

Guidance for Transplant Program Participation in the Transplantation of Non-A₁/Non-A₁B (A₂/A₂B) Donor Kidneys into Blood Group B Candidates

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Summary and Goals

Blood type B candidates, a blood group more common in underrepresented minorities, have longer kidney waiting times. In December 2014, the new Kidney Allocation System (KAS) went into effect, including *Policy 8.5.D: Allocation of Kidneys by Blood Type*, which allows for blood types A, non-A₁ and AB, non-A₁B kidneys to be transplanted to blood type B recipients who meet certain criteria.¹ Allocation of deceased donor kidneys from blood group A, non-A₁ and AB, non-A₁B to blood group B kidney recipients has improved transplant rates among disadvantaged blood group B patients with equivalent long-term graft outcomes compared to blood type compatible transplants.^{2 3} However, the 18 month KAS post-implementation data analysis revealed that an overwhelming majority of transplant programs (82 percent) do not perform any non-A₁/non-A₁B (A₂/A₂B) transplants and that overall transplant programs have not taken advantage of this policy change, which provides greater access to deceased donor kidneys for disadvantaged blood group B candidates.⁴ Further, a 2016 OPTN/UNOS Minority Affairs Committee (MAC) survey to all active U.S. kidney transplant programs revealed that many programs cited a difficulty in establishing a protocol for patient enrollment as the major barrier to performing these transplants. Specifically, the transplant programs identified the following obstacles when developing the required protocols to participate in non-A₁ transplants:

- Difficulty establishing titer thresholds (32 percent)
- Difficulty developing an informed consent policy (21 percent)
- Difficulty determining patient eligibility (18 percent)

Based on these survey findings, these best practice guidelines are offered in an effort to increase the number of kidney transplant programs that perform non-A₁/non-A₁B (A₂/A₂B) transplants.

Background

One of the factors impacting access to transplantation is candidate blood type, and it has been well-established that blood group O and B candidates have longer waiting times as shown in the table below.⁵

¹ OPTN Policies, Section 8.5D: Allocations of Kidney by Blood Type

² Forbes RC, Feurer ID, Shaffer D. A2 incompatible kidney transplantation does not adversely affect graft or patient survival. *Clin Transplant* 2016; 30:589-597

³ Williams WW, Cherikh WS, Young CJ et al. First report on the OPTN national variance: Allocation of A2/A2B deceased donor kidneys to blood group B increases minority transplantation. *AJT* 2015; 15:3134-3142.

⁴ Aeder, Mark. The New Kidney Allocation System (KAS): The First 18 Months. Prepared for OPTN Minority Affairs In-Person Meeting, September 20, 2016.

⁵ Hart A, Smith JM, Skeans MA, et al. *Kidney*. *AJT* 2016; 16, s2: 11-46.

Candidate Blood Type	Average Waiting Time (in years)
AB	2
A	3
O	5
B	6

Blood group B candidates comprise 16 percent of candidates listed on the kidney transplant waiting list per OPTN data as of November 14, 2016, but received only 13 percent of the total kidney transplants between January 1, 2015 and September 30 2016. Furthermore, because blood group B candidates on the kidney waiting list in 2016 were composed of 72.7 percent minority candidates, defined as Black, Asian, Hispanic, American Indian/Alaska Native, Native Hawaiian/other Pacific Island, and multiracial candidates, this disparity affects minority populations most of all.

Multiple studies have demonstrated the safe and effective transplantation of blood group B kidney transplant recipients with kidneys from donors having the less immunogenic, non-A₁ subtype. Equivalent long-term graft outcomes have been demonstrated after the transplantation of non-A₁/non-A₁B (A₂/A₂B) donor kidneys into blood group B recipients as compared to blood type compatible transplantation^{6,7,8,9,10}. As such, the new kidney allocation system (KAS) included the provision to allow non-A₁ transplants to blood group B recipients to provide better equity among candidate blood types, which likely includes minority groups disadvantaged on the transplant waiting list. According to an 18-month KAS post-implementation analysis, there has been an increase in non-A₁/non-A₁B (A₂/A₂B) deceased donor kidney transplants, but still many candidates who could benefit from these transplants are not registered for these organs.¹¹ Compared to the 19 (0.2 percent) non-A₁/non-A₁B (A₂/A₂B) transplants performed 1-year pre-KAS, there were 179 (1.0 percent) performed in the 18-months post-KAS, a 5-fold increase. Despite these gains, OPTN data available on April 30, 2017, shows that only 7.8 percent of active blood group B candidates on the kidney waiting list were registered as eligible for these transplants.

