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JAYPEE

Challenges & Controversies in KIDNEY TRANSPLANTATION



SANDIP KAPUR

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Kidney Paired Donation as a Strategy to Increase Living Donor Kidney Transplantation

CHAPTER 3

Meredith J Aull, Sandip Kapur

ABSTRACT

Kidney paired donation (KPD) is a mechanism designed to provide kidney transplant candidates with willing but incompatible living donors the ability to enroll in a registry of other incompatible pairs in order to find a compatible transplant. Blood-type incompatible, crossmatch incompatible, and compatible donor-recipient pairs may benefit from transplantation facilitated by KPD. For highly sensitized kidney transplant candidates, desensitization therapy in combination with KPD offers an important option. KPD represents the most promising resource available to increase the number of kidneys available for transplantation due to the ongoing shortage of deceased donor organs.

INTRODUCTION

It was estimated that about 2 million people worldwide would have end-stage renal disease by 2010.[1] On January 17, 2014, >99,000 patients in the United States were on the United Network for Organ Sharing (UNOS) waiting list for a kidney transplant from a deceased donor.[2] It is presumed that the vast majority of these patients have no potential living donors, or have willing but incompatible donors and are unaware of the KPD option. Prior to the introduction of KPD, blood type (ABO) and/or immunologic incompatibility has limited living donor kidney transplantation.

Based on overall blood-type distributions in the United States, approximately one of every three potential living kidney donors is blood-type incompatible with their intended recipient. Immunologic incompatibility, as evidenced by a positive crossmatch and development of donor-specific antibody (DSA), occurs when transplant candidates are exposed to non-self (foreign) human leukocyte antigens (HLA) through blood transfusion, pregnancy, and/or prior transplantation. Exposure to foreign HLA leads many patients to develop anti-HLA antibodies, leading to reactivity against potential organ donors (DSA). Patients with a high degree of sensitization (i.e. a high antibody load/high DSA levels) often cannot find an organ donor against whom they do not have a significant immunologic reaction, which might lead to early and severe rejection of the allograft if transplantation

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were to occur. In the United States, approximately 40% of adult patients awaiting a kidney transplant have some degree of sensitization against HLA, while about 10% are considered highly sensitized, defined as a panel reactive antibody level above 80%.[3]

Although successful transplantation using ABO incompatible donors or by transplanting across a positive crossmatch is possible,[4,5] these methods do not necessarily represent the best solution for patients with incompatible donors. Both incompatible transplantation methods require "desensitization," which requires the use of interventions such as plasmapheresis, intravenous immunoglobulin (IVIG), rituximab, splenectomy and/or mycophenolate mofetil to reduce anti-ABO (anti-A or anti-B) or anti-HLA titers in order to enable transplantation between the incompatible donor and recipient. The excess immunosuppression, morbidity [via increased risk of antibody-mediated rejection (ABMR) and its associated treatment], and cost associated with incompatible transplants leave room for alternative solutions.[6,7] A meeting report from a Roche Organ Transplantation Research Foundation-organized symposium agreed that the goal of the transplant community should be to prevent ABMR rather than treat it once it occurs in order to avoid the negative consequences of ABMR on the transplant allograft.[7]

KIDNEY PAIRED DONATION: A SOLUTION TO THE SHORTAGE OF ORGANS FOR TRANSPLANT

The concept of paired exchange, as a mechanism to facilitate living donor kidney transplantation, was first introduced by Rapaport in 1996 as a potential solution to the shortage of deceased donor organs.[8] Rapaport proposed an international registry where eligible and willing, but blood-type incompatible donors could donate via organ exchange facilitated through this registry. Donors would undergo simultaneous nephrectomy, donated organs would be transported via courier, and transplantation into the recipients would occur simultaneously.

