Tx SAB DSA -ve

Patients with HLA-DSA (n=67)
P=0.0001

Patients without HLA-DSA (n=267)

Probability of AMR [%]

Days post-transplant

55% of patients with HLA-DSA developed clinical/subclinical AMR
if not desensitized pre-transplant

Amico P. Transplantation (2009) 87:1681-1688
Patients with HLA-DSA and clinical/subclinical AMR had a 20% lower death-censored graft survival at 5 years.
78% subclinical ABMR had pre-transplant DSA

At 1 year all subclinical ABMR had DSA detectable
SAB MFI = 2550 ± 580
Baseline Donor-Specific Antibody Levels and Outcomes in Positive Crossmatch Kidney Transplantation

J. M. Gloora,*, J. L. Wintersb, L. D. Cornellb
L. A. Fixc, S. R. DeGoeyb, R. M. Knauerb,
F. G. Cosioa, M. J. Gandhind, W. Kremersd
and M. D. Stegalli

AJT (2010) 10: 582-589

A

XM -

FCXM <300

FCXM >300

AHG+

MCS (Mean Channel Shift)

Post Transplant Day

B

NO DSA

Cl/II DSA <5,000

Cl/II DSA >5,000<10,000

Cl/II DSA >10,000

MFI (Mean Fluorescence Intensity)

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

J. M. Gloor\textsuperscript{a,\,*}, J. L. Winters\textsuperscript{b}, L. D. Cornell\textsuperscript{b}, L. A. Fix\textsuperscript{c}, S. R. DeGoey\textsuperscript{b}, R. M. Knauer\textsuperscript{b}, F. G. Cosio\textsuperscript{a}, M. J. Gandhi\textsuperscript{b}, W. Kremers\textsuperscript{d} and M. D. Stegall\textsuperscript{c}

A

XM -

FCXM <300

FCXM >300

AHG+

B

NO DSA

Cal/II DSA <5,000

CI/II DSA >5,000 <10,000

CI/II DSA >10,000

AJT (2010) 10: 582-589
De novo DSA and Outcomes

ETIOLOGY AND NATURAL HISTORY
Class II is the dominant de novo DSA

Only 1 patient with an isolated Class I dnDSA has resulted in graft failure, out of 596 transplants

Non-Adherence is a major risk factor for de novo DSA

Wiebe et al., AJT (2015) 15: 2921-2930
At onset of de novo DSA, 76% meet ABMR criteria (Banff 2013)

<table>
<thead>
<tr>
<th>Banff Grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>g</td>
<td>(55%, 32%, 13%, 0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i</td>
<td>(28%, 24%, 24%, 24%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t</td>
<td>(39%, 32%, 11%, 18%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>v</td>
<td>(94%, 3%, 0%, 3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ptc</td>
<td>(24%, 10%, 45%, 21%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C4d</td>
<td>(52% C4d positive)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cg</td>
<td>(87%, 8%, 5%, 0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ci</td>
<td>(29%, 37%, 19%, 5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ct</td>
<td>(11%, 53%, 26%, 10%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cv</td>
<td>(40%, 47%, 13%, 0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TCMR** (Banff 2007) common (91% with ABMR)
- 32% Borderline
- 29% ≥ Grade 1

Only 18% have no TCMR or ABMR

**Transplant glomerulopathy uncommon**

**IFTA common**

Wiebe et al., AJT (2015) 15: 2921-2930
Biopsy Predictors for Graft Loss at DSA onset
Consecutive Adult and Pediatric Kidney Transplants (n=508, 1999 to 2012)

76% ABMR\textsubscript{(Banff 2013)} at biopsy for \textit{de novo} DSA

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>g</td>
<td>1.53 (0.8-2.9)</td>
<td>0.2015</td>
</tr>
<tr>
<td>i</td>
<td>1.77 (1.2-2.9)</td>
<td>0.0083</td>
</tr>
<tr>
<td>t</td>
<td>2.73 (1.6-5.0)</td>
<td>0.0002</td>
</tr>
<tr>
<td>v</td>
<td>0.95 (0.1-2.1)</td>
<td>0.9240</td>
</tr>
<tr>
<td>ptc</td>
<td>1.11 (0.7-0.9)</td>
<td>0.6663</td>
</tr>
<tr>
<td>C4d</td>
<td>1.33 (0.4-4.4)</td>
<td>0.6203</td>
</tr>
<tr>
<td>cg</td>
<td>2.14 (1.0-4.1)</td>
<td>0.0575</td>
</tr>
<tr>
<td>ci</td>
<td>1.38 (0.8-2.5)</td>
<td>0.2735</td>
</tr>
<tr>
<td>ct</td>
<td>1.36 (0.8-2.4)</td>
<td>0.2840</td>
</tr>
<tr>
<td>cv</td>
<td>1.11 (0.6-2.1)</td>
<td>0.7434</td>
</tr>
</tbody>
</table>