Recommendations for Protocol Development

Participant transplant programs must develop a program-specific written protocol in order to receive offers of non-A₁ deceased donor kidneys for their blood group B candidates. This written protocol must include:

- 1. The maximum titer levels for candidate eligibility**
- 2. The process for obtaining informed written consent from each blood group B candidate for acceptance of a non-A₁ kidney**
- 3. Confirmation of each candidate's eligibility every 90 days in UNetsm**

The guidelines below for developing each of these protocol requirements are based on MAC survey results, literature reviews, sample policy, and informed consent forms provided by several transplant programs that are already performing these transplants.

1) Titer Testing of the Blood Group B Candidate

OPTN/UNOS policy allows each transplant program to develop and implement its own approach for ascertaining the appropriate method and threshold for anti-A titers used in determining candidate eligibility. The information below is summarized from published literature and is provided for informational use only.

⁶ Forbes RC, Feurer ID, Shaffer D.

⁷ Bryan CF, Cherikh WS, and Sesok-Pizzini DA. A₂/A₂B to B renal transplantation: past, present, and future directions. *AJT* 2016; 16: 11-20.

⁸ Bryan CF, Winkhofer FT, Murillo D, Ross G, et al. Improving access to kidney transplantation without decreasing graft survival: long-term outcomes of blood group A₂/A₂B deceased donor kidneys in B recipients. *Transplantation* Jul 2005 15;80(1):75-80.

⁹ Bryan CF, Shield CF, Nelson PW, et al. Transplantation rate of the blood group B waiting list is increased by using A₂ and A₂B kidneys. *Transplantation* 1998; 66: 1714-1717.

¹⁰ Williams WW, Cherikh WS, Young CJ et al.

¹¹ Aeder, Mark.

Most programs perform anti-A₁ titer typing through their local hospital blood bank and use different methods for titer detection. The majority of respondent transplant programs participating in the survey use an anti-A titer cutoff of 1:8 as acceptable for candidate eligibility, but it is up to an individual program to determine titer thresholds. Some programs are more comfortable using a more stringent cutoff of 1:4 to determine candidate eligibility, and it is worth noting that the original outcomes data used this more stringent titer threshold. To confirm eligibility, the survey showed that most programs require two consecutive titer results.

Specific Considerations for Labs Performing Titer Testing:

The identification of red blood cell antibodies as IgM or IgG provides useful information. DTT (dithiothreitol) has been used in blood banking for decades to distinguish one type of antibody from the other since DTT can inactivate IgM in the patient's serum; however, it does not interfere with IgG. Therefore, since IgM is the predominant Ig subclass of anti-A produced by blood group B individuals, the use of DTT in the patient's serum sample and in controls is necessary to distinguish between the two types of antibodies. The use of serial dilutions with and without DTT on patient serum and controls such as anti-P1 antisera, high IgG control, and IgM control are necessary to prove that the titer of anti-A determined is indeed an IgM. Note that early studies demonstrating the success of non-A₁ kidneys into B recipients used predominantly IgG titers.

Specific Considerations for Titer Testing:

- High control IgG: is an IgG antibody that should result in a titer >8 before DTT treatment and not be reduced after DTT treatment, maintaining a titer >8.
- High titer IgM antibody control is an IgM antibody that should result in a titer of >8 without DTT treatment and be reduced by DTT treatment to a titer <8.
- Anti-P1 antisera is a low level IgM antibody that should have a positive result undiluted and be reduced by DTT treatment to a negative result.

