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Expanding Opportunities for Kidney Transplantation

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1. Introduction

Despite the increased use of living donors and marginal donor kidneys, there still exists a significant discrepancy between the organ supply and demand in renal transplantation [1]. This has led to excessive waiting times affecting patient survival. More than half of all patients with end-stage renal disease (ESRD) over the age of 60 die before receiving a kidney transplant [2]. These patients face a mortality rate of 6% per year while awaiting an acceptable donor. Thus, transplant surgeons and physicians have turned to other potential sources of allografts to meet the ever growing demand. Potential resources include maximizing the utilization of pediatric donors, increasing use of marginal donors, and transplanting hepatitis C (HCV) positive donor kidneys into HCV positive recipients. Finally, the advent of kidney paired donation has significantly improved and maximized the use of living donor renal transplants.

The following chapter will discuss these sources of allografts and their associated outcomes. The goal of these donors is to maximize the potential opportunities for any patient on the deceased donor waiting list. Ultimately, these modalities will lead to improved patient survival and slightly offset the burden of the deceased donor waitlist.

2. Pediatric donor

2.1. Introduction

The first attempt at using pediatric donors was in 1972 when en bloc kidneys were successfully transplanted in adult recipients [3]. By the late 1990's, single pediatric donors were being successfully transplanted into adult recipients [4, 5]. This use of pediatric donors in adults has not disadvantaged the pediatric recipient population. In 2005, the United



Network for Organ Sharing (UNOS) mandated that pediatric recipients will be prioritized young adult deceased donor kidneys known as the Share-35 policy [6].

Pediatric kidneys can be transplanted as individual organs or en-bloc as dual kidneys. Some strongly advocated the use of single kidneys from pediatric donors, as opposed to en-bloc transplantation, to avoid the potential for technical complications [7]. Additionally, opponents of single pediatric donor kidney argue that the hyperfiltration syndrome associated with single kidneys leads to early graft failure in adult recipients [8, 9]. Pediatric donor size has been implicated as one of the important risks for graft failure. Initial studies demonstrated that technical complications, most notably graft thrombosis, was significantly higher in small pediatric donors (<10 kg) [9]. Moreover, as a result, pediatric donors represent the highest discard group with rates approaching 40% in donors less than 10 kg.

In the following sections, we will discuss the advantages and disadvantages of the various types of pediatric donors. Short and long-term outcomes will be discussed with attention to perioperative outcomes associated with each.

2.2. Small pediatric donor

Several groups, including our own, have demonstrated the safety and feasibility of using young and small pediatric donors. Initial concerns regarding the use of these donors were related to both technical complications and allograft function. Given the high discard rate in this group, a discussion of their proper utilization and outcomes is important.

Small pediatric donors, defined as weighing <10 kg and ages 5 years or younger, have been successfully transplanted into adult recipients. Balachandran et al. described a successful series of 27 small pediatric donors transplanted into adult recipients weighing >60 kg [10]. All kidneys were transplanted as single kidneys both with and without aortic cuffs (Carrel patch, Figure 1), with an end-to-side anastomosis to the recipient external iliac vessels. The majority of patients underwent rabbit antithymocyte globulin (r-ATG) induction therapy. In this series, no patient experienced a vascular complication and only 2 kidneys had primary non-function (both from the same donor). Patient and graft survival in this cohort at 2 years were 100% and 92.5%, respectively, which was not significantly different to their comparison group of standard adult kidney recipients of adult deceased donor kidneys. Borboroglu et al. also described a successful series of 15 single pediatric donors less than 2 years of age transplanted into adult recipients [11]. The 2 years graft survival rate was 93% with a vascular thrombosis rate of 6.7%.

In a review of over 12,000 pediatric donors, Bresnahan et al. demonstrate inferior graft survival in recipients of these kidneys compared to standard adult donors [8]. Pediatric donors 5 years of age or younger had the worst 1 year graft survival (76.3% in en-bloc kidney recipients and 72.2% in single kidney recipient). In this series, pediatric donors had a graft thrombosis rate of 10% in donors 5 years of age or less, 6% in donors aged 6 to 11 years, and 5% in donors aged 12-17 years. The rate of primary non-function was 5%. Others have also described the increased incidence of vascular complications in these young and small pediatric donors [12].

