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Increasing Access to Kidney Transplantation: Easy as A-B-O

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EDITORIAL

Increasing Access to Kidney Transplantation: Easy as A-B-O

This issue of *Advances in Chronic Kidney Disease* is focused on kidney transplantation. It is shepherded by Drs Anita Patel and Millie Samaniego-Picota who have produced, with their selected group of authors, a contemporaneous and coherent view of kidney allograft survival. In discretely dissected steps, the authors have delineated their thoughts regarding their issue's theme, and the readers will undoubtedly pivot their viewpoint. This brief treatise has the same intent to convince one that ABO-incompatible (ABOi) kidney transplantation is compatible with one's current practice of kidney transplantation.

There are 4 major Landsteiner blood groups: A, B, AB, and O. These polysaccharide immunogens are expressed on multiple tissues including erythrocytes, platelets, and endothelial cells and generate hemagglutinating immunoglobulins of the immunoglobulin (Ig) M and IgG types, with the latter pathogenic in kidney transplant rejection. Blood group A has subtypes A1 and A2, the latter of which is less immunogenic, thereby facilitating transplantation of A2 kidneys to ABOi donors.[1] Transfusion of an incompatible blood group to a recipient can be devastating with resulting hemolysis, acute kidney injury, and even death. Transfusion of compatible blood group red cells can produce allosensitization; however, this issue is possibly exaggerated. Even after essentially the Food and Drug Administration mandated reductions in erythropoiesis-stimulating agent use, there has not been a substantial increase in allosensitization despite an absolute increase in transfusion event rates per patient after 2011.[2]

Renal transplantation among the 4 blood groups yields a 4×4 matrix with 16 possible donor-recipient blood group combinations (Table 1). Immediately, one recognizes the challenge of 7 ABOi donor-recipient combinations and 9 ABO-compatible (ABOc) donor-recipient combinations that are eminently feasible. Outcomes for ABOc donor-recipient combinations are startlingly successful. One-year patient and allograft survival achievement thresholds are established by the United Network for Organ Sharing and aspirational. Fulfillment of these goals by most transplant centers requires diligence and vigilance plus, in the majority of cases, adherence to protocolized management by patients and their health care providers.

For those 7 ABOi combinations, the recipient-in-waiting has 3 choices: await a deceased donor, become the fortunate recipient of an allograft via a kidney paired donation exchange (KPDE) program, which may involve a multiplexed, multicenter coordinated effort, or undergo kidney transplantation through an ABOi kidney transplantation. The Organ Procurement and Transplantation Network reported that there were 86,500 patients on deceased donor waitlists in 2011.[3] This number increases by 28,000 yearly. The median waiting time for a kidney transplantation across all blood groups is 4 years,[3] but there is significant variation in time depending on blood type, race, and location. To add to the nearly 5000 patients who received a living kidney transplant, which only offsets the 5000 individuals who died on their waitlists, KPDE programs have been a godsend. It has enriched the donor pool and has several other advantages. There is the avoidance of immunologic desensitization, reduced waiting time, and cost-effectiveness. However, the majority of potential transplant recipients are not availed the opportunity for paired kidney donor exchange. What next?

The answer may lie in ABOi kidney transplantation. This procedure may resolve the infeasibility of transplantation for many waitlisted end-stage kidney disease patients undergoing kidney replacement therapy. This issue is of particular concern to maintenance hemodialysis patients because increasing dialysis vintage begets worse allograft and patient survival rates.[4] ABOi transplantation is not new. In fact, it was first successfully reported in 1987, and involved a respectable series of 26 patients as described by Alexandre and colleagues.[5] In their groundbreaking strategy, plasmapheresis and splenectomy were the mainstays of their immunologic desensitization protocol.

In Japan, due to a paucity of deceased donors primarily because of the country's taboo view of death and its 1997

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Table 1. Donor-Recipient Landsteiner Blood Group Combinations and Kidney Transplantation Compatibility: ABO-compatible (•) and -Incompatible (○) Transfusion Blood Group Combinations

	Recipient			
Donor	A	B	AB	O
A	•	○	○	•
B	○	•	○	•
O	○	○	○	•
AB	•	•	•	•

Japanese organ transplantation law, there is the dichotomy of extreme organ shortage (and not just of kidneys) in an exceptionally medically advanced nation.[6,7] This perverse duality is poignantly described in painstaking and ethnographic detail by Yasuoka.[7] To increase organ availability for kidney recipients, the Japanese who are nearly devoid of the A2 subtype have nonetheless established expertise in ABOi kidney transplantation. In Japan, nearly 30% of renal allografts, therefore, are the product of this expertise. In the United States, kidney transplantation across ABO blood types was 30 times less frequent between 1995 and 2010 and represented only approximately 1.5% of kidney transplants.[8] Refreshingly, the number of ABOi kidney transplantations has been increasing, buoyed by the outcomes of several centers of excellence.

