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Chapter 34.16.2

Liver paired exchange

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Introduction

Living donor liver transplantation (LDLT) has been a successful alternative to deceased donor liver transplantation, offering several advantages, including reduced

waiting times, better graft quality, less or no transmission of donor-derived infections and malignancies, and improved survival rates. However, finding a well-matched living donor with suitable anatomy and a compatible blood group remains a significant challenge for many patients. Paired exchange programs have served as an innovative solution to overcome incompatibility issues and thus have a potential impact on expanding the living donor pool. In this chapter, we explore the basis, challenges, success, outcomes, considerations, and future of liver paired exchange (LPE) in LDLT by following the steps of establishing a new paired exchange program in a liver transplantation institute.

Paired exchange programs: Definition and history

LPE is an innovative approach to expanding the pool of compatible living donors for patients in need of a liver transplant (LT). This concept involves two or more donor-recipient pairs that are incompatible within their respective pairs. Donors who are incompatible with their intended recipient offer their graft to the program while receiving a compatible liver for their recipient from another donor within the program. Thus, otherwise, incompatible donors can be utilized for successful transplantation.

The kidney paired exchange (KPE) programs have been successfully used in kidney transplantation to overcome organ shortages and enable the exchange of ABO-incompatible (ABOi) and HLA-incompatible living donors by swapping between two or more pairs (see Chapter 18.17.1).^{1,2} While KPE was first proposed earlier,³ it flourished in the United States and Europe in the mid-2000s because of collaborations between members of the transplantation community and experts in the field of market design.^{4–6} These collaborations materialized in the formation of centralized kidney exchange clearing houses in the United States and Europe that use tools from the fields of optimization and market design, and in 15 years, the number of patients who benefit from KPEs in the United States alone increased from a few dozen in the early 2000s to more than 1100 patients by 2021.⁷ Two constraints limiting the applicability of KPE were the allocation and matching of pairs and the number of cases included in the single-run KPE, both of which have been overcome using optimal matching algorithms,⁸ and the use of groups larger than two-way exchanges,⁹ which created the underlying success for the increase in the number of KPEs. These collaborations also contributed to the 2012 Nobel Prize for economics won by economist Alvin Roth in the economic sciences.¹⁰

Likewise, LPE can mitigate the problem of incompatible donor-recipient pairs; exchanging donors to enable compatible transplants has been a subject that has been emphasized for more than a decade. The efficiency of screening potential living donors is not high, and many of

the potential donors cannot qualify for an actual donation. The study by Dirican et al.¹¹ showed that out of 342 donor candidates, 330 completed their evaluation, 106 were accepted as suitable for donation, and 10 were excluded preoperatively. Therefore, only 29% of the 330 candidates were effective donors. Many of these potential candidates may be eligible for the LPE program. Organizing an LPE is more complex compared to a KPE since LT involves a more extensive surgical procedure with more technical challenges and since partial hepatectomy can carry a higher risk compared to the donation of one of the kidneys. Indications for LPE are also more complex compared to KPE and consist of ABOi, suboptimal hepatic mass leading to an insufficient graft-recipient weight ratio, and anatomical variations that may reduce the success of LT.

By 2010, high-volume centers in Asia started to establish LPE programs,^{12,13} and they later reported that LPE made up 1.2% of LDLT.¹⁴ A study using aggregate data from the South Korean population indicated that an organized LPE system can increase the number of LDLTs by as much as 30%–40%, even if exchanges are limited to two-way donor swaps between incompatible patient-donor pairs.¹⁵ Based on earlier research by the authors and field implementation of KPE systems, they have also indicated that the increase in LDLTs will likely be considerably higher if LPEs involving more than two pairs can be organized.^{9,16} The United Network for Organ Sharing has launched a national paired liver donation pilot program involving 15 transplant centers to increase LDLTs and decrease waitlist mortality in the United States.¹⁷

However, there have been very few publications on this subject, each reporting less than a dozen two-way donor exchanges between incompatible pairs.¹⁸ While the possibility of donor exchanges involving three or more pairs has also been discussed in the literature,¹⁹ the first three-way LPE has recently been reported from Pakistan.²⁰ In high-volume centers in South Korea and India, existing LPE programs generate 1%–1.5% of the LDLT.^{12,14,21} Lately, the first results of a collaboration between members of the Liver Transplant Institute at Inonu University and two experts in the field of market design, involving a one four-way donor exchange—a first in the world—have been reported.²²

Paired exchange program principles and protocols

Equality and simultaneous operations are two crucial principles in the LPE program. Equality means that donor graft quality, graft volume and anatomy, remnant volume, and recipient The Model for End-Stage Liver Disease (MELD) score are within acceptable limits after swapping. The principle of equality is intended to ensure no additional

disadvantages from donor exchange. The principle of simultaneity means the start of transplantation surgeries at the same time to prevent cancellation of a donation due to later conflict or emotional change, which could occur if the LDLT procedures were performed sequentially.

