FINAL REPORT

OPTN/UNOS Operations & Safety Committee

Quantifying the Risks Associated with Incorrect ABO Subtyping of Donors

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Background

On May 7, 2009, the Operations (now Operations & Safety) Committee reviewed information regarding a situation where a kidney from a living donor, thought to be type A2[1], was transplanted into a type O recipient. After graft failure, it was discovered that the donor was actually type A1, and thus blood type incompatibility was the cause of this hyperacute rejection incident.

Current OPTN policy requires two separate tests to verify recipient ABO (double-typing) and two different individuals to verify deceased donor ABO (double-checking). When ABO *sub*-typing is used for placement, policy does not require either separate tests or confirmation by

[1] In this document, A2 technically refers to all "non-A1" subtypes of ABO Type A.

different individuals to verify the accuracy of the donor subtype. Furthermore, if an OPO does perform multiple blood tests to confirm ABO sub-typing of a deceased donor, or double-checks the initial sub-typing, UNet^{SM} currently does not allow the subtype to be changed or corrected; instead, the user must create a new donor record to enter the correct subtype (or to revert back to primary ABO type). A report shown to the Operations Committee on May 7, 2009, revealed 49 instances from 2006-2008 in which DonorNet® users changed the initial ABO (or subtype) by entering a new donor record for a previously registered donor. In 6 of these cases, the initial ABO of A1 was changed to A2. There were 22 cases where initial ABO of A2 was changed to either A or A1 on the second donor record. In 2 cases, initial ABO of A2B was changed to AB.

The OPTN is currently considering policy requiring double verification (double-subtying and/or double-checking) of ABO subtyping, as well as programming enhancements to allow DonorNet to accept changes to previously entered donor records. A briefing paper on verifying ABO subtyping is in development. The intent of this data request is to quantify the number of opportunities for and potential impact of incorrect ABO subtyping to lead to graft failure – i.e., how often are A2 or A2B subtypes used for placement and transplanted into Type B or O recipients? This analysis also assesses the potential impact of donors are who are incorrectly subtyped as A1 or A1B.

In this report, the risks associated with incorrect ABO subtyping are calculated jointly for both deceased and living donors. However, the processes of ABO typing and subtyping, including the available time for testing and circumstances surrounding the donation, differ greatly for deceased versus living donors. The aforementioned ABO subtyping briefing paper will address these differences and the implications of various policy proposals on deceased and living donation.

Analysis Request

- Tabulate the number of donors recovered in 2008 by ABO subtype. (Update: to increase sample sizes and evaluate trends, data from July 2004 – March 2009 was used instead.)
- Tabulate the number of deceased donor transplants performed in 2008, by donor and recipient ABO subtype. (Update: July 2004 – March 2009 data, including living donors, was used instead.)

Data/Methods

The tables and graphs are based on OPTN data as of July 24, 2009. The data are subject to change based on future data submission or corrections.

All transplants for all organs occurring between July 2004 and March 2009 were included. The July 2004 cut point was selected because OPTN policy was changed at that time to require double confirmation in DonorNet® of ABO type prior to generating a match run.

The first stage of the analysis estimates the number of annual opportunities for hyperacute graft failure, if the donor ABO subtype is mistyped as A2 or A2B and transplanted into a B or O recipient. The second stage of the analysis uses mathematical calculations to estimate the probability a single test indicating a donor subtype of A2 (or A2B) is incorrect and the true subtype is A1 (or A1B). Multiplying the number of opportunities by the error probability provides an estimate of the number of graft rejection incidents per year due to unintentional

incompatibility, assuming each OPO only uses a single test to verify donor subtype. The final part of the analysis estimates the error probability and expected number of graft failure incidents per year if two independent tests are done, instead of one, to verify donor ABO subtype.

Reported recipient ABOs, which must be verified with two independent tests according to OPTN policy, are assumed to be correct for this analysis. Reported donor ABOs are also assumed to be correct; only the reported *donor ABO subtype*, which is not required to be double-verified, is assumed to have inherent uncertainty and potentially be incorrect.

Summary & Interpretation of Results

Transplanting A2 organs into B or O recipients (or A2B organs into B recipients), as permitted by allocation policy, will result in severe graft rejection if the donor typing was incorrect and truly A1 (or A1B). As shown in Table 2, 318 of these "ABO-subtype compatible"[2] transplants were performed between July 2004 and March 2009. As shown in Table 2, earlier years had about 40-50 such cases per year, but 81 of these transplants were done in 2008. Given this increasing trend, the subsequent risk assessment assumes 100 such "ABO-subtype compatible" transplants per year.