Naysayers to advancing ABOi efforts have cited the high-level immunosuppression that is required to carry out such a program. However, multiple modifications of the immunosuppression and plasmapheresis plus splenectomy (B-cell depletion) paradigm have emerged. Splenectomy is associated with hemorrhage and infections, but splenectomy-free protocols are readily available and prevalent now. In addition, anti-CD20 monoclonal antibody-mediated B-cell depletion is as effective as splenectomy.[9,10] Plasmapheresis is supplantable by selective antibody immunoadsorption strategies, particularly for high-titer anti-A/B IgG, which evades some of the complications (e.g., bleeding, infection, hypocalcemia) associated with intensive apheresis treatments. Moreover, plasmapheresis may be altogether dismissed if the offending anti-ABO antibody titer is sufficiently low at the outset, that is, in some instances as low as $<$1:16.[8,11] In the case where desensitization is required for a recipient with an anti-HLA antibody, the outcomes are worse.

In accordance with the high standards for graft survival established by the United Network for Organ Sharing (UNOS), clinical outcomes for ABOi kidney transplantation must be acceptable. Thus far, they are, and 3-year patient and graft survival are statistically equivalent between ABO-compatible and -incompatible transplantations.[12] These results originate from 1420 ABOi living donor kidney recipients who underwent ABO antibody reduction at 101 transplantations centers in the Collaborative Transplant Study from 2005 to 2012.[13] The analysis matched ABOi transplants against ABOc control cases. Induction therapy vs anti-CD20 antibody made no difference among cases in terms of death-censored graft of patient survival. As stated earlier, utilization of column adsorption provided equal efficacy to that of plasmapheresis. Notably, early patient survival was significantly lower in the ABOi cohort, attributable to mortality from early-onset infections, which may occur at up to twice the frequency in ABOc recipients.[1]

As mentioned earlier, what may the blood type O recipient do aside from likely wait many years for his/her "lucky day?" Entry into a KPDE program is not a truly viable option because the recipient must accept a kidney from a type O donor. The recipient, at this point, has already been unsuccessful at locating a living-related or -unrelated and altruistic donor, so the ABOi option is the most compatible one and obviates the deleterious effect of long-term dialysis exposure on allograft outcome.[14]

If the science of ABOi kidney transplantation is currently considered sound, the last barrier to adoption of this practice is indubitably financial. Hospitals that offer and profit from kidney transplantations have much to gain from conducting ABOi transplants. I submit that the overall level of competency of the transplant team is elevated by conducting ABOi desensitization protocols and scrupulously managing these patients. Moreover, the reputation of the team is elevated. Simply, the work is worth it and in more ways than one. The marginal cost of ABOi kidney transplantation is favorable over the lifespan of the patient by 15% when considering all possible scenarios including death and return of the patient to dialysis and subsequent death.[8] Furthermore, an additional 3.5 quality-adjusted life years are added to the ABOi recipient. In societal terms, this is another win because at $50,000 USD per quality-adjusted life years, in addition to resource savings, the net financial cost differential per ABOi transplantation is nearly $232,000 USD[8,15] using Medicare payment rates for physician rates and hospital charges and resource utilization.

In conclusion, if transplantation is truly the optimal renal replacement therapy, we must advocate for its use in all respects. ABOi kidney transplants are not inferior to ABOc ones. This procedure does not cost more and may cost less. Plus, an ABOi program can complement a KPDE program. For smaller centers that do not offer ABOi transplantations the financial argument must be presented to those yet unconvinced of the merits of ABOi. For smaller transplant centers, given the level of expertise required for successful ABOi transplantation, should these patients be referred to larger centers with sufficient expertise? And, what is necessary to bring a smaller center to the level of competency required for ABOi transplantation? The higher, short-term marginal cost to the hospital performing ABOi is the principal concern here, and this issue is a societal one, which the Centers for Medicare and Medicaid Services should address. Health care institutions should not be expected to pay for short-term risk as Medicare reaps long-term financial benefits. Otherwise, the woeful statistic that only 43% of kidney transplant centers carried out only 1 or more ABOi transplants will remain.[8] Cost neutrality or an upfront, inflation-adjusted payment for performing ABOi transplants is required to facilitate and distribute ABOi kidneys more widely to potential recipients. If this

is accomplished, the conduct of ABOi kidney transplantation will be as easy as A-B-O. Otherwise, we will face again the question of whether vendor (paid donor) kidneys are a cost-effective means to an end.[16]

Try it! You'll like it!
—Wells, Rich, Green Advertising (1971)

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