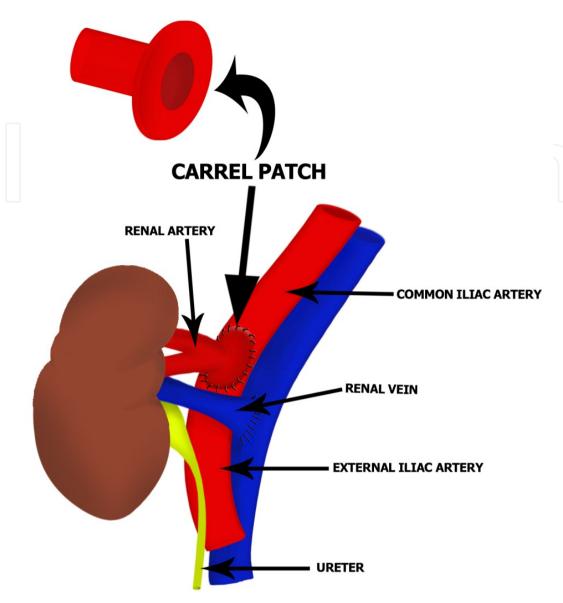


Figure 1. A pediatric kidney is implanted into the external iliac artery with the use of a Carrel patch.

The inferior outcome of small pediatric donors was partly explained in the past by hyperfiltration injury. Hyperfiltration injury describes the compensatory mechanisms in the pediatric kidney that increase the glomerular capillary pressure in response to the inadequate filtration ability of the small graft. This concept was used to explain why transplanting en-bloc pediatric donors lead to improved outcomes as more "renal mass" was transplanted [8, 9]. However, opponents of this approach cite that en-bloc transplantation is a technically more challenging procedure with a relatively high surgical complication rate as well as a graft thrombosis rate of >10% [10, 13].

2.3. En-bloc vs. single kidney transplantation

Initial transplants from pediatric donors consisted of en-bloc transplantation in the recipient (Figure 2). As previously stated, this was described in 1972, and was the primary method

used for several years [3]. Solitary pediatric renal allografts were then later performed in the 1990's. The initial concerns regarding the use of single pediatric donors were two-fold: technical complications and poor graft survival.

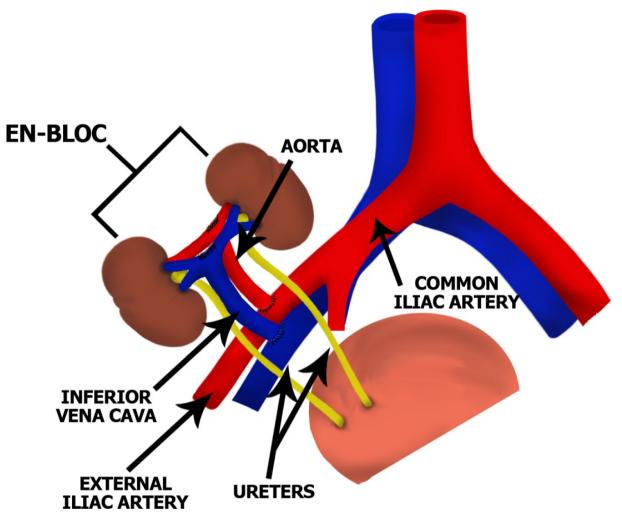


Figure 2. En-bloc pediatric kidney transplant. The following figure depicts en-bloc transplantation of pediatric kidneys into an adult recipient. The anastomosis is performed to the external iliac artery. The donor aorta and inferior vena cava are anastomosed to the recipient vessels as shown.

Technical concerns regarding the use of single pediatric donors were the major concerns initially. Bresnahan and colleagues found that recipients of en-bloc pediatric donor allografts were less likely to develop graft thrombosis compared to single pediatric donor allografts (OR 0.688, P<0.01) [8]. A series of 20 en-bloc pediatric donor allografts demonstrated no vascular complications [14]. Borboroglu et al. compared 15 single pediatric donors to 33 en-bloc pediatric donors [11]. Four recipients of en-bloc pediatric donors experienced arterial thrombosis, whereas only one recipient of a single pediatric donors developed arterial thrombosis. Moreover, three recipients of en-bloc pediatric donors experienced ureteral complications, whereas none occurred in the single pediatric donor group. In a series of 27 single pediatric donor allografts, no recipient developed vascular thrombosis postoperatively [10].

Inferior graft survival has also been implicated as a reason to avoid using single pediatric donors. The initial studies by Bresnahan et al. demonstrated poorer graft survival in recipients of single versus en-bloc pediatric donor allografts at 1 year (72.2% versus 76.3%, respectively [8]. Additionally, a study utilizing the Scientific Registry of Transplant Recipients (SRTR) data demonstrated that recipients of single pediatric donors had a 78% increased risk of graft loss compared to en-bloc donors [9]. Graft survival of en-bloc pediatric donor allografts was similar to standard deceased donors. However, a more recent analysis of the SRTR database demonstrated that single pediatric donors 35 kg had similar graft survival to SCD [15]. Moreover, graft survival of single pediatric donors 10-35 kg was similar to SCDs. A later study by Balachandran et al. demonstrated better outcomes than their initial studies. The 2 years graft survival rate in single pediatric donor recipients had improved to 92.5% [10]. Similarly, Borboroglu et al. demonstrated similar graft survival between single versus en-bloc pediatric donor allografts [11]. Effectively, the use of single pediatric donors compared to en-bloc pediatric donors has resulted in more cumulative graft years in recipients.