Almost two decades after the concept was first introduced, paired exchange had become a somewhat routine occurrence at a few transplant centers.[9,10] The logistical issues associated with international exchanges, such as those proposed by Rapaport, have not yet been fully solved; however, an international exchange has been reported between the Unites States and Canada.[11] National exchange programs have been successfully developed in Korea,[9] the Netherlands,[10] and the United States.[12,13] Most importantly, the concept has dramatically evolved from simple exchanges between two incompatible donor-recipient pairs to complex chains consisting of up to 30 incompatible pairs.[14] A 2012 consensus conference described KPD as an "elegant but complex solution" to the shortage of organs available

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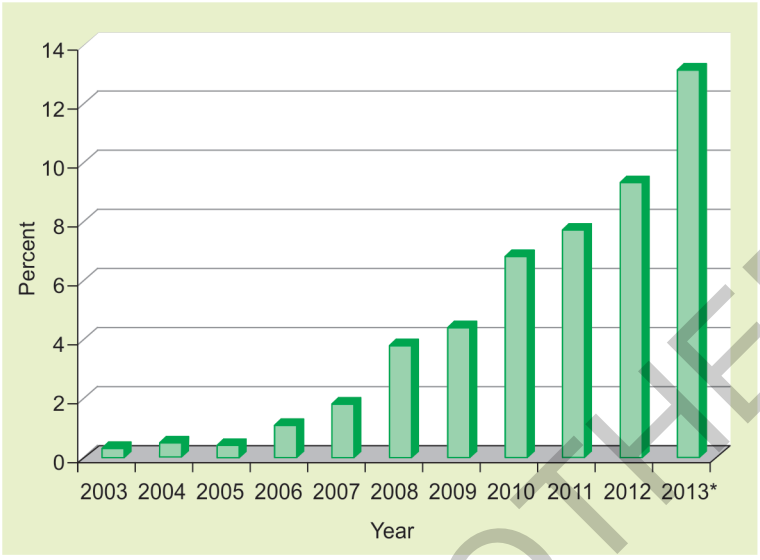


Fig. 3.1: Percent of living donor transplants from paired donation in the United States. *2013 data includes transplants performed through 31/10/2013.

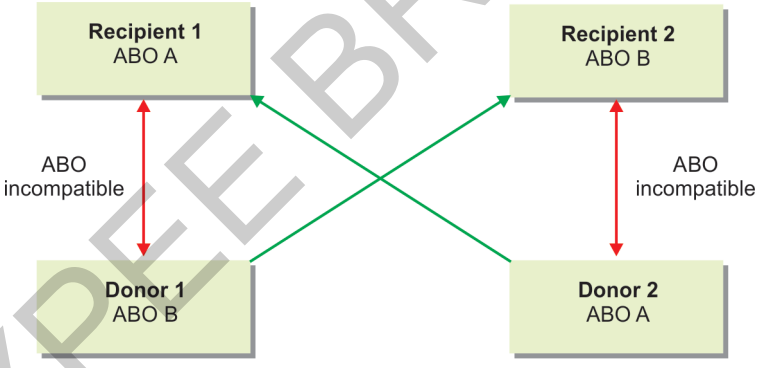


Fig. 3.2: "Conventional" kidney exchange. Recipient-donor pair 1 and recipient-donor pair 2 are both blood-type (ABO) incompatible. By exchanging donors through KPD, recipient 1 will receive a kidney from donor 2, while recipient 2 receives a kidney from donor 1.

for transplant.[15] As seen in Figure 3.1, paired donation has facilitated an increasing percentage of living donor kidney transplants in the United States over the past decade.[2]

Kidney Paired Donation Models

The initial concept proposed by Rapaport has rapidly progressed into much more complex exchanges. The types of exchanges are described in this chapter, and are illustrated, from simple to complex, in Figures 3.2 through 3.6.

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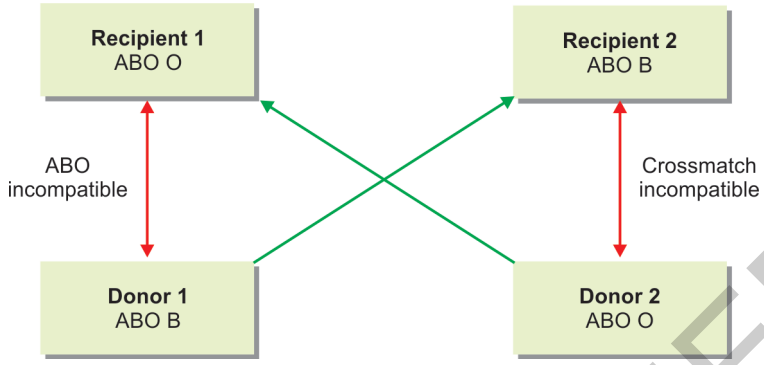