Risk Assessment – Single Subtyping of Donor ABO

Each of these 100 transplants represents an opportunity for graft failure due to hyper-rejection, if the A2 (or A2B) typing is incorrect, and the true subtype is A1 (or A1B). Conditional probability calculations can be used to determine the risk posed by each transplant – the probability that the donor is truly A1 when the test said A2. To make these calculations, the first input required is the relative frequency of A2's relative to A1's. It turns out that in the general population, only about 20% of A's are A2, while 80% are A1 ([3]Bryan, et al.) According to OPTN reported data on donors, this appears to be a reasonable estimate for the donor population as well. Because of this relatively low incidence of A2's compared to A1's, very high sensitivity and specificity of A2 subtyping is required to avoid an unacceptably high risk associated with each of these transplants. This holds true in general: the more rare a condition, the more accurate the test needs to be to avoid a high error rate.

The sensitivity and specificity are the final two inputs required for this calculation. Such estimates are also available in [2]Bryan, et al, and are as follows: probability(test says A1|true subtype is A1)[4] =0.991853, and probability(test says A2|true subtype is A2)=0.9091. Combining these three inputs using Bayes Rule[5] results in an A2 subtyping error rate – probability(true subtype is A2|test says A1) – of about 0.035, or 3.5%. Thus, with an estimated 100 or so "ABO-

[2] The term "ABO-subtype compatible" refers to (A2->O,B or A2B->B) transplants, which are compatible only because the subtype is A2 or A2B.
[3] Bryan, et al, "Implications of ABO Error Rates in Proficiency Testing for Solid Organ Transplantation," Transplantation 2006.
[4] This probability expression is read, "the probability that the test says A1, given (or assuming) the true subtype is known to be A1."
[5] Bayes Rule: P(A|B)=P(B|A)*P(A)/P(B). The denominator, P(B), is expanded by the Law of Total Probability to complete the calculation.

subtype compatible" transplants per year, we would expect 3-4 hyperacute rejection incidents per year due to erroneous subtyping, assuming only one donor ABO subtyping is performed.[6]

Recently, there have been about 40-80 such transplants each year. Given these numbers, we would have expected to have seen about 1-3 hyperacute rejections per year. However, some OPOs are already double-testing donor subtype, this practice may be helping to avoid such incidents. Only one such incident has been reported, the living donor mis-subtype that led to graft rejection in 2008.

Cross-matching, either actual or virtual, is only designed to detect degrees of HLA cross-reactivity and does not indicate ABO incompatibility. So any cross-match practices or requirements will not serve to alleviate the risk associated with a single ABO subtying.

Risk Assessment – Two Independent Subtypings for Donor ABO

If two independent tests with the same error rate of 3.5% are conducted and both indicate A2 (or A2B), the per-donor risk of an incorrect subtype decreases substantially, to 0.032%[7]. Assuming 100 such transplants per year, we would only expect about 1 such incident in 30 years if two independents subtypings were always performed. These results are summarized in Table 1.

Table 1: Summary of Risk of Graft Rejection Due to ABO Mis-Subtyped as A2 (or A2B)

		Single ABO subtyping		**Double ABO subtyping**	
Test result	**Actual subtype**	**Error rate**	**Expected # events**	**Error rate**	**Expected # events**
A2 (or A2B)	A1 (or A1B)	3.5%	3-4 per year	0.032%	~ 1 in 30 years

Impact of Incorrect A1 (or A1B) Subtyping

The primary focus of this analysis is evaluating the risk of A2 (or A2B) subtyping being incorrect and resulting in graft failure. However, there are also implications – in the form of potential missed opportunities for "ABO-subtype compatible" transplants for Type B and O candidates – if the subtype is reported as A1 (or A1B), but the true subtype is A2 (or A2B).

Columns highlighted in Table 4 show that there are many such transplants, where an organ from a donor subtyped as A1 (or A1B) is transplanted into an A or an AB candidate. The relatively high subtyping test discrepancy rate – nearly 10%[3] when the true subtype is A2 – suggests that these missed opportunities are not rare, especially given the large number of such transplants. Confirming the subtype truly is A1 with a second test would reduce the frequencies of these missed opportunities and allow B or O candidates to at least be considered for more potential transplants.

[6] The vast majority (about 93%) of these "ABO-subtype compatible" transplants have donors subtyped as A2. Since only 7% of cases are subtyped as A2B, and A2B testing sensitivity/specificity estimates are not both readily available, the error rate of 3.5% is assumed for both A2 and A2B donors for this analysis.