The LPE program is completely feasible at centers with significant LDLT experience.²³ Many difficulties, such as equality and simultaneity, can be overcome only if swaps can be made in the same center. Logistic issues and intra-operative planning can be done more easily.¹³ However, in more recent case reports published from the United States, LDLTs in a pair were performed on consecutive days^{24,25} or at two different centers.²⁶ Altruistic donors can trigger a chain of events leading to a successful exchange,^{19,27} but such donations are almost nonexistent in many countries. Cross-center exchanges are logistically more difficult and have different surgical techniques that make it more challenging to achieve the principle of equality of transplant outcomes. A simultaneous, single-center two- or more-than-two-way liver swap at a high-volume institution is the optimal way to mitigate risk while establishing the LPE program.

In a center planning to initiate an LPE program, having a test run by performing multiple LDLTs simultaneously might act as an introductory step in assessing the center's ability to handle such challenging situations and serve as a rehearsal for the LPE program.²³ The success of the LPE program depends on complex parameters, including an experienced team, excellent equipment, and sufficient physical facilities and resources. To test the potential logistics and coordination issues and to evaluate both the personnel and organizational capacity of the center, a simultaneous independent LDLT can be considered before commencing an LPE program.

Another parameter of success in the LPE program is the utilization of optimization tools. In matching donors and recipients and finding compatible pairs, computer algorithms play a critical role. Within the first month of launching a centralized LPE system that uses tools from optimization and market design, the system generated compatible LTs for eight patients in one four-way donor exchange—a first in the world—along with two two-way donor exchanges. The four-way LPE and one of the two-way LPE were generated in the same match run in the first week of July 2022 (22) (Fig. 34.16.2.1).

Outcomes and complications

Although the literature is limited and mostly two-way exchanges are reported, the results of LPE are favorable, and it can be undertaken without any increased rate of complications compared to LDLT. Jung et al. have reported the results of 26 paired exchange LDLT cases 22 were elective and 4 were emergency cases.¹⁴ The 1-year and 5-year