Fig. 3.3: "Unconventional" kidney exchange. Recipient-donor pair 1 is blood-type (ABO) incompatible, while recipient-donor pair 2 are ABO compatible, but a positive crossmatch prevents the donation. By exchanging donors through KPD, recipient 1 will receive a kidney from donor 2, while recipient 2 receives a kidney from donor 1.

Kidney Exchange

As first described by Rapaport, kidney exchange occurred between two blood-type incompatible donor-recipient pairs, who through participation in an exchange, were matched to create ABO compatible transplants (Fig. 3.2). This has been described as a "conventional" exchange.[16]

The initial concept was then expanded to allow both ABO incompatible and crossmatch incompatible pairs to participate (Fig. 3.3), thus expanding the patient population that could be helped by donor exchange. This has been described as an "unconventional" exchange.[16]

In 2005, Johns Hopkins first reported their single center experience using 10 paired donations to facilitate 22 kidney transplants, using a combination of both conventional and unconventional exchanges.[16] For each paired donation, operations were performed simultaneously, and anonymity was maintained until after the surgeries. Being a referral center for challenging transplants (due to center's experience with ABO incompatible and positive crossmatch transplants), the Hopkins experience is particularly notable for its success in transplanting within their difficult-to-match pool of transplant candidates.

List Exchange

List exchange (Fig. 3.4) allows the incompatible donor of a donor-recipient pair to donate their kidney to the deceased donor waiting list, and in exchange, their intended recipient receives priority on the deceased donor waiting list. Critics of this model point out that the majority of pairs participating in such an exchange will be blood-type incompatible, with an ABO non-O donor and an ABO O recipient, which is unfair to the ABO O recipients on the waiting list who will have to wait longer for an ABO O deceased donor kidney.

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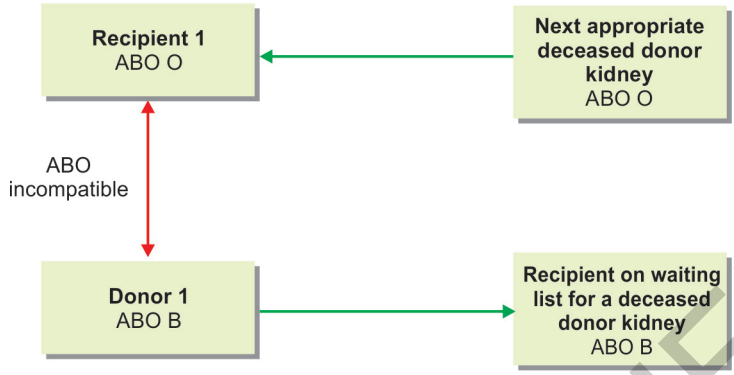


Fig. 3.4: List exchange. Recipient-donor pair 1 are blood-type (ABO) incompatible. In list exchange, the incompatible living donor donates a kidney to a patient on the waiting list for a deceased donor kidney. Then, the original intended recipient receives priority for the next appropriate deceased donor kidney.

In 2004, representatives from transplant centers in the United States UNOS Region 1 (New England) reported on implementation of a living donor/list exchange program, which had facilitated 17 transplants by the end of 2003.[17]

Domino Paired Donation

The domino paired donation (DPD) model (also called a "closed" chain) begins with donation by a nondirected donor (NDD), also known as an altruistic or "Good Samaritan" donor (Fig. 3.5). NDDs are living kidney donors who choose to donate despite not having an intended recipient for their kidney. The first reported kidney donation by a NDD occurred in the United States in August 1999.[18] By representing the general population, these NDDs present an important source of blood type O donors. This initial donation starts a "chain" of transplants where the NDD kidney recipient's intended but incompatible donor is matched to a compatible recipient, then that recipient's intended but incompatible donor is matched with a compatible recipient, and so on. If a compatible recipient cannot be found for the last donor's kidney within the KPD registry, the kidney is allocated to the deceased donor waiting list according to UNOS policy, and the chain ends (thus the term "closed" chain).