[7] Several equivalent approaches can be used for this calculation, including replacing 0.20 by 0.965 as the new "prior probability" of a donor being A2, and executing the same calculation as in [5].

Data tables

Table 2: ABO for Transplant Recipients whose Donors were Subtyped as Either A2 or A2B
By Organ Type and Donor Type
Transplants Performed between July 2004 - March 2009

		Recipient ABO				
		A	**AB**	**B**	**O**	**Total**
Organ	**Donor Type**					
KI	**Deceased**	855	167	87	12	1,121
	Living	33	2	12	60	107
LI	**Deceased**	451	90	1	139	681
	Living	.	.	.	2	2
HR	**Deceased**	175	20	1	2	198
LU	**Deceased**	125	20	.	.	145
KP	**Deceased**	68	18	2	.	88
PA	**Deceased**	36	.	.	.	36
IN	**Deceased**	21	.	.	.	21
HL	**Deceased**	2	1	.	.	3
Total		1,766	318	103	215	2,402

** About 93% of cases are A2, only 7% are A2B.*

** 316 of 318 highlighted cases represent "ABO-subtype compatible" transplants, where compatibility is contingent on accuracy of the ABO subtyping. The other two were A2B into O heart transplants, which is incompatible regardless of whether the donor was A2B or A1B, and presumably represent intentional incompatible transplants.*

Table 2 Interpretation:
From July 2004-March 2009, 318 transplants (highlighted in orange) occurred where the donor was subtyped as A2 or A2B, and the recipient was either B or O. Annually, this translates into roughly 63 opportunities per year for an incorrect donor subtyping to result in hyperacute rejection. Analysis of this data by year (see Table 3) reveals an increasing trend, and in 2008 there were 81 such cases.

Most of these "ABO-subtype compatible" transplants occurred in either kidney or liver, but a few occurred with other organs, namely heart and KP. (Two of these heart transplants were A2B into O, which is incompatible regardless of whether the donor was A2B or A1B, and thus presumably represented cases of intentional incompatible transplant.) 42% of these kidney transplants were living donor transplants.

Table 3: ABO for Transplant Recipients whose Donors were Subtyped as Either A2 or A2B
By Year of Transplant
Transplants Performed between July 2004 - March 2009

	Recipient ABO				
	A	**AB**	**B**	**O**	**Total**
TRR TRANSPLANT DATE					
2004 (July – Dec)	156	18	4	16	194
2005	225	43	20	26	314
2006	321	59	27	41	448
2007	386	89	17	51	543
2008	490	76	23	58	647
2009 (Jan – March)	188	33	12	23	256
Total	1,766	318	103	215	2,402

** About 93% of cases are A2, only 7% are A2B.*

** 316 of 318 highlighted cases represent "ABO-subtype compatible" transplants, where compatibility is contingent on accuracy of the ABO subtyping. The other two were A2B into O heart transplants, which is incompatible regardless of whether the donor was A2B or A1B, and presumably represent intentional incompatible transplants.*

Table 3 Interpretation:

Table 3 shows an increasing trend in the number of "ABO-subtype compatible" transplants, with 81 such transplants occurring in 2008. The pace for 2009 – 35 cases in the 1st quarter alone – represents a continued increase. For the risk analyses conducted above, 100 such transplants per year is assumed.

Table 4: ABO for Transplant Recipients whose Donors were Subtyped as Either A1 or A1B
By Organ Type and Donor Type
Transplants Performed between July 2004 - March 2009

		Recipient ABO				
		A	**AB**	**B**	**O**	**Total**
Organ	**Donor Type**					
KI	**Deceased**	7,755	959	.	.	8,714
	Living	210	21	2	16	249
LI	**Deceased**	4,651	406	5	32	5,094
	Living	1	1	.	.	2
HR	**Deceased**	1,568	123	1	6	1,698
LU	**Deceased**	1,091	66	.	.	1,157
KP	**Deceased**	709	57	.	.	766
PA	**Deceased**	320	36	.	.	356
IN	**Deceased**	134	13	.	.	147
HL	**Deceased**	18	2	.	.	20
Total		16,457	1,684	8	54	18,203

About 95% of cases are A1, only 5% are A1B.

Table 4 Interpretation:
From July 2004-March 2009, 18,141 transplants (highlighted in yellow) occurred where the donor was subtyped as A1 or A1B, and the recipients were either A or AB. If the reported subtype was incorrect for some of these donors, and the true subtype A2 or A2B, it is a potentially missed opportunity for Type B or O candidates.