3. Marginal donor kidneys

3.1. Overview

The lack of available kidneys for transplantation in ESRD has lead to an increase use of suboptimal donors. As a result, more institutions are using expanded criteria donors (ECD) and deceased after cardiac death donors (DCD), sometimes referred to as marginal donors, to lessen the shortage [16-19]. The increased utilization of these organs has expanded the donor pool by 30% [19]. Nevertheless, there has been a concomitant increase in the rate of delayed graft function (DGF) and even primary non-function in DCD grafts [16-18]. Utilization of these kidneys may contribute to the donor pool, although it is important to maximize the outcomes of these allografts.

3.2. Hypothermic machine perfusion

Towards the end of the twentieth century, static cold storage was introduced to preserve kidneys procured from deceased donors, which lead to a decreased incidence of DGF and improvements in survival of DCD allografts [20]. Hypothermic machine perfusion (HMP) is an alternative to static cold storage (Figure 3). Several reports have demonstrated improvements in immediate graft function with the use of HMP compared to static cold storage [21-24]. Additionally, HMP permits longer preservation times without significant consequences to the allograft. Current notions suggest that HMP prevents and/or ameliorates injury to the kidney suffered as a result of preagonal hemodynamic and metabolic perturbations to the donor [25, 26].

Various studies have demonstrated that vascular flow and resistance data of hypothermic machine perfused organs had a decrease in ischemic injury to the allograft prior to implantation compared to static cold storage [27-29]. Additionally, biochemical markers of ischemic injury can be measured and used to assess and evaluate pretransplant ischemic organ damage. In a study by Moers et al, 306 deceased donor kidneys, including DCD

donors, undergoing HMP were evaluated for relative concentrations of biomarkers associated with renal and tubular injury [30]. In this study, elevated levels of total glutathione-S-transferase (GST), N-acetyl- β -D-glucosaminidase (NAG), and heart-type fatty acid bind protein (H-FABP) were independent predictors of DGF. Thus, perhaps the phenomenon observed is an increase in ischemic injury to the kidney. The benefits of HMP may be somewhat negated if the allograft is removed prematurely and placed in static cold storage.

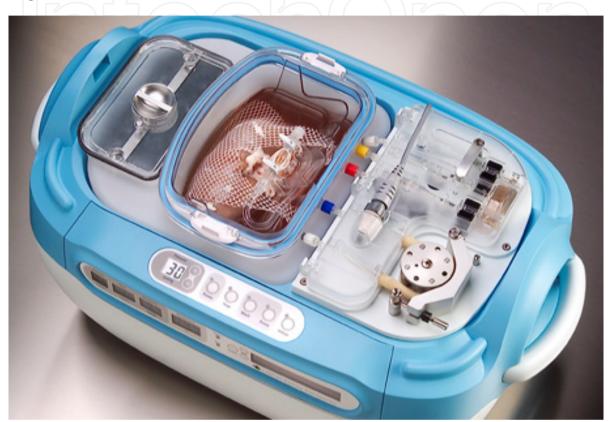


Figure 3. LifePort® Kidney Transporter. The figure depicts the LifePort ® Kidney Transporter that gently pumps the kidney with cold storage solution which can increase the cold ischemia duration compared to static cold storage and potentially improve allograft outcomes in marginal donor kidneys.

3.3. Allograft outcomes

ECD allografts have decreased graft survival rates in comparison to SCD. In general, these kidneys have a life expectancy of 6 to 8 years, whereas standard or ideal kidneys last about 10 to 12 years [31]. Prolonging allograft survival by preventing or minimizing mitigating factors for the development of DGF is imperative since DGF is a known risk factor for decreased allograft survival. Marginal donors are known to have a higher incidence of DGF, which could affect survival.

Several studies have examined the incidence and effects of DGF in marginal donor kidneys. A study by Serur et al evaluated deceased donors over more than a 40 years period and demonstrated that the most significant risk factors for short-term graft survival were DGF and acute rejection, not just the mere utilization of ECD allografts [32]. A large prospective,

international, randomized controlled trial examined the efficacy of rATG versus basiliximab in patients at high risk of DGF [33]. Patients were maintained on a cyclosporine-based triple drug immunosuppression regimen and eligibility criteria included ECD or DCD allografts, SCD allografts with greater than 24 hours of cold ischemia time (CIT), repeat transplants, panel-reactive antibody value exceeding 20% before transplantation, donors with acute tubular necrosis (