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Evolving Swaps in Transplantation: Global Exchange, Vouchers, Liver, and Trans-Organ Paired Exchange

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Abstract

Purpose of Review: With the ongoing organ shortage, several mechanisms to facilitate organ exchanges and expand the scope of living kidney or liver donation have been proposed. Although each addresses at least one barrier to transplantation, these innovative programs raise important ethical, logistical, and regulatory considerations.

Recent findings: This review addresses four recent proposals to expand living donor transplantation. For kidney transplantation, we discuss global paired exchange and advanced donation programs (“vouchers”) and for liver transplantation, liver paired exchange. Lastly, this review considers trans-organ exchange. We explore the conceptual framework of the exchange, current status, benefits, and concerns for implementation among each of these evolving pathways.

Summary: Through highlighting these novel mechanisms in organ exchange, greater awareness, discussion or support can occur to create more avenues for transplantation.

Keywords

global paired exchange; Advanced Donation program; liver paired exchange; trans-organ paired exchange; paired exchange; donors and donation

Introduction:

In the US, over 100,000 individuals are awaiting a transplant, and this number does not capture the thousands removed from the waitlist because they die or deteriorate before transplant (1–3). The majority of individuals are waiting for a kidney or liver transplant. Organs from living donors offer more immediate access to transplantation, a decreased risk of clinical decline while waiting, and improved outcomes over deceased donation (4–6). Many patients have potential living donors who are unable to donate specifically to them for immunologic or anatomical reasons. Increasingly, organ exchanges are offered to facilitate living donor transplantation. This review article examines four recent concepts in organ

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Conflicts of Interest:

None

exchanges: global paired exchange, advanced donation programs (“vouchers”), liver paired exchange and trans-organ exchange.

Global Paired Exchange (GPE) for Kidney

The goal of GPE is to expand the reach of kidney paired exchange (KPE) and to increase the immunologic diversity of donors by including donor and recipient pairs from countries with limited health care resources for end stage renal disease (ESRD). Global exchanges support a donor/recipient pair without financial means for dialysis and/or transplant in their native country to participate in KPE in a country that offers these services. The first report of GPE was a couple that was an immunologic match, but the cost of transplant or dialysis was prohibitive in their home country. The addition of this pair facilitated a donor chain that included 11 US transplant recipients. The Alliance for Paired Donation paid for the cost of travel, hospitalization, and procedure and created an escrow account for additional post-operative care in their home country (7)*.

Proponents of global exchange highlight the “win-win” outcome for both donor-recipient pairs (8). The structure of GPE overcomes financial barriers that prevent recipients from receiving organs, matching “countries with funding...to countries with organs” (7). Expanding the potential donor pool globally is advantageous for exceptionally difficult matches and may unlock multiple transplants (9). Proponents argue that the cost incurred by sponsoring the care of the international pair may be offset by facilitating multiple transplants, which over the long-term is more cost-effective than the alternative of dialysis (10, 11). Advocates also point to the ethical acceptability of GPE, because it does not unduly induce donation, but rather removes financial barriers for donors (12). As with all living organ donations, a GPE exchange improves quality of life in the recipients (10), whether national or international.

Critics of the GPE program point to a lack of regulatory controls and oversight as causes for concern. Across cultures and thousands of miles, it may be difficult to discern if donors are fully informed of risks and participate without coercion (13). Countries targeted by the GPE program are sites of high organ trafficking activity (13) with media reports emphasizing the large scale of the problem (14–17). As donors may be at a slightly elevated risk for developing ESRD, they require vigilant screening and management of comorbidities that compound the risk of renal disease, such as hypertension and diabetes. Critics worry the structure of the program does not allow for such long-term follow up and management (10). Additionally, the World Health Organization (WHO) and The Transplantation Society (TTS), organizations with international presence to oversee such an initiative, currently oppose global paired exchange (10, 13). Lastly, critics wonder if such efforts would be better directed at reducing financial barriers to donation within the United States (8), as donors incur personal costs beyond their donation associated medical care, which is covered by the recipient’s insurance. These costs are not inconsequential, and may limit an individual’s ability to donate. A recent analysis found that median out-of-pocket costs were \$1,254 with a 75th percentile cost of \$2,589 (18).

Prior to widespread implementation of GPE, additional considerations need to be addressed. Culturally appropriate counseling regarding organ donation, belief systems, and decision-making needs to be established (12, 19). The structure of the financial support for the medical care of donors and recipients post-operatively needs to be formally established to ensure follow-up care, especially as complications can occur years after transplant. With such complex logistics and current lack of regulatory oversight, advocates have suggested starting on a small scale with decisions being made on a case-by-case basis.

Advanced Donation Program/Vouchers

Advanced Donation Program (ADP), or “vouchers,” aims to expand the pool of potential kidney donors by addressing “chronologically incompatible” pairs (20)*. There are three main scenarios. The first consists of a preplanned structured exchange between several known donor/recipient pairs, however due to scheduling considerations the donations occur non-sequentially. For example, a teacher, who may want to donate during a school break, donates several weeks prior to the rest of the planned exchange. The second type of advanced donation involves a donor who has a narrow window of time to donate, but the donor and intended recipient do not have a match in the exchange program. However, due to time constraints (e.g. limited time off work), the donor will donate to start a chain before the identified recipient has a matched donor. The third type of advanced donation involves a donor who wishes to donate at the present time so that their intended recipient, who does not currently require a transplant, could receive a kidney at some unknown point in the future.

