

Editorial

Kidney Paired Donation: Something Special in the Air!

David Serur, MD and Gabriel M. Danovitch, MD[†]*

**Rogosin Institute and Division of Nephrology, New York Presbyterian Weill Cornell, New York, New York; and [†]Department of Medicine, David Geffen School of Medicine, UCLA, Los Angeles, California*

Kidney paired donation (KPD), the exchange of kidneys from living donors, deemed by virtue of blood group or histocompatibility criteria to be incompatible to their intended or designated recipients, was first proposed by one of the founding fathers of modern organ transplantation, Dr. Felix Rapaport, in 1986 (1). In 1991, a transplant program in South Korea started the first KPD system in a single center and without the benefit of computerized matching (2). In 2004, a Dutch national system was created comprising of seven centers, matched by computer, utilizing a central tissue typing laboratory, and arranging for simultaneous transplants: the donor traveled to the recipient's hospital (3). Several KPD systems then became active in the United States: the Johns Hopkins program, the Alliance for Paired Exchange, the Paired Donation Network, the New England Program for Kidney Exchange (NEPKE), and the National Kidney Registry (NKR), which has facilitated over 300 transplants in less than 4 years (4). The United Network for Organ Sharing (UNOS) began a pilot KPD program in late 2010 as part of evaluating the development of a national program.

Why Engage in KPD?

Patients with an ABO-incompatible or a cross-match-positive living donor were traditionally relegated to waiting on the deceased donor list and their potential donors were excluded from donation. With the advent of desensitization protocols, some patients have been able to receive incompatible transplants, but at a price. There is the risk of the extra immunosuppression (plasmapheresis, IVIG, greater use of biologic agents) required for desensitization, coupled with outcomes that are good but are associated with higher rates of rejection compared to traditional living

donor transplants (5). KPD avoids the extra immunosuppression and allows for the usual excellent outcomes associated with living unrelated transplants. Patients, and their donors, who chose the option of enrolling in a KPD program can expect to quickly find another donor/recipient pair to match with (called a match offer) if they are simply ABO incompatible with their donors and unsensitized (except for blood type O recipients), but wait longer if they are cross-match-positive with their donor or have a very high levels of preformed antibodies.

How Does KPD Work?

Incompatible pairs enroll in one or more KPD programs, usually at no cost to the patient. Recipients may enter with more than one incompatible donor, thereby raising their chances for a match offer. Some programs allow the patients to set donor preferences, such as donor age, antigen match, donor size, and whether they are willing to accept a kidney flown in from another center (shipped kidney). The more preferences desired, however, the longer the wait for that organ. To prevent failed crossmatches, the patient's own HLAs, as well as the antigens to which they react strongly are uploaded into the computer matching system so as to avoid donors with those antigens (incompatible antigens) in a process similar to the virtual crossmatch that is now part of matching for deceased donation (6).

The computer then performs a match run based on the concept of optimization: obtaining the best results with limited resources (7). The more pairs in the system, the better the chance for a quick match. When a match is offered to the patient, it is not necessarily the first possible match, but one that incorporates the recipient's preferences and allows for

the most transplants to occur. The transplants can be between two pairs, three pairs, or more (Fig. 1). However, the more transplants (with their associated donor nephrectomies), the more difficult it is to secure the requisite number of operating rooms, surgeons, staff, etc. The transplants may have to occur in several different hospitals and in different time zones, making simultaneous procedures unfeasible. The chains of multiple transplants described by Rees *et al.* (8) and Butt *et al.* (9) took several months to complete.

Never Ending Altruistic Donor (NEAD) Chains

Rees *et al.* (7) popularized the concept of the NEAD chain. Here a nondirected donor (NDD) (we prefer this term to the loosely used altruistic donor) initiates a chain of transplants that ends with a donor who has not yet donated (bridge donor, see Fig. 1). The bridge donor can initiate a new cluster of transplants that will have another bridge donor at the end of it and so on. In this schema one NDD can initiate a self-perpetuating chain of transplants assuming that all the bridge donors donate. One of the potential disadvantages of NEAD chains is that the bridge donor may wait weeks or months to donate as the next cluster of transplants has not yet formed. This can occasionally lead to a donor backing out of his or her decision to donate (renege) (10). To minimize this possibility, the next cluster can be started quickly, or the bridge donor can donate to the deceased donor list: to a child, a patient who is highly sensitized, or to the next waitlist candidate.

