$A_2/A_2B \rightarrow B$  Renal Transplantation

is a component of the new national (UNOS) kidney allocation algorithm (for deceased donor kidneys) that will be implemented in the United States in late 2014

by

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Chief of lab services
Midwest Transplant Network
Introduction

Blood group B waiting list candidates are relatively disadvantaged (compared to other blood groups) in access to kidneys from deceased donors....
% Patients Transplanted within 2 years of going on the national wait list (2000-01)

- O candidates: 22.4%
- B candidates: 18.3%
- A candidates: 38.0%
- AB candidates: 52.6%

OPTN/UNOS Data
### National (OPTN/UNOS) Data from 2005

<table>
<thead>
<tr>
<th>ABO</th>
<th>% of UNOS Waiting List</th>
<th>% Minority</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>30%</td>
<td>46%</td>
</tr>
<tr>
<td>B</td>
<td>16%</td>
<td>71%</td>
</tr>
<tr>
<td>O</td>
<td>51%</td>
<td>55%</td>
</tr>
<tr>
<td>AB</td>
<td>3%</td>
<td>52%</td>
</tr>
</tbody>
</table>

African American, Hispanic & Asian ethnicities comprise the bulk of the B wait list.
### 2011 UNOS/OPTN/SRTR transplant rate

<table>
<thead>
<tr>
<th>Candidate Ethnicity</th>
<th>n</th>
<th>% Live Donor (n)</th>
<th>% Deceased Donor (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>white</td>
<td>8,388</td>
<td>44% (3,668)</td>
<td>56% (4,720)</td>
</tr>
<tr>
<td>black</td>
<td>4,174</td>
<td>18% (766)</td>
<td>82% (3,408)</td>
</tr>
<tr>
<td>hispanic</td>
<td>2,340</td>
<td>31% (738)</td>
<td>69% (1,602)</td>
</tr>
<tr>
<td>asian</td>
<td>965</td>
<td>26% (249)</td>
<td>74% (716)</td>
</tr>
</tbody>
</table>

Minority candidates depend more on the deceased donor list than do white candidates.
<table>
<thead>
<tr>
<th>ABO</th>
<th>White</th>
<th>Black</th>
<th>Hispanic</th>
<th>Asian</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>9%</td>
<td>19%</td>
<td>10%</td>
<td>25%</td>
</tr>
<tr>
<td>A</td>
<td>44%</td>
<td>27%</td>
<td>31%</td>
<td>27%</td>
</tr>
<tr>
<td>O</td>
<td>44%</td>
<td>49%</td>
<td>57%</td>
<td>43%</td>
</tr>
<tr>
<td>AB</td>
<td>3%</td>
<td>5%</td>
<td>3%</td>
<td>5%</td>
</tr>
</tbody>
</table>
Solutions

How can we provide B candidates with more access to kidneys?
Blood group distribution of kidneys (dd) transplanted in B candidates from 1989 to 2001

B candidates (n=10,589)

91%

B

8.6%

O

(zero mismatch)

0.4%

A2/A2B

OPTN/UNOS data
Goal of allocation policy change (2001): Divert B kidneys from AB to B candidates so as to increase transplant rate of B candidates.

Diagram:
- B kidneys
- AB candidates
- O (zero mismatch) candidates
- A candidates
- B candidates
- A\textsubscript{2}/A\textsubscript{2}B candidates

Arrows indicate the flow of kidneys, with a 7.6% reduction noted.
# Blood group B candidate transplant rate

<table>
<thead>
<tr>
<th>Donor to recipient ABO</th>
<th>12 year epoch before policy</th>
<th>12 year epoch after policy</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% all transplants</td>
<td>% all transplants</td>
<td></td>
</tr>
<tr>
<td>B to B</td>
<td>10.68 (9,634)</td>
<td>11.79 (13,693)</td>
<td>10.1 ↑</td>
</tr>
<tr>
<td>O to B (zero mismatch)</td>
<td>1.01 (909)</td>
<td>0.91 (1,053)</td>
<td>10.1 ↓</td>
</tr>
<tr>
<td>A₂/A₂B to B</td>
<td>0.05 (46)</td>
<td>1.51 (226)</td>
<td>280 ↑</td>
</tr>
<tr>
<td>Total B transplants</td>
<td>11.74 (10,589)</td>
<td>12.87 (14,972)</td>
<td>9.6 ↑</td>
</tr>
</tbody>
</table>

| All transplants        | 90,188                      | 116,347                   | 29 ↑     |
A second solution … for B candidates is….