Banff cg score increases 1 grade per 3 years of post \textit{de novo} DSA follow-up
(R\textsuperscript{2} = 0.36, p=0.0018)

Wiebe et al., AJT (2015) 15: 2921-2930
Biopsy Predictors for Graft Loss at DSA onset
Consecutive Adult and Pediatric Kidney Transplants (n=508, 1999 to 2012)

Microvascular inflammation grade & C4d⁺ does not correlate with graft loss

Wiebe et al., AJT 2015; 15: 2921-2930
Time to Graft Loss from de novo DSA Onset
Consecutive Adult and Pediatric Kidney Transplants (n=508, 1999 to 2012)

Mean time to graft failure from 1st detection of de novo DSA
~ 3.3 to 8.3 years

Wiebe et al., AJT (2015) 15: 2921-2930

Multivariate
- de novo DSA
- early TCMR\textsubscript{0-12}mo
- non-adherence

Post-dnDSA Graft Survival

Follow-up (years)

Subclinical dnDSA
Clinical dnDSA

p<0.0001

Mean time to graft failure from 1st detection of \textit{de novo} DSA
~ 3.3 to 8.3 years
Model of Alloimmune Mediated Graft Loss

Under Immunosuppression
- Physician guided
- Non-adherence

HLA MM (Class II)
- CNI Toxicity
- Donor Age
- Brain Death
- IRI
- DGF

Subclinical > Clinical
- TCMR
- “smoldering”
- dnDSA
- ABMR

“smoldering”

IFTA

Graft Loss

Wiebe et al., Transplantation (2016) 100:2048-2052
Memory vs. De Novo
Preexisting, compared to *de novo*, DSA ABMR occurs sooner and has a lower rate of graft failure.
**Antibody-Mediated Rejection Due to Preexisting versus De Novo Donor-Specific Antibodies in Kidney Allograft Recipients**

Olivier Aubert,* Alexandre Loupy,*‡‡ Luis Hidalgo,§‖ Jean-Paul Duong van Huyen,¶ Sarah Higgins,** Denis Viglietti,**†† Xavier Jouven,* Denis Glotz,*‡‡ Christophe Legendre,*†† Carmen Lefaucheur,*†† and Philip F. Halloran‖‖

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**de novo DSA ABMR has more TG, TCMR, IFTA and proteinuria at diagnosis**

- likely delayed recognition of the process with de novo DSA

→ Subclinical ABMR 22.3% pre-existing vs. 8.8% de novo DSA

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<table>
<thead>
<tr>
<th>Parameters</th>
<th>Preexisting Anti-HLA DSA ABMR (n=103)</th>
<th>De Novo Anti-HLA DSA ABMR (n=102)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>g (0–3), mean (SD)</td>
<td>1.71 (1.02)</td>
<td>1.06 (0.91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ptc (0–3), mean (SD)</td>
<td>1.76 (0.98)</td>
<td>1.66 (1.00)</td>
<td>0.47</td>
</tr>
<tr>
<td>C4d positive, n (%)</td>
<td>53 (51.46)</td>
<td>39 (42.39)</td>
<td>0.13</td>
</tr>
<tr>
<td>cg (0–3), mean (SD)</td>
<td>0.48 (0.94)</td>
<td>1.28 (1.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>i (0–3), mean (SD)</td>
<td>0.61 (0.92)</td>
<td>1.23 (1.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>t (0–3), mean (SD)</td>
<td>0.59 (0.90)</td>
<td>1.01 (1.11)</td>
<td>0.003</td>
</tr>
<tr>
<td>v (0–3), mean (SD)</td>
<td>0.32 (0.65)</td>
<td>0.22 (0.60)</td>
<td>0.29</td>
</tr>
<tr>
<td>ci (0–3), mean (SD)</td>
<td>0.96 (1.04)</td>
<td>1.60 (0.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ct (0–3), mean (SD)</td>
<td>0.99 (0.99)</td>
<td>1.60 (0.91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>cv (0–3), mean (SD)</td>
<td>1.26 (1.00)</td>
<td>1.44 (0.98)</td>
<td>0.2</td>
</tr>
<tr>
<td>ah (0–3), mean (SD)</td>
<td>0.97 (0.92)</td>
<td>1.53 (1.05)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Immunology at the time of the ABMR biopsy**

| Anti-HLA DSA class 1, n (%) | 40 (38.83) | 26 (25.49) |        |
| Anti-HLA DSA class 2, n (%) | 63 (61.17) | 76 (74.51) | 0.02 |
| Anti-HLA DSA MFI, median [IQR] | 2561 [1252–6937] | 7295 [1948–11,814] | <0.001 |