While the first two types of vouchers are less controversial, the third type of voucher has only been reported through case reports. For example, a grandfather of a young boy with chronic kidney disease, who was expected to progress to ESRD within the next decade, donated his kidney because he was concerned his age would exclude him when his grandson eventually needed a transplant (20). Another case involved a young girl who had already received a living donor kidney transplant, but two other family members proceeded to donate their kidneys. The family members thought the young girl’s current graft may eventually fail and worried they may be too old to donate at that time (20). Both kidneys sparked a chain of multiple transplants. Although the third type of advanced donation is just beginning to be reported in the literature, the National Kidney Registry, one of the matching systems in the United States, has offered an ADP since 2011 (21).

The advantage of this setup allows for individuals who have a limited window for donation to become donors and benefit their intended recipient (20). Advocates argue that a voucher system creates an influx of organs in the present. Many recipients have multiple living donors, and ADP provides a mechanism by which these potential donors, motivated by their recipient’s need, can still donate without “saving” their kidney if their recipient requires a second transplant (22, 23). ADP benefits both the voucher recipient and also initiates a kidney chain in the present.

The strongest criticisms of this program lie in the uncertainty of whether the voucher recipient will receive a kidney when the voucher is “redeemed” and concerns about the non-transferability of the voucher. “Priority” does not guarantee a compatible kidney will be

available for the potential recipient and is limited to the paired-exchange pool the donor entered. Additionally, critics fear that such a program may widen the already existing disparity of certain groups who participate in living donation at lower rates, such as minorities and those of low socioeconomic status (24). Others raise concerns that vouchers may start the slippery slope of treating human organs as commodities (25), potentially leading to vouchers in exchange for other goods that generate societal benefit (e.g. college education credit).

Prior to expansion, more clarity on donor education and logistical rules is needed. Donors must understand that there is no guarantee *if*, *where*, and *when* their recipient will receive an organ (26). In the case of an organ that matches with multiple voucher redeemers, the relative priority of a voucher holder among other voucher holders also remains unclear (20). Deterrents from “gaming” the system, i.e. advanced donation in the hopes that the voucher holder receives a better organ (e.g. younger), must be created to ensure the integrity of the program (20).

The non-transferability of vouchers remains a point of debate (23). Currently, if only one recipient is designated the voucher holder, and the intended beneficiary dies, never requires a transplant, or is too highly sensitized to match, the donor cannot transfer this voucher to another recipient (24), including a family member in more immediate need (26). Some fear that such a predicament may lead to another manifestation of donor regret, whereby the donor is unable to help a loved one in a future situation. Proposed solutions include requiring a waiting period for donors to consider their decision or allowing multiple designated recipients. A waiting period is intended to promote reflection on donation and more observation of the clinical status of their intended recipient, thereby possibly enhancing the donors ability to make an informed decision (23). Currently, when multiple beneficiaries are listed, the donor does not have the ability to indicate preference. Therefore, the voucher may be redeemed by a family member who may not have been the first preference of the kidney donor (26).

Lastly, the protection and status of an ADP donor who subsequently requires a kidney transplant after donation varies by organization. The National Kidney Registry (NKR) does not categorize ADP donors as living donors who start non-directed chains and thus do not provide them the same priority in the NKR pool assured to non-directed donors (26). Yet, the United Network for Organ Sharing (UNOS) still considers these donors as living donors, so they receive priority for a deceased donor organ (27). Of course, voucher donors can list themselves as a potential recipient, but their use of their own voucher negates the intended purpose of the donation. Further work establishing the logistics, education of donors, and transferability of vouchers should be completed to create a long-term and sustainable voucher program.

Liver Paired Exchange

Liver paired exchange (LPE) aims to apply the concept and benefits of KPE to the liver (Figure 1) (28)*. In addition to ABO incompatibility, liver-pairs may incur a mismatch because of insufficient or excessive hepatic mass for the recipient, inadequate residual mass

in the donor, or complex anatomical reconstruction of the artery or bile ducts in the recipient (28). The benefits of a LPE are similar to KPEs: expanding the donor pool and offering better outcomes compared to deceased donor livers (4, 6). Although not yet conducted in the U.S., centers in Asia have reported LPE (29).

Prior to widespread adoption, LPEs face logistical challenges including development of a matching program and multi-site coordination. Few centers have a robust living liver donation program- in 2017 only 10 transplant centers in the US performed more than 10 living donor liver transplants (30). The limited number of possible participating centers over a wide geographic area complicates optimizing organ transport and operating room times as the liver tolerates less cold ischemia time than a kidney. A potential ethical issue arises because the different types of donor surgery are associated with different operative risks. The mortality for living right lobe donors may be ten times higher than that of left lobe donors (0.5% vs. 0.1%) (31). Complications after a right lobe donation have been reported in as many as 28% of donors, whereas complication of donation from a left lobe or left lateral segment are under 10% (32, 33). Advocates of LPE hope to use KPE as a roadmap to guide the creation of an equally successful parallel program for livers.