\[
\text{A}_2/\text{A}_2\text{B} \rightarrow \text{B}
\]

Kidney transplantation
Kidney graft survival; USRDS data; first transplants; 1995-2006

From Hurst et al. Transplantation 2010

Long-term graft survival of A2 kidneys into O or B candidates is equivalent to ABO-compatible transplants.
Safety of Blood Group A2-to-O Liver Transplantation: An Analysis of the UNOS Database

A₂/A₂B → B Renal Transplantation

• Introduction
  – Why increase access to kidneys for B candidates
  – A subgrouping & donor A subgroup frequency
  – Blood group A antigen expression on renal vasculature

• A isoagglutinins (anti-A) in B wait list candidates
  – Clinical relevance/wait list relevance
  – Natural history of anti-A in ESRD patients for A₂/A₂B → B transplantation

• Clinical Transplantation Outcome
  – Midwest Transplant Network A₂/A₂B → B transplantation
  – National (UNOS) A₂/A₂B → B transplantation
Distinction between $A_1$ & $A_2$ RBC's

- $A_1$ RBC's
  - $\approx 1,000,000$ A molecules/RBC
  - Reactivity with *Dolichos bifloris*

- $A_2$ RBC's
  - $\approx 200,000$ A molecules/RBC
  - No reactivity with *Dolichos bifloris*
  - A, non-$A_1$

99% of all A's are $A_1$ or $A_2$
Distinction between $A_1$ & $A_2$ kidney’s

Does the kidney vasculature (of $A_1/A_2$ kidneys) reflect a similar blood group A molecule expression distinction as do RBC’s?

<table>
<thead>
<tr>
<th>$A_1$ RBC’s</th>
<th>$A_2$ RBC’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\approx 1,000,000$ A molecules/RBC</td>
<td>$\approx 200,000$ A molecules/RBC</td>
</tr>
<tr>
<td>Reactivity with dolochis bifloris</td>
<td>No reactivity with dolochis bifloris</td>
</tr>
</tbody>
</table>
Blood group A antigen expression on renal vasculature

A₁ Kidney

3+

A₂ kidney

1+ to +

Breimer et al. Transplantation 82:479, 2006
Blood group A antigen expression on renal vasculature

\[ \text{A}_2 \text{ kidney} \]

\[ 1^+ \text{ to } + \]

50% of \text{A}_2\text{ kidneys} were 1+
50% of \text{A}_2\text{ kidneys} were +

Is difference due to molecular genotype?
\[ \text{A}_2/\text{A}_2 = 1^+ \]
\[ \text{A}_2/\text{O} = + \]

Breimer et al. Transplantation 82:479, 2006
Blood group A antigens expressed in the cortex of the kidney; most vascular endothelial cells of arteries, veins, glomerulus, peritubular capillaries, & intense staining of epithelial cells of distal convoluted tubules & collecting ducts.

By immunoelectron microscopy............

ABO antigens are localized to both apical & basal membranes of vascular endothelial cells.

*From Tasaki et al. Transplantation 2009, Vol. 87:pp1125-33*
Clinical relevance, wait list relevance, & natural history of Anti-A IgG titer in A₂ → B renal transplantation
Anti-A (IgG) titer clinical relevance

In our first 25 A₂/A₂B to B & O kidney transplants, when the pre-transplantation anti-A IgG titer was:

- < 8 (1:8) 0% (0/14) early (1st month) non-function
- ≥ 8 (1:8) 55% (6/11) early (1st month) non-function

The American Journal of Surgery 164: 541-545, 1992

Malcolm Beck, Community Blood Center, Kansas City
Anti-A titer procedure to MTN
• B patient is eligible for $A_2$ kidney if history of anti-A titers is consistently low ($<8$)

Our current practice for anti-A titer testing of B candidates on wait list
Old practice of anti-A titer testing