The use of AHG (anti-human globulin) is not necessary to determine IgM titers; however, some programs might be concerned with low titer anti-A₁ IgG that the B recipient might produce. AHG simply increases the sensitivity or detection of low titer IgG antibodies only. This is called the indirect antiglobulin or Coombs Test.

Titer Variability:

Antibody titer reproducibility intra and inter laboratory is still a major concern. The lack of reagent standardization and the multiple methods in use contribute to titer variability among labs. In an effort to control such variability, Thorpe et al reported on an international collaborative study using a World Health Organization (WHO) reference reagent to try to standardize hemagglutinin testing for anti-A and anti-B titers in serum and plasma.¹² In this study where 300 samples were tested among 24 laboratories in different countries, they reported an 8 to 64 fold variation in titers per preparation and methods across laboratories. However, the intra-laboratory variability was generally good with over 90 percent of replicate titers within a 2 fold range.

The problem with such a wide variability among laboratories is multi-factorial. There is no standardized procedure; there are multiple methods (gel vs. tube), diluent, incubation times, cutoff reading and testing cell among others. The College of American Pathologists (CAP) proficiency testing titer surveys from 2014-2016 indicate that the gel method produces a closer range in variation when compared to the tube method.¹³ The gel method has shown to be more consistent and more sensitive and less subjective than the tube method, according to the American Association of Blood Banks (AABB). However, the gel tube method for A subgroup typing of samples is not yet approved by the FDA. Laboratories that want to use this method for A subgroup typing must validate the protocol for its use.

¹²Thorpe SJ, Fox B, Sharp G, White J, Milkins C. A WHO reference reagent to standardize haemagglutination testing for anti-A and anti-B in serum and plasma: international collaborative study to evaluate a candidate preparation. Vox Sang.2016 Aug; 111(2):161-70

¹³2014-2016 Proficiency Testing Surveys, College of American Pathologists. www.cap.org. Web. September 2017.

2) Obtaining Candidate Informed Consent for Acceptance of Non-A₁/non-A₁B (A₂/A₂B) Type Kidneys

The following items should be included in the protocol for obtaining candidate informed consent:

- Create a general statement about why it is advantageous to receive offers of non-A₁/non-A₁B (A₂/A₂B) deceased donor kidneys, emphasizing that blood group B candidates have historically the lowest rate of transplant. In addition, a statement regarding the similarity between transplant outcomes with non-A₁/non-A₁B (A₂/A₂B) donation to B blood group recipients should be included.
- Include both the risks and benefits. Benefits could include more organ offers, with the possibility of an earlier transplant. Risks should include that participants are always at risk for rejection but there is no current evidence that the risk for rejection is higher in blood group B recipients with low anti-A IgG titer who have received non-A₁/non-A₁B (A₂/A₂B) kidneys in comparison to blood group B matched kidneys.¹⁴
- Include a statement on how often you will require the recipient to come in for a blood draw to obtain anti-A titers.
- Include a statement that the program has explained the nature, risks, and benefits to accepting non-A₁/non-A₁B (A₂/A₂B) deceased donor kidneys and has answered all of the candidate's questions.

The candidate, as well as the program representative obtaining consent, must sign the form. It is also recommended that candidates be informed of additional program-specific care requirements that may come along with acceptance of a non-A₁/non-A₁B (A₂/A₂B) deceased donor kidneys (for example, additional blood draws, biopsies).

3) Confirming Eligibility to Receive non-A₁/non-A₁B (A₂/A₂B) Deceased Donor Organ Offers

Programs must confirm non-A₁/non-A₁B (A₂/A₂B) eligible candidates every 90 days in UNet. A transplant program has discretion for how frequently titers are re-checked. Some programs require confirmatory titer testing every 90 days for eligibility, while other programs perform testing less frequently, in addition to UNet confirmation every 90 days.