After successfully implementing KPD in the mid-1990s, the Korean KPD program began utilizing DPD in 2001, and performed 179 transplants as a result between 2001 and 2007.[19] Seventy transplant chains, the majority of which transplanted 2 or 3 patients, were initiated by an altruistic donor, and the last kidney went to a patient without a living donor. Donors traveled to the recipient transplant center, and operations were not simultaneous, but did occur within a short time frame (goal <7 days). In the United States,

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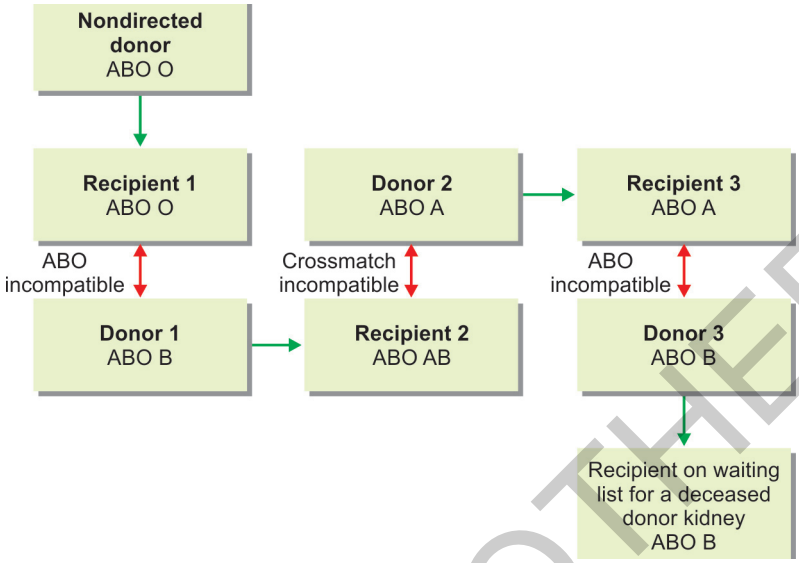


Fig. 3.5: Domino paired donation. Recipient-donor pairs 1 and 3 are blood-type (ABO) incompatible, while recipient-donor pair 2 is crossmatch incompatible. In Domino paired donation, a nondirected (altruistic) donor begins a chain of transplants by donating to recipient 1; recipient 1's donor (1) then donates to recipient 2, recipient 2's donor (2) donates to recipient 3, and recipient 3's donor (3) donates a kidney to a patient on the waiting list for a deceased donor kidney; the chain then ends.

Montgomery and colleagues first proposed the use of NDDs to generate multiple transplants via DPD in 2006.[20] Roth and colleagues performed simulations that showed that utilizing NDDs to start chains of transplants in the DPD model could increase the number of kidneys available for transplant.[21]

Nonsimultaneous Extended Altruistic Donation

Similar to the DPD model, a transplant chain in the nonsimultaneous extended altruistic donation (NEAD) model (also referred to as an "open" chain) also begins with donation by a NDD (Fig. 3.6). Like the DPD model, the NDDs donation starts a chain of transplants where the NDD kidney recipient's intended but incompatible donor is matched to a compatible recipient, then that recipient's intended but incompatible donor is matched with a compatible recipient, and so on. If a compatible recipient (with a willing but incompatible living donor as opposed to a patient on the waiting list who has no potential donor) cannot be found for the last donor's kidney, the donor serves as a "bridge" donor who waits until a suitable recipient-donor pair enters the registry, and the chain continues on at a later date (thus the term "open" chain).