• In the early 1990’s we were performing anti-A titers on the eligible B & O candidates at the point in time the A₂/A₂B kidney donor became available……
  – Which ↑ CIT & lab time
    (since same lab that does anti-A titers does HLA & crossmatches)

• Our current approach……….
Our current practice for anti-A titer testing of B candidates on wait list

- Perform monthly anti-A titers for ≈6 months, then quarterly….since 1998
  
  - Allows us to quickly establish the patient’s titer history
  
  - So that when an A₂/A₂B donor becomes available we have a history to determine if the B candidate is eligible
Natural History

Incidence of consistently low (<8) anti-A IgG titer history

O: 34%
A: 80-90%
B: None
AB: None
Ethnicity does not influence a candidate's likelihood of having a low anti-A IgG titer history.

- 80% (97/121) for white B candidates
- 81% (65/80) for black B candidates

– Midwest Transplant Network data
Further anti-A titer history data

• From UNOS voluntary variance
  – B wait list candidates \((n=409)\) with low anti-A history:
    – White 87%
    – Black 89%
    – Asian 81%
    – Hispanic 88%

• Asians on a United Kingdom blood group B wait list
  – 100% \((25/25)\) had low anti-A IgG titer history
    • Haji et al. Transplantation 77:630-633, 2004

For Blood group B wait list candidates, ethnicity should not create a differential anti-A titer barrier to eligibility for \(A_2/A_2B\) kidneys!
Does graft loss influence anti-A titer levels?
Demographics of primary and regraft blood group B deceased donor renal transplants in Midwest Transplant Network donor service area from 1994-2007

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Blood Group B Transplants</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary</td>
<td>Regraft</td>
</tr>
<tr>
<td></td>
<td>(n=225)</td>
<td>(n=49)</td>
</tr>
<tr>
<td>Male</td>
<td>64%</td>
<td>61%</td>
</tr>
<tr>
<td>(145/225)</td>
<td>(28/46)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>54%</td>
<td>67%</td>
</tr>
<tr>
<td>(120/225)</td>
<td>(33/49)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>36%</td>
<td>27%</td>
</tr>
<tr>
<td>(81/225)</td>
<td>(13/49)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>(15/225)</td>
<td>(2/49)</td>
<td></td>
</tr>
<tr>
<td>HLA Class I sensitized(≥ 30%)</td>
<td>7%</td>
<td>41%</td>
</tr>
<tr>
<td>(16/225)</td>
<td>(20/49)</td>
<td></td>
</tr>
<tr>
<td>Low anti-A IgG titer history (&lt;8)</td>
<td>87%</td>
<td>88%</td>
</tr>
<tr>
<td>(184/212)</td>
<td>(43/49)</td>
<td></td>
</tr>
</tbody>
</table>

*This comparison was done by the Fisher’s exact test due to small cell numbers.
Those data demonstrate that Blood group B retransplant candidates have equivalent access to $A_2$ kidneys as do primary candidates, with respect to anti-A titer history.
Does HLA sensitization level influence anti-A titer levels?
Relationship of Anti-A IgG History and HLA Class I Sensitization

<table>
<thead>
<tr>
<th>HLA Class I Sensitization (peak)</th>
<th>Anti-A IgG Titer History</th>
<th></th>
<th>p Value ($\chi^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low (≤4)</td>
<td>High (≥8)</td>
<td></td>
</tr>
<tr>
<td>0 – 19%</td>
<td>85%</td>
<td>15%</td>
<td>0.25*</td>
</tr>
<tr>
<td></td>
<td>(208/244)</td>
<td>(36/244)</td>
<td></td>
</tr>
<tr>
<td>20 – 100%</td>
<td>79%</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(59/75)</td>
<td>(15/75)</td>
<td></td>
</tr>
</tbody>
</table>

* NSD, not significantly different.
Mechanism of anti-A antibody production

anti-A antibody production blocked by anti-CD1d

Blood 10 October 2013, Volume 122, #15:2527-28
Allocation & Transplantation outcome
National (UNOS) deceased donor kidney allocation algorithm by ABO