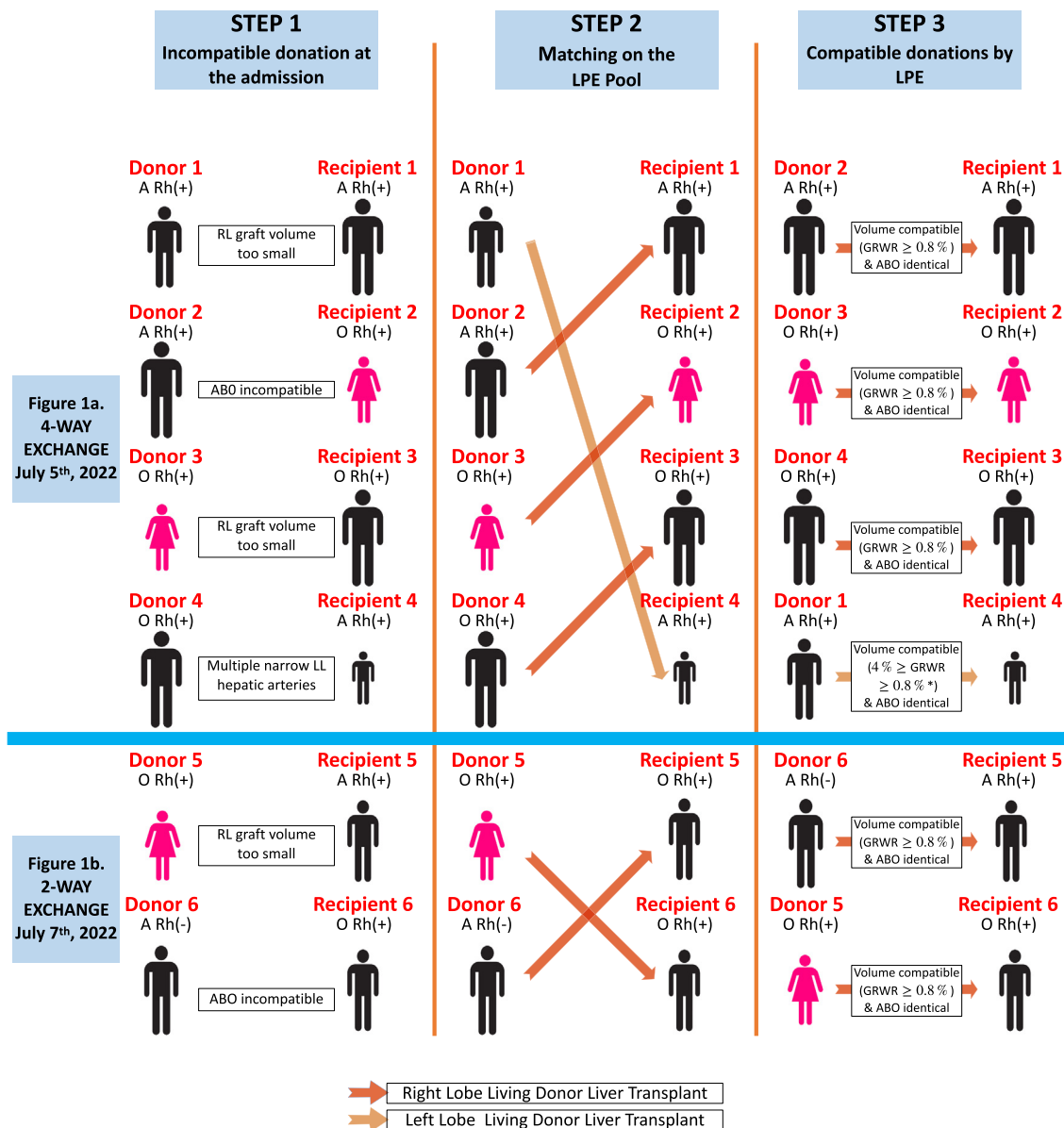


FIGURE 34.16.2.1 The four-way and two-way LPEs were conducted in the first week of July 2022. LL, liver left lobe; LPE, liver paired exchange; RL, liver right lobe. (Permission to use this figure has been obtained from the authors of the article.)

patient and graft survival rates were found to be 96.2% and 90.1%, respectively. A more recent study by Agrawal et al. reported the 9-year experience of 34 patients.²¹ The median follow-up period was 27 months (1–108 mo), and the 30-day and 1-year survivals were 88.2% (n = 30) and 85.3% (n = 29), respectively.

Following on from Asia, recent reports on LPE from centers in North America have also started to become more frequent. Klair et al. reported two two-way exchanges performed on two consecutive days, and recipient outcomes were uneventful for 9 months postoperatively.²⁴ Patel et al. reported a two-way exchange involving one 51-year-old and one 53-year-old recipient who was discharged

uneventfully on postoperative days 9 and 13.²⁷ Braun et al. performed a two-way exchange over the course of two consecutive days rather than simultaneously.²⁵ This two-way exchange involved a 71 year and a 55-year-old female. The 55-year-old recipient was discharged on postoperative day 8, while the 71-year-old female developed a cut surface leak, which was managed by ERCP interventions, and was discharged on postoperative day 18. A study from Pittsburgh reported 10 two-way LPEs involving twenty recipients.²⁸ Seventeen of the twenty recipients were alive with good allograft function. One recipient was lost in the early postoperative period, while COVID-19 (at 8 months) and peritoneal carcinomatosis and gram-negative

sepsis (at 9 months) caused two late deaths in patients with functioning allografts.

Kwon et al. reported LPE involving pediatric and adult recipients.²⁹ A 10-year-old female with biliary atresia and a 69-year-old male with alcoholic liver cirrhosis underwent LPE transplants simultaneously. The postoperative courses were uneventful, and the female child was discharged on postoperative day 14, while the male adult was discharged on postoperative day 6.

The first three-way exchange was reported by Salman et al. from Pakistan.²⁰ The first four-way exchange was reported by Yilmaz et al. who performed eight operations for the four-way exchange simultaneously. The four recipients of the four-way exchange were a 50-year-old man, a 66-year-old female, a 62-year-old man, and a 12-year-old boy.²² All four recipients had an uneventful postoperative period and are alive to date with the normal function of their grafts.

Ethical and legal considerations

LPE provides an ethically acceptable innovative solution to donors who want to provide a graft for their recipient but are, for medical or surgical reasons incompatible. However, compared to LDLT, new ethical considerations arise with LPE. The autonomy and well-being of donors should be guaranteed to eliminate any possibility of coercion in the LPE setting. Concerns about coercion may be heightened by indirect exchanges such as LPE, as a reluctant or hesitant donor may no longer be able to put forward the causes of incompatibility as a rational and accepted excuse for withdrawing as a living donor.³⁰ For this reason, donors in LPE programs need to undergo a very thorough psychological evaluation to assess their willingness and ambivalence. While some donors may have questions and initial reservations about donating to someone they do not know, once they are well-informed about the LPE process, the majority of donors will be motivated by the final result of helping their recipient.