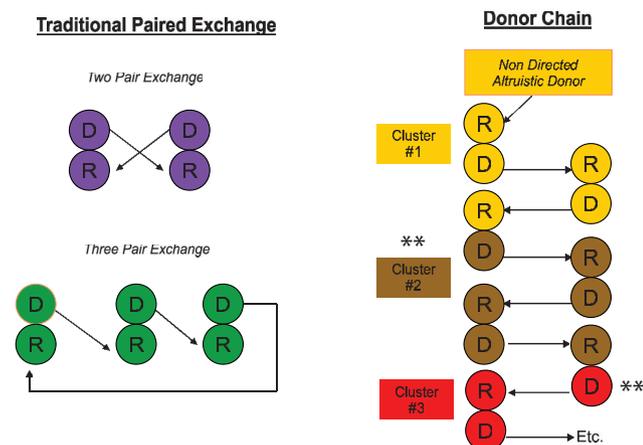


Figure 1. Traditional paired exchange and donor chains. **, Bridge donors with permission from the National Kidney Registry.

Ethical Considerations

Could a bridge donor feel pressured or obliged to donate? Clearly, no attempt should be made to influence a bridge donor to donate against their will, even if they had originally expressed their sincere intention to donate. Programs rely on an honor system based on the presumption that bridge donors are motivated to donate as their designated recipients have already received a kidney from a stranger. As a result, donors in KPD may have extra stress placed on them. They cannot invoke incompatibility as a reason not to donate, as this is the reason why they are in a paired exchange program in the first place. The donor in KPD knows that backing out can result in more than one person not getting transplanted, thus placing additional pressure on them (11). Careful education and evaluation of the psychologic health of all living kidney donors is a core necessity if an unfavorable pre- or post-donation outcome is to be avoided (12, 13).

Another concern has been that KPD results in the diversion of living donor kidneys from NDDs away from the deceased donor list (14). But as Gentry *et al.* (15) have shown, an NDD donating to the deceased donor list does not result in as many transplants as one donating in KPD. Furthermore, many programs close the chains of transplants with a donation to the deceased donor list. NEAD chains are theoretically never-ending, but in reality they are closed out after 10 to 20 transplants are completed. In fact donating to the list has closed most of the chains in the NKR program. (Of 62 chains started, 55 have so far ended with the deceased donor list; personal communication Gareth Hil, July 19, 2011). So for every NDD donating to a KPD program, a candidate on the deceased donor list is typically transplanted. It has been suggested that KPD may disadvantage minorities who are less likely to receive living donor transplants, yet all the recipients of KPD are listed on the deceased donor wait-list and by transplanting them, whatever their ethnic identity, the competition for deceased donor kidneys is reduced. Candidates on the deceased donor list are not disadvantaged by KPD; on the contrary, they benefit from it.

Are Blood Type O Recipients Disadvantaged?

A legitimate concern with KPD is that fewer transplants from living donors are offered to blood type O recipients. The O recipient is disadvantaged as O donors can usually donate to their intended recipient

(unless they are crossmatch positive), resulting in a scarcity of O donors in paired exchange. One way to alleviate this problem is to enter ABO compatible pairs into the system (16). By doing this, blood group O patients will get transplant offers and the recipients who had compatible O donors may benefit from a younger, better matched kidney by being exposed to a larger pool of live donors. It would generally not be recommended for compatible pairs with a well-matched young donor to enter into KPD, as they would not likely reap any direct benefit from it.

Kidneys that Fly

Ideally all the surgeries in KPD would occur simultaneously in contiguous operating rooms, the donor traveling to the recipient hospital, or *vice versa*. Most donors however, prefer to undergo surgery closer to home where family and friends can help them recover. Getting on a plane to travel home several days after donor nephrectomy is generally not an attractive option. So in most large KPD programs, the donor kidney is recovered locally and shipped by land or air to the recipient hospital in the same manner as organs from deceased donors.