Trans-organ Paired Exchange

Trans-organ paired exchange is a newer concept that allows donors who are ruled out for the donation of one organ to still benefit their intended recipient through donation of another organ. For example, an individual intending to donate to a kidney recipient may be ruled out for a kidney-specific reason (e.g. mild reduction in glomerular filtration rate, a single kidney, a family history of kidney disease, complex anatomy, or history of kidney stones) but may still be an appropriate liver donor. This pair may match with another donor/recipient pair that needs a liver (Figure 2,(34))* . Liver donors with aberrant anatomy or insufficient hepatic mass may be appropriate kidney donors. To date, only a single trans-organ paired exchange has been reported in the United States. A 19 year-old ruled out as a kidney donor requested to be a liver donor in exchange for a kidney for her mother with ESRD (35). The donor and her mother were matched to another pair where the potential liver donor had been ruled out as a liver donor due to size/volume mismatch but was a compatible match as a kidney donor for the initial recipient with ESRD (35).

Advocates of trans-organ paired exchange note that while the organs exchanged are different, those who benefit remain the same (34). Therefore, donors motivated by the need of their recipient can still benefit their recipient. Additionally, such swaps are permissible under the National Organ Transplant Act (34). The combined pool of donors would likely increase the number of matches and exchanges for those donor/recipient pairs who previously would have been declined.

The main criticism is the disproportionate risk between the donor operations. The mortality risk of kidney donor death is 1/3000 (36) whereas the mortality of liver donation has been reported to be as high as 1/500 among right lobe donors (37, 38). The normal recovery period for liver donors in general is twice that of kidney donors (34). While the immediate post-operative risks for liver donors appear greater, kidney donors have a slightly increased

risk of ESRD (37) and liver donors have little or no increased risk of liver failure during prolonged follow-up (34).

The implementation of a trans-organ exchange program requires thorough education and a detailed consent process. Potential donors would need to be aware of the differential risks for each donor operation (34). As more avenues to donate become available, transplant teams must be mindful to always protect the donor and ensure voluntariness of their act. Sometimes, during the evaluation process, a donor reveals he/she does not wish to donate and, therefore, are declined by the transplant team for vague medical reasons. Alternative donation options might create more pressure on these donors and make it harder to provide a vague medical excuse that applies to both liver and kidney donation. Programs would need to be sensitive to this and still protect potential donors from the public guilt or shame if they choose to decline the donation (34).

Conclusion and Summary

Although distinct models, the four concepts described all have the same purpose: to increase the opportunities for organ donation. Global paired exchange aims to overcome financial barriers and increase the pool of donors for hard to match recipients, while advanced donation programs aim to overcome temporal incompatibility between donors and recipients. Liver paired and trans-organ exchange aim to increase the number of available organs by addressing biologic contraindications. Despite their potential to address organ scarcity, each program has its own ethical and logistical considerations prior to widespread implementation.

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Abbreviations:

ADP	Advanced Donation Program
ESRD	end-stage renal disease
GPE	global paired exchange
KPE	kidney paired exchange
LPE	liver paired exchange
NKR	National Kidney Registry
UNOS	United Network for Organ Sharing

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Summary Points

- Organ exchange programs allow living donors with anatomic, immunologic, financial or time incompatibility to still donate
- Cases of global paired exchange, advanced donation programs, liver paired exchange, and trans-organ exchanges have all been reported
- All novel exchange programs have significant logistical considerations prior to widespread adoption

Figure 1.

Example of potential liver paired exchanges. The dashed arrow represents a rejected pairing, and the solid arrow represents an exchange. (a) A two-way exchange: one pair is ABOi, in the second pair the GRWR is inappropriate ($GRWR < 0.6\%$) (b) A 3-way exchange: D1-R2 pair; appropriate remnant donor volume and ABO compatible, D2-R3 pair; donor graft is appropriate size for larger recipient and ABO compatible, D3-R1 pair; ABO compatible, size appropriate. (c) A nondirected donor starts a chain. (d) Patient with FAP receives a deceased or living donor organ and starts a chain with a domino liver. Reproduced with permission. FAP. Familial amyloid polyneuropathy; GRWR graft-to-recipient weight ratio. Figure 1 reproduced with permission from: Mishra, A., Lo, A., Lee, G. S., Samstein, B., Yoo, P. S., Levine, M. H., ... & Abt, P. L. (2018). Liver paired exchange: Can the liver emulate the kidney?. *Liver Transplantation*, 24(5), 677-686.

Figure 2.

Example of a tran-organ paired exchanged. The dashed arrow represents a rejecting pairing, and the solid arrow represents an exchange. In this scenario, a swap occurs between a kidney donor of low GFE but normal liver anatomy. Reproduced with permission.

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