The main purpose and underlying ethical framework of the LPE program should be to provide as many patients as possible with the opportunity of LDLT through the match run while sustaining the standards of a direct transplant with donor safety and favorable recipient benefits. This has been explained with principles of utilitarianism and the Pareto principle by the Inonu Liver Transplant Institute.²² In essence, this means that with LPE, neither a donor can undergo a riskier operation nor a patient can receive a less favorable transplant than the standard option with similar graft quality and volume.

Drawing on our knowledge and understanding, we determined that balancing relative donor risk and anticipated recipient outcomes would be critically important to optimize equity between pairs in the LPE. If a parent is

unable to donate segments two and three to their infant because of ABOi, too large graft size, or very thin and more than two hepatic arteries, they may pair with a recipient who is an adult in need of a right lobe. Although there is an increase in the risk of harm to the donor parent, this may be an acceptable risk for the parent who is trying to save a child. This may be also ethically acceptable.

The priority for inclusion in an LPE program is based on the MELD score and other disease complications. We discuss the details for each patient and donor in our weekly multidisciplinary council, which includes our transplant surgeons, transplant hepatologists, radiologists, anesthesiologists, intensivists, and psychiatrists, and decide as a council whether to include them in the LPE program. We believe it is important from both an ethical and legal perspective to have an official council decision. Although the success rate is high, especially in large-scale LPE programs, all possible adverse outcomes of transplantation, including loss of the graft and/or the recipient, should be explained thoroughly. As the number of pairs in LPE increases, the risk of aborting one pair also increases. Even though in our series this risk decreased from 3.8% to 1% with experience,^{22,31} the possibility of aborting the donor hepatectomy should always be considered. Although it has never occurred in our center and has not been reported in any to-date LPE series, the possibility of recipient death during surgery with a completed donor hepatectomy leading to an 'orphan graft' should also be discussed during the informed consent negotiations.³² Pairs should be well informed preoperatively for all possibilities, and the necessary consents should be obtained beforehand.

Running simultaneous LDLTs involves consent from multiple donors and recipients, and fair allocation of graft may necessitate specific legal frameworks depending on the certain country. Legislation should be well outlined to protect the rights of all the parties involved in LPE, especially if an exchange between different centers is planned.

Future directions and advancements

Despite challenges, LPE has the potential to significantly increase the donor pools and number of successful LTs, reduce waiting times, and improve patient outcomes. Current reports from around the world have shown favorable results. With better immunological profiling, HLA matching, the use of advanced and refined algorithms incorporating genetic and immunological data, and the gained experience in dealing with logistical issues, higher postoperative success rates can be achieved.

In the future, the establishment of larger centralized networks of collaboration between transplant centers within a country or international networks of collaboration may also help to exchange donors and thus create greater compatibility. The creation of multicenter programs will

also help to support larger than two-way exchanges, which are valuable for their capacity to match more patients for LDLT.

Further research is needed to demonstrate the improved outcomes with better matching of donors and recipients, the impact of shorter waiting times on recipients, and the effect of utilizing donors who would otherwise be considered incompatible. Also, the development of comprehensive clinical guidelines and logistical frameworks is required to implement and optimize LPE programs and possibly establish LPE programs among centers with larger pools.

Conclusions

LPE programs are used to overcome incompatibilities between living donor-recipient pairs and should be considered as a means of expanding the donor pool and reducing deaths on the LT waiting list. In this chapter, we have laid out the rationale for LPE, the principles of setting up an LPE program with clinical and logistical infrastructure, ethical considerations, clinical outcomes, and possible future developments.

As LPE programs expand and become more widely adopted, not only a small number of high-volume centers but also many experienced LDLT institutions may be able to participate and collaborate in LPE programs, and these programs will continue to evolve. There will be a growing need for ongoing research into the long-term benefits and outcomes of LPE programs, along with guidelines for standardizing best practices among transplant centers and how to run an optimal program. Barriers to LPE can be overcome with greater organizational experience and refined algorithms to ensure better matching. By addressing these challenges and harnessing the potential of this innovative approach, LPE programs have the potential to change the landscape of LDLT and ultimately improve the quality of life for countless patients in need of a life-saving LT.

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