- **O → O** (except 0 antigen mismatches)
- **B → B**
  - August 2001, UNOS policy changed so AB’s don’t get B
    - Increases access of B candidates to B kidneys by ≈ 10%
    - Precedent of providing ↑ access to B candidates
- **A → A & AB**
- **AB → AB**
MTN  A₂/A₂B → B kidney allocation variance

Kidneys from A₂/A₂B donors allocated to:

- **High PRA A & AB candidates**
  - 2% (1/76)

- **B candidates (low anti-A IgG titer)**
  - 68% (56/76)

- **O candidates (low anti-A IgG titer)**
  - 30% (19/76)

- **Low PRA A & AB candidates**
  - 0%

Study Group
Graft Survival Comparison

• 185 consecutive blood group B recipients (of kidneys from deceased donors)
  – 1994 – 2003 (10 years)
  – Compared B recipients by donor blood type (B vs. A$_2$/A$_2$B)
  – Kaplan-Meier comparison method

123 B patients who received B kidneys

Compared with

56 B patients who received A$_2$ or A$_2$B kidneys
Clinical immunogenicity of A₂ kidneys is no different from that of B kidneys, when transplanted into B patients.

<table>
<thead>
<tr>
<th>ABO</th>
<th>Transplants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor → recipient</td>
<td>1994 to 2009 (16 years)</td>
</tr>
<tr>
<td>B &amp; O → B</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>(264/354)</td>
</tr>
<tr>
<td>A₂/A₂B → B</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>(90/354)</td>
</tr>
</tbody>
</table>
Redistribution of A\textsubscript{2} kidneys from blood group A into B patients

<table>
<thead>
<tr>
<th>ABO</th>
<th>% of UNOS Waiting List</th>
<th>% Transplants</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>30%</td>
<td>37%</td>
</tr>
<tr>
<td>B</td>
<td>16%</td>
<td>13%</td>
</tr>
<tr>
<td>O</td>
<td>51%</td>
<td>45%</td>
</tr>
<tr>
<td>AB</td>
<td>3%</td>
<td>5%</td>
</tr>
</tbody>
</table>

UNOS 2005 data

Distribution of B Recipients Transplanted from 1994 to 2007

Donor ABO→Recipient | 1994-2007

<table>
<thead>
<tr>
<th>B &amp; O→B</th>
<th>73%</th>
</tr>
</thead>
<tbody>
<tr>
<td>(200/274)</td>
<td></td>
</tr>
</tbody>
</table>

A\textsubscript{2}/A\textsubscript{2}B→B | 27% |
| (74/274) |

We feel it is justified to redistribute 6% of A kidneys to B candidates, since A candidates, after removal of 6% A\textsubscript{2} kidneys, still receive more transplants than their wait list composition.
The Result of $A_2 \rightarrow B$ Deceased donor Kidney Transplantation in Midwest Transplant Network DSA

- Graft outcome of $A_2$ kidneys equivalent to $B$
- $B$ wait list transplant rate ↑ 27%
- $A$ wait list transplant rate ↓ 6%
- $B$ waiting time ↓
Would $A_2 \rightarrow B$ allocation algorithm work in other DSA’s to increase access of B wait list candidates?
In 2002, UNOS Minority affairs committee implemented a voluntary variance allowing OPO’s to transplant deceased donor kidneys from $A_2/A_2B$ donors to B patients

- **Goals of the UNOS variance:**
  - To increase the number of transplants in B candidates by allocating $A_2$ or $A_2B$ deceased donor kidneys into B patients without negatively impacting the post-transplant outcomes.
  
  - Since the majority of B candidates are minority patients, this variance will also decrease the barrier to access to transplantation for minorities (71% B wait list are minority candidates).
  
  - Based on the experience of Midwest Transplant Network DSA
    - *But MTN did not participate in this voluntary variance*
Data

- Number of B transplants from A\(_2\)/A\(_2\)B donors, including donor and recipients characteristics and post-transplant outcomes (serum creatinine, acute rejection, graft and patient survival).

- Numbers of A and B transplants were compared during 3.5 years before and 3.5 years after the variance was implemented.

- 5 OPO’s/DSA’s participated.