**Renal function**

| eGFR, ml/min per 1.73 m², mean (SD) | 39.00±18.26 | 41.65±21.19 | 0.34 |
| Proteinuria, g/g creatinine, mean (SD) | 0.51±1.05 | 1.51±2.51 | <0.001 |
de novo DSA ABMR has more IFNγ, NK and T-cell transcripts
Differences in pathologic features and graft outcomes in antibody-mediated rejection of renal allografts due to persistent/recurrent versus de novo donor-specific antibodies

Mark Haas¹, James Mirocha², Nancy L. Reinsmoen³, Ashley A. Vo⁴, Jua Choi⁴, Joseph M. Kahwaji⁴, Alice Peng⁴, Rafael Villicana⁴,⁵ and Stanley C. Jordan⁴

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**Table 1 | Comparison of pathologic and clinical features of types 1 and 2 ABMR**

<table>
<thead>
<tr>
<th></th>
<th>Type 1 (n = 37)</th>
<th>Type 2 (n = 43)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(median, IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy indication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute graft dysfunction</td>
<td>25 (68%)</td>
<td>14 (33%)</td>
<td>0.005²</td>
</tr>
<tr>
<td>Progressive graft</td>
<td>8 (22%)</td>
<td>23 (53%)</td>
<td></td>
</tr>
<tr>
<td>dysfunction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>4 (11%)</td>
<td>6 (14%)</td>
<td></td>
</tr>
<tr>
<td>No CMR</td>
<td>27 (73%)</td>
<td>15 (28%)</td>
<td>0.0008³</td>
</tr>
<tr>
<td>CMR ≥ Banff 1a</td>
<td>10 (27%)</td>
<td>28 (72%)</td>
<td></td>
</tr>
<tr>
<td>+ borderline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No CMR + borderline</td>
<td>29 (78%)</td>
<td>26 (60%)</td>
<td>0.007³</td>
</tr>
<tr>
<td>CMR ≥ Banff 1a</td>
<td>8 (22%)</td>
<td>17 (40%)</td>
<td></td>
</tr>
<tr>
<td>No CMR + borderline + isolated v</td>
<td>33 (89%)</td>
<td>27 (63%)</td>
<td>0.009³</td>
</tr>
<tr>
<td>CMR ≥ Banff 1a (excluding isolated v)</td>
<td>4 (11%)</td>
<td>16 (37%)</td>
<td></td>
</tr>
<tr>
<td>Banff scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t (median [IQR])</td>
<td>1 [1–2]</td>
<td>1 [1–2]</td>
<td>0.84⁴</td>
</tr>
<tr>
<td>ptc (median [IQR])</td>
<td>2 [1–2]</td>
<td>2 [1–2]</td>
<td>0.83⁴</td>
</tr>
<tr>
<td>cg (median [IQR])</td>
<td>0 [0–1]</td>
<td>1 [1–2]</td>
<td>0.010⁴</td>
</tr>
<tr>
<td>max.ptcbm layers (median [IQR])</td>
<td>3 [2–5] (36)</td>
<td>5 [4–7] (39)</td>
<td>0.0004⁴</td>
</tr>
<tr>
<td>(cl + ct) (median [IQR])</td>
<td>0 [0–2]</td>
<td>2 [2–4]</td>
<td>&lt;0.0001⁴</td>
</tr>
<tr>
<td>C4d score (median [IQR])</td>
<td>3 [0–3]</td>
<td>3 [1–3]</td>
<td>0.30⁴</td>
</tr>
<tr>
<td>cg score 0</td>
<td>27 (73%)</td>
<td>20 (47%)</td>
<td>0.023⁴</td>
</tr>
<tr>
<td>cg score ≥1</td>
<td>10 (27%)</td>
<td>23 (53%)</td>
<td></td>
</tr>
<tr>
<td>(cl + ct) &lt;3</td>
<td>33 (89%)</td>
<td>27 (63%)</td>
<td></td>
</tr>
<tr>
<td>(cl + ct) ≥3</td>
<td>4 (11%)</td>
<td>16 (37%)</td>
<td></td>
</tr>
<tr>
<td>C4d score 0–1</td>
<td>11 (30%)</td>
<td>11 (26%)</td>
<td></td>
</tr>
<tr>
<td>C4d score 2–3</td>
<td>26 (70%)</td>
<td>32 (74%)</td>
<td></td>
</tr>
<tr>
<td>ABMR activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute/active</td>
<td>26 (70%)</td>
<td>16 (37%)</td>
<td>0.005⁴</td>
</tr>
<tr>
<td>Chronic, active</td>
<td>11 (30%)</td>
<td>26 (60%)</td>
<td></td>
</tr>
<tr>
<td>Chronic</td>
<td>0</td>
<td>1 (2%)</td>
<td></td>
</tr>
</tbody>
</table>