Rees and colleagues were the first to report use of a NEAD chain in 2009; the chain facilitated 10 living donor kidney transplants.[12] Their group

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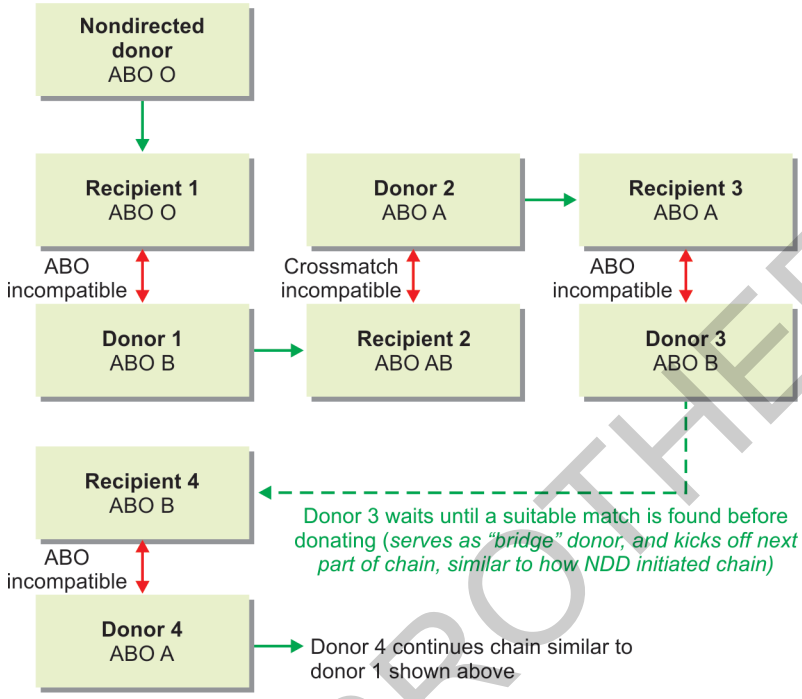


Fig. 3.6: NEAD (non-simultaneous extended altruistic donation). Recipient-donor pairs 1 and 3 are blood-type (ABO) incompatible, while recipient-donor pair 2 is crossmatch incompatible. In Domino paired donation, a nondirected (altruistic) donor begins a chain of transplants by donating to recipient 1; recipient 1's donor (1) then donates to recipient 2, recipient 2's donor (2) donates to recipient 3, and recipient 3's donor (3) then waits to donate until a suitable match is found within the KPD registry, and the chain continues at that time. Donor 3 is considered a "bridge" donor, and the donor's role in kicking off the continuation of the chain mimics that of the initial NDD.

combined several different techniques, including KPD combined with ABO incompatible transplantation and combined with desensitization, as well as participation of a compatible donor-recipient pair.

The National Kidney Registry (NKR) has had great success in transplanting patients via NEAD chains.[13] The NKR model represents a combination of NEAD and DPD; bridge donor characteristics guide the decision for that bridge donor to wait and start another transplant chain (e.g. if ABO O) vs donating to the waiting list (e.g. ABO AB or unable to wait to donate).

Active KPD Programs

Korea

The Korean KPD program was initiated for crossmatch incompatible pairs in 1991, and after early success, was expanded to include ABO incompatible pairs, as well as spousal pairs seeking a better genetic (HLA) match.[9] Three

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Korean hospitals were involved in the early program, and operations occurred simultaneously. More recently, 16 transplant centers now perform more complex exchanges, including the domino KPD transplants initiated by an altruistic donor, as described earlier.[19] The Korean Network for Organ Sharing (KONOS) allocation system used for deceased donor transplants is used to identify suitable recipients who do not have a living donor. The system utilizes HLA matching, pediatric status, waiting time, history of positive crossmatch (>2) or prior transplant, and history of kidney donation by the recipient or their family members to allocate the organs. The Korean program attributes some of its success to the lower proportion of ABO O candidates in Korea, as well as participation of compatible pairs in the KPD program.

The Netherlands

Encouraged by the early success of the Korean KPD program, seven Dutch transplant programs developed a KPD program in 2004, creating a national crossover pool of donor-recipient pairs.[22,23] A national organization, the Dutch Transplantation Foundation, serves as the central allocation mechanism for KPD, and the National Reference Laboratory performs all crossmatches. Participating donor-recipient pairs are crossmatch or ABO incompatible, and the algorithm calculates the "match probability" or "MP" for each recipient, based on their degree of sensitization, blood type, and unacceptable HLA antigens (those against which the recipient has antibodies). Blood-type identical pairs are allocated first, in attempts to reserve ABO O donors for ABO O recipients, and the MP is then used to rank the recipients. More recently, de Klerk and colleagues describe the barriers faced by the Netherlands exchange program, which transplanted 46.3% of participants (128/276) between January 2004 and July 2008; all participants had incompatibility with their original intended donor.[10]