- Prospective trial

- Does not include Midwest Transplant Network
First Report on the OPTN/UNOS National Voluntary Variance to Allocate A₂/A₂B Deceased Donor Kidneys to Blood Group B Candidates

Reported to American Transplant Congress 2005 & 2006

Submitted to Amer J Transplantation 2014

Winfred W. Williams, MD¹, Wida S. Cherikh, PhD²,
Carlton J. Young, MD³, Pan-Yen Fan, MD⁴,
Christopher F. Bryan, Ph.D.⁵

¹ Massachusetts General Hospital and Harvard Medical School, Boston, MA; ² UNOS, Richmond, VA; ³ Univ. of Alabama at Birmingham, Birmingham, AL; ⁴ Univ. of Mass Memorial Medical Ctr, Worchester, MA; ⁵ Midwest Transplant Network, Westwood, KS
DSA’s that adopted the $A_2/A_2B \rightarrow B$ kidney allocation algorithm
Characteristics of $A_2/A_2B$ Kidney Donors

- There were 63 $A_2$ and 5 $A_2B$ donors whose kidneys were recovered for transplant
- Median age: 30 yrs
- Ethnicity of donors:
  - 83% of donors White
Recipients of $A_2/A_2B$ Kidneys

- These 68 donors donated 96 $A_2$ and 10 $A_2B$ kidneys:
  - 43 (41%) transplanted to $B$ recipients
  - 60 (57%) transplanted to $A$ recipients
  - 3 (3%) transplanted to $AB$ recipients
Ethnic distribution of the B recipients of $A_2/A_2B$ kidneys

- 74% (32/43) $A_2 \rightarrow B$ kidneys went to minority candidates
  - 14 black
  - 12 asian
  - 3 hispanic
  - 3 american indian/Alaska native

<table>
<thead>
<tr>
<th>ABO</th>
<th>White</th>
<th>Black</th>
<th>Hispanic</th>
<th>Asian</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>9%</td>
<td>19%</td>
<td>10%</td>
<td>25%</td>
</tr>
</tbody>
</table>

B $\rightarrow$ B minority transplant rate was 58%

71% national waiting list is minority
UNOS A2/A2B → B National Voluntary Variance

Graft survival of B recipients

- B → B (n=902)
- A2/A2B → B (n=101)
UNOS Voluntary $A_2/A_2B$ to $B$ Variance: Impact on $B$ and $A$ Wait List

<table>
<thead>
<tr>
<th>Voluntary Variance Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>• <strong>B</strong> transplants:</td>
</tr>
<tr>
<td>– 23% ↑ (11.1% to 13.6%)</td>
</tr>
<tr>
<td>• <strong>A</strong> transplants:</td>
</tr>
<tr>
<td>– 8% ↓ (39% to 35.7%)</td>
</tr>
</tbody>
</table>
Summary

- Results continues to demonstrate that these transplants are clinically successful

- The data support the proposition that this allocation algorithm provides a robust mechanism to increase the access of blood group B candidates, most of whom are minority candidates (predominantly black & asian), to kidney transplantation.

- This is now part of the new kidney allocation system (2014)

- Validates/confirms Midwest Transplant Network DSA experience
Blood group distribution of kidneys transplanted in B candidates

- B candidates
  - 10% ↑ since 2001
  - O (zero mismatch)
  - A2/A2B
  - 20-25% ↑ in 2015…
The composition of the national B wait list averaged 14.1% and 14.9% in the epoch before and after policy change.

12 year epoch before B to B

12 year epoch after B to B

8/29/2001 B kidneys are diverted from AB to B candidates.

A_\alpha/A_\beta to B epoch ≥ 2015 (projecting a 20% ↑)
Live donor $A_2$ to $O$ or $B$ Transplantation

- **Utah**
  - 14 live donor $A_2$ to $O$ or $B$ transplants

- **Oregon**
  - 6 live donor $A_2$ to $O$ transplants

- **Midwest Transplant Network**
  - 9 live donor $A_2$ to $O$ or $B$ transplants
    - *Bryan et al.* *AJT* 7:1181-84, 2007
A_2 to B
or
not A_2 to B,

….is no longer the question,

but one answer
to providing B patients

(most of whom are minority candidates)
with increased access (≈25%) for renal transplantation