There has been some understandable reluctance to shipping kidneys from living donors, and there has been legitimate concern that the function of the living donor kidney might be impaired. Segev *et al.* (17) have shown, however, that live kidneys perform well when cold ischemic time is less than 14 h. Data from NKR show that delayed graft function (DGF) occurs about 3.5% of cases (7 cases in 200 shipped kidneys). This compares favorably with the national DGF rate of 3.6% for living donor kidneys transplanted simultaneously (18).

Shipping a kidney also runs the risk, albeit remote, of a misadventure to the kidney en route. There have been reported cases of deceased donor kidneys "lost" en route or severely delayed in their arrival, usually as a result of bad weather or missed connection. In paired exchange, this would be particularly disastrous.

Fortunately there are no reports of lost kidneys in KPD. Attaching a GPS tracking device to the kidney box has been helpful in tracking delayed kidneys. Samples of donor blood accompany the kidney so that in the unlikely event that the intended recipient cannot accept the kidney (*i.e.* sudden cardiac event, etc.), the

donor blood can be used to match a different recipient from the deceased donor list.

Indirect Benefits of KPD

The direct benefit to the recipients of exchange living donor transplants are clear. But there are other benefits to KPD that are less obvious, but nonetheless of great importance. Desensitization to permit apparently incompatible living donation is medically complex, expensive, and associated with what we describe as clinical angst. The angst of KPD is real, but it is largely bureaucratic and usually not medical in nature. The actual living donor transplants are typically uncomplicated, with short hospital admissions and straightforward post-operative course. Bureaucratic angst is always to be preferred to clinical angst. But desensitization protocols should not be regarded as competing with KPD: by exposing highly sensitized recipients to a large number of potential donors, an exchange with a lower level of sensitization can be found and a less complex desensitization protocol employed. KPD and desensitization to either ABO or HLA incompatibility should be regarded as complementary.

KPD is financially beneficial on both a local and national level. It permits patients with chronic kidney disease to be removed from expensive dialysis treatments to the less expensive transplantation option (19). For hospitals, the living donor transplants that result from KPD are money-makers, with typically short post-operative stays and a medically uncomplicated course. KPD does, however, require investment by transplant programs in an administrative infrastructure to permit the matching protocols to function. For example, a common feature of well-functioning KPD programs is the availability of designated transplant nurse coordinators to interact with patients, their donors, the chosen paired donation network, and the other transplant programs involved in the exchange. This investment in staffing is well worthwhile.

Organ transplantation, from the living or the deceased, is the epitome of teamwork. In KPD, this teamwork is expanded from the level of an individual program to the multiple programs that are exchanging living donor organs. The morale boost to transplant teams involved in KPD is most gratifying as their teamwork generates multiple chains of transplants that would otherwise not have occurred. The frequent news stories describing living donor chains and their bene-

ficiaries that have appeared in the lay press (20-22) are reflections of the attractive, magnetic impact of paired donation. By popularizing organ donation from the living, we believe that KPD can have also have a positive impact on society's attitude to organ donation from the deceased, promoting the social solidarity (23) that is a core component of the national response to the organ donation shortage.

Future Developments

Paired exchange is proving to be highly successful thanks to innovative strategies that have been utilized to affect the greatest number of transplants and minimize risks. It has been estimated that 3000 more living donor transplants per year could occur as a result of a national KPD program (24), which will eventually replace the multiple programs currently available. Learning from the experience and innovations of the individual KPD program in the United States, we anticipate that such a national program would include the following characteristics:

1. It would use NDDs to initiate large chains as well as facilitate traditional two- and three-way matching.
2. Computer match runs would occur any time new pairs are introduced into the system, perhaps weekly or even daily if need be.
3. Virtual crossmatches, using unacceptable antigen data, would be initially used to help minimize true crossmatch failures.
4. Bridge donors would initiate a new cluster of transplants quickly or would alternatively donate to the deceased donor list, thus minimizing the risk of renegeing.
5. Compatible pairs could be entered into paired exchange as well as incompatibles to alleviate any disadvantage to O recipients.
6. Medicare would finance the system and facilitate financial interaction between programs and save on dialysis costs.
7. The highest standards of living donor education, consent, advocacy, medical and surgical care, and follow-up must always be employed.

KPD is arguably the most important positive development in organ donation in recent history. The nationalization of KPD in the United States, building on the skills and experience of the devoted innovators in the field, is a worthy goal for the nephrology and transplant community. There is no time to lose.

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