North America

There are several single and multicenter KPD Registries that are actively facilitating transplants today in North America, as described below. Although KPD has undergone significant growth in the United States within the past 6 years, a recent study showed that a limited number of transplant centers are responsible for the majority of transplants being facilitated by KPD.[24] This analysis showed that at the 10% of transplant centers with the highest rates of KPD, between 9.9% and 38.5% of those center's living donor kidney transplant volumes came from KPD participation between 2009 and 2011. Importantly, the study found that if all transplant centers participated in KPD in a similar fashion to these successful centers, >1,000 additional living donor kidney transplants could be generated each year in the United States.

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Table 3.1: United States multicenter kidney paired donation programs

KPD program	*Transplants facilitated**	*Website*
Alliance for Paired Donation	22 (between 7/18/07 and unk/2010)[25]	http://www.paireddonation.org
Johns Hopkins	45 (between 2001 and 8/27/07)[26]	http://www.hopkinsmedicine.org/transplant/programs/kidney/incompatible/paired_kidney_exchange.html
National Kidney Registry	942 (between 2/14/2008 and 1/26/2014)[27]	http://www.kidneyregistry.org
North American Paired Donation Network	Not available	http://www.paireddonationnetwork.org
North Central Donor Exchange Cooperative	Not available	http://www.ncdec.org
United Network for Organ Sharing	68 (between 10/2010 and 11/4/2013)[28]	http://optn.transplant.hrsa.gov/resources/KPDPP.asp
Washington Regional Transplant Community	Not available	http://www.beadonor.org

*Transplants facilitated derived from published literature or publicly available sources.

Multicenter KPD in the United States

There are currently seven multicenter KPD programs functioning in the United States,[15] providing a driving force for competition and innovation among programs (Table 3.1). Despite the individual successes of these multicenter KPD programs, a single national KPD program is a proposed ultimate goal, as it would generate the largest pool of donor-recipient pairs and thus could facilitate more transplants. As compared to geographically smaller countries with a small number of transplant centers (such as the Netherlands and Korea), implementation of a national KPD program in the United States is understandably more challenging due to its size and >225 kidney transplant programs.[2]

As can be seen in Table 3.1, the NKR is the most successful KPD program in the United States, likely attributable to several factors. The NKR was founded by a father familiar with the struggles of finding a compatible

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living donor for his daughter, and who approached the problem from a new and different perspective. In addition, collaboration among many of the major United States' national kidney transplant programs (>65 centers as of January 2014[27]), utilization of advanced software to match donors with recipients, and transparent policies and procedures followed by all participating transplant centers (publicly available at www.kidneyregistry.org) have contributed to the success of NKR.

Single Center KPD in the United States

The kidney transplant program at Methodist San Antonio has been the most successful single center KPD program in the United States, having performed 134 kidney transplants over approximately 3 years.[29] This program includes incompatible donor-recipient pairs as well as compatible pairs with an age discrepancy and utilizes the database developed at Johns Hopkins for the purpose of matching donors and recipients for KPD. This program attributes its success (in spite of being a single center with a limited pool of donors and recipients) to prospective education of donor-recipient pairs about KPD, comprehensive immunological profiling of donor and recipient, flexible assignment of unacceptable antigens, storage of blood samples for future testing, use of desensitization, subtyping of ABO A donors, and inclusion of compatible pairs.

Multicenter KPD in Canada

In Canada, the Living Donor Paired Exchange kidney transplant registry is a partnership between Canadian Blood Services and transplant programs across the country designed to facilitate living kidney donations between patients with a willing but incompatible donor and other pairs in the same situation. The program, initially launched as a pilot program in 3 Canadian provinces in 2009, had performed 171 kidney transplants by October 2012.[30]

Other Countries

In addition to the programs mentioned above, there are also KPD programs in Australia,[31] the United Kingdom,[32] and Spain.[33]

CLINICAL OUTCOMES

Experience with KPD to date shows that transplants facilitated by KPD have equivalent outcomes compared to traditional living donor kidney transplantation.[13,16,23,26,34] These excellent outcomes are particularly impressive considering the extent of sensitization exhibited by many recipients in the registry pool. Patient and graft survival rates have been similar to those expected with traditional living unrelated kidney transplantation.