Summary Chart: Non-A₁/non-A₁B (A₂/A₂B) Protocol Development Recommendations

Protocol Requirements	Key Components	Examples of Program Variability
Maximum Titer Levels	<ol style="list-style-type: none"> 1. Titer testing methodology (see "Specific Considerations for Labs") 2. Establish titer cutoff (discretion of transplant program) 3. Confirm eligibility 	<p>≤ 1:4 (more stringent) 1:8 (most common) ≥ 1:16 (less stringent)</p> <p>Two consecutive titer levels</p>

¹⁴Bryan C.F., Cherikh W.S., Sesok-Pizzini D.A. A2/A2B to B Renal Transplantation: Past, Present, and Future Directions. American Journal of Transplantation. 2015. Nov. 10

Protocol Requirements	Key Components	Examples of Program Variability
Consent Development	<ol style="list-style-type: none"> 1. Develop statement about why it's advantageous to receive offers of A₁/non-A₁B (A₂/A₂B) deceased donor kidneys 2. Develop statement of risks/benefits 3. Develop statement on specified requirements for maintaining eligibility 4. Create statement of acknowledgement by both patient and physician 	Frequency of lab draw
Routine Update of Candidate Eligibility (UNet)	Confirmation of eligibility every 90 days	Either of the following: <ul style="list-style-type: none"> • Repeat titer testing every 90 days • Less frequent titer testing (semiannual, annual), but with UNet confirmation every 90 days

Possible Financial Implications and Other Concerns

In order to begin transplantation of non-A₁/non-A₁B (A₂/A₂B) deceased donor kidneys into blood group B candidates, there is a modest financial investment at start-up followed by ongoing expense for each candidate. The following table describes the approximate resources that are needed to prepare your program for implementation. Expenses will vary from program to program and are intended as a framework for beginning analysis within your own program. You could adopt best practices from other programs, which could markedly reduce the initial investment.

All pre-transplant efforts should be considered for reimbursement under the Medicare cost report and included in your institution's standard acquisition charge for kidney transplants. The remainder of the services should be reimbursed through third party payers as customary and contracted by your institution.

Resource Summary:

Potential One-Time Implementation Staff Effort:	Potential Recurring Per Patient Effort:
<ul style="list-style-type: none"> ✓ Review of draft protocols ✓ Protocol development ✓ Development of informed consent document ✓ Coordination with blood bank to educate and clarify blood use and typing ✓ Coordination with histocompatibility laboratory to establish order set, non-A₁ titer process and associated EMR (Electronic Medical Record) changes as needed ✓ Training development ✓ Staff training 	<ul style="list-style-type: none"> ✓ Description ✓ Education of patient ✓ Consent of patient ✓ Pre-authorization for non-A₁/non-A₁B titer test (IgG titration) ✓ Standing order placement for quarterly non-A₁/non-A₁B titers (IgG titration) ✓ Review and UNetSM reporting of non-A₁/non-A₁B titers at evaluation and confirmation every 90 days ✓ Non-A₁/non-A₁B titer testing for both evaluation and maintenance

Conclusion

One of the primary goals of the KAS is to broaden patient access for historically disadvantaged kidney transplant candidates, which includes blood group B candidates, who have experienced greater waiting times compared to other blood groups. Available data support that access to non-A₁/non-A₁B (A₂/A₂B) donor kidneys has improved transplant rates for blood group B candidates and has effectively shortened wait times for this population.^{15 16} Use of the non-A₁/non-A₁B (A₂/A₂B) provision for blood group B candidates is not automatic and requires transplant program protocol development and maintenance. The guidelines provided in this document will aid transplant programs interested in protocol development.

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¹⁵Forbes RC, Feurer ID, Shaffer D. A2 incompatible kidney transplantation does not adversely affect graft or patient survival. Clin Transplant 2016; 30:589-597

¹⁶Williams WW, Cherikh WS, Young CJ et al. First report on the OPTN national variance: Allocation of A2/A2B deceased donor kidneys to blood group B increases minority transplantation. AJT 2015; 15:3134-3142.