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**Table 2 | Comparison of donor-specific antibodies in types 1 and 2 ABMR**

<table>
<thead>
<tr>
<th></th>
<th>Type 1 (n = 37)</th>
<th>Type 2 (n = 43)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-class I DSA only</td>
<td>15 (41%)</td>
<td>5 (12%)</td>
<td>0.0004ᵃ</td>
</tr>
<tr>
<td>Anti-class II DSA only</td>
<td>10 (27%)</td>
<td>30 (70%)</td>
<td></td>
</tr>
<tr>
<td>Anti-classes I + II DSA</td>
<td>12 (32%)</td>
<td>8 (19%)</td>
<td></td>
</tr>
</tbody>
</table>

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**de novo DSA associated ABMR**

- More Class II DSA
- More TCMR (borderline / Ia+)
- Worse graft survival

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Early and Late Acute Antibody-Mediated Rejection Differ Immunologically and in Response to Proteasome Inhibition


<table>
<thead>
<tr>
<th></th>
<th>&lt; 6mo</th>
<th>&gt; 6mo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunologic Response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of patients with &gt;50% decline in DSA MFI D14 post-treat</td>
<td>77%</td>
<td>35%</td>
</tr>
<tr>
<td><strong>Histologic Response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% patients resolved or resolving with repeat bx</td>
<td>88%</td>
<td>54%</td>
</tr>
<tr>
<td><strong>Allograft Function Response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean pre-treatment eGFR (ml/min/1.73m2)</td>
<td>40±17</td>
<td>27±12</td>
</tr>
<tr>
<td>Mean post-treatment eGFR (ml/min/1.73m2)</td>
<td>66±31</td>
<td>37±25</td>
</tr>
</tbody>
</table>

Walsh et al, Transplantation (2011) 91:1218
## Summary

<table>
<thead>
<tr>
<th></th>
<th>Pre-existing DSA</th>
<th>De novo DSA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HLA DSA</strong></td>
<td>Class II ≥ Class I</td>
<td>Class II &gt;&gt; I</td>
</tr>
<tr>
<td><strong>Level of Immunosuppression</strong></td>
<td>↑↑↑↑</td>
<td>⇔</td>
</tr>
<tr>
<td><strong>Non-adherence</strong></td>
<td>⇔</td>
<td>↑↑↑↑</td>
</tr>
<tr>
<td><strong>ABMR</strong></td>
<td>↑↑↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td><strong>TCMR</strong></td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td><strong>Response to Therapy</strong></td>
<td>↑↑↑↑</td>
<td>↑</td>
</tr>
</tbody>
</table>
DSA

Role for Non-HLA?
Epitope Spread to Auto-antigens

1. Peritubular Capillary
2. Auto-Ag
3. Lymph Node
4. Plasma Cell

- Anti-Class II
- Anti-LG3
- Anti-Perlecan
- Anti-Collagen IV
- Anti-AT1R
- Anti-MICA
- Anti-Endothelial Ab

INFLAMMATION

MICA

ENDOTHELIUM

ECM

Renal Tubule
Non-HLA Antibodies in Kidney Transplantation

**AT₁R Ab**
- Pre-existing → acute rejection and/or graft loss
  - Giral et al, AJT (2013) 13:2567-76

**Anti-Perlecan Ab**
- Associated with vascular rejection
- Associated with chronic allograft rejection

**Anti-Collagen IV and Fibronectin**
- Associated with transplant glomerulopathy
  - Angaswamy et al, AJT (2014) 14:685-93
- Associated with chronic allograft rejection

**Issues:**
- Frequently confounded by pre-existing HLA DSA
- Inadequate assessment for HLA DSA using solid phase technology
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