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WHAT FACTORS HAVE DRIVEN THE INCREASE IN PAIRED DONATION FACILITATED TRANSPLANTS?

Keys to Success

Participation of Nondirected Donors

It is through the participation of NDDs that KPD programs have had greater success in facilitating transplants in recent years. By introducing a donor to the KPD pool who has no linked recipient, the pool of donors increases and mimics the characteristics of the general population, bringing much-needed ABO O donors into the pool. A recent analysis shows that utilization of NDDs for transplant chains has the ability to significantly amplify the benefit provided by NDDs, since each NDD generates an average of five transplants, or even more if the donor is ABO O.[35] Most KPD programs require psychiatric evaluation as part of the evaluation process for potential NDDs.

Large Pool Size

By having a large pool of incompatible donor-recipient pairs, there is an increased chance of finding an acceptable match. A large pool generally also increases the heterogenicity of the pool, which is beneficial in matching donors with recipients. In conjunction with the advanced software utilized by successful KPD programs, a larger pool can generate many more potential matches for incompatible pairs.[36]

Mathematical Modeling Software/Matching Algorithm

Many mathematical models have been developed to identify matches for the donor-recipient pairs participating in KPD registries. These models vary greatly in terms of the factors used in the model; however, most use similar criteria for determining matches. The frequency at which "match runs" occur also varies greatly among KPD programs.

The common factors include the following:

- Donor and recipient ABO type
- Virtual crossmatch results using donor HLA antigen and recipient anti-HLA antibody profile
- Preferences related to donor travel (i.e. distance willing to travel)
- Waiting time within KPD registry
- Limiting ABO O donors from donating to ABO non-O recipients
- Entering ABO A2 donors as ABO O* donors[37]

As more advanced software has been developed to facilitate KPD, there has been movement away from the traditional integer programming

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algorithms used in early models. For example, the NKR software is built upon technology utilizing concepts from capital market exchange systems.[36] In order to improve both the quantity and quality of transplants, an outcome-based strategy for generating matches within KPD has also been proposed.[38]

Much research has focused on the ability of the two newest KPD models (DPD vs NEAD) to generate the highest numbers of transplants. However, there does not yet appear to be a definitive answer due to the numerous factors involved in the modeling process.[39,40]

Virtual Crossmatch

The availability of advanced tools from the field of immunology has also been instrumental to the growth of KPD. Traditionally, a crossmatch is performed utilizing serum from both the potential organ donor and transplant candidate, and uses the complement-dependent cytotoxicity test and flow cytometry to detect antibodies that react with donor HLA antigens. An advanced method, called a virtual crossmatch, utilizes identified DSA titers/unacceptable antigens for a particular candidate (via screening with single antigen beads such as Luminex) and the detailed HLA typing of the potential donor to assess for potential reactivity. Virtual crossmatching has been successfully employed by several large KPD registries,[41,42] reducing logistical issues and cost associated with performing a traditional crossmatch. Traditional crossmatch testing is then performed between matched donor-recipient pairs in order to ensure compatibility prior to the scheduled transplant.

Flexible assignment of unacceptable antigens may be important,[29,43] particularly when attempting to identify potential donors for highly sensitized transplant candidates. By not excluding antigens to which the candidate has a low level of antibody, a KPD registry can increase the pool of potential donors for that recipient; this is where willingness to employ a combination of KPD and desensitization can increase success in identifying a suitable donor for a sensitized patient.

Willingness to Combine KPD with Desensitization Protocols

Montgomery and colleagues have described success with a "hybrid" model that uses KPD to identify a more immunologically favorable donor (although not completely free of reactivity against the donor) and then utilize desensitization techniques to facilitate transplantation.[43] This enables use of less immunosuppression for desensitization, and an increased chance of successful transplantation. This option is of great importance, given that highly sensitized recipients (PRA >80%) have had low match rates (<15%)

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in KPD experience to date.[43] Blumberg and colleagues also report on their experience performing desensitization with IVIG alone in highly sensitized patients who had DSA against the donor they received through the KPD program.[44] After 22 months of follow-up, graft survival was excellent (100%) and the rate of ABMR was low (25%), considering the extent of sensitization in the patient population studied. Sharif reports another strategy successfully employed by the Hopkins transplant program, termed "rescue KPD".[45] Patients unsuccessfully desensitized against their donor are reprofiled for anti-HLA antibody after the desensitization therapy, and the incompatible pair is then entered into the KPD program in attempts to find a more compatible donor.

Transplant Center Dedication of Resources to KPD Program

The complexity of today's KPD exchanges requires participating transplant centers to allocate dedicated staff to the KPD program. KPD transplants are logistically challenging and centers wishing to participate must give thought to the infrastructure and resources needed for meaningful participation. Coordination and logistical support throughout the process is essential. Flexibility in scheduling of both donor and recipient cases is desirable, as there may be need to reschedule or rearrange on short notice in order to ensure continuity of the transplant chains.

Active participation and support from hospital administration and finance are essential, as complex insurance and financial issues may arise. A clear understanding of the benefits of transplantation over dialysis and the positive financial impact of a successful living donor transplant by hospital administrators is essential.

It has been suggested that transplant programs considering joining a KPD registry should identify a KPD Champion to lead their program, and that each KPD registry should identify mentors that have successfully implemented KPD at their own center, to provide guidance and support to new transplant centers.[15] A KPD Champion is essential in bringing together key players from both the transplant program and administration.

A transplant coordinator with hands-on experience is needed to manage the complex logistics of KPD, including entry of donors and recipients into the registry, receiving match offers, and managing logistics among transplant centers involved in a particular chain. The coordinator also maintains medical records for donor organs procured at outside centers needed for the recipient medical record, tracks the organ(s) en route to the transplant center, fields issues arising on the day of the surgery, and arranges contact between donors and recipients who wish to meet after their surgeries.

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ONGOING ETHICAL ISSUES AND CONTROVERSIES

As KPD has evolved and become more complex, several ethical debates have dominated discussions about the field. The reader is referred to Chapter 4 of this textbook for a thorough discussion of these controversial issues.

CONCLUSION

Kidney paired donation is an exciting and promising solution to the current shortage of organs available for kidney transplantation. By enabling kidney transplant candidates and their willing but incompatible donors to join a KPD registry with the goal of being matched up with other pairs, KPD facilitates an increase in living donor kidney transplantation. The participation of compatible donor-recipient pairs has the potential to significantly increase the number of transplants facilitated through KPD. Benefits of living donor transplantation include superior outcomes compared to deceased donor kidney transplantation and to remaining on the deceased donor waiting list. In addition to increasing the quantity of kidney transplants, KPD offers an improvement in the quality as well, by increasing the numbers of living donor organs available to patients who might otherwise wait years on the deceased donor waiting list. KPD also provides a new opportunity for highly sensitized patients who might otherwise never receive a transplant. Movement toward one national KPD program and continued collaboration between currently participating centers may enable continued exponential growth of transplants facilitated through KPD and offers a viable strategy to address the organ shortage.

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Despite significant accomplishments to date, kidney transplantation is a relatively young field in medicine. Novel concepts to increase organ availability have been adapted by progressive transplant centers due to the shortage of organs available for transplant. Kidney paired donation and single site laparoendoscopic donor nephrectomy are important methods of increasing access to living donor transplantation. Utilization of expanded criteria, donation after cardiac death, hepatitis C positive, and pediatric donor organs are discussed as methods to increase deceased donor transplant opportunities for patients awaiting a kidney transplant. In addition, this book addresses challenging patient populations with complex comorbidities that require special consideration when designing immunosuppression regimens and when developing management strategies.

We hope that the reader finds *Challenges and Controversies in Kidney Transplantation* to be a comprehensive resource on the topics mentioned above as well as others that can help centers offer transplantation to as many candidates as possible, and improve post-transplant outcomes in order to maximize the organs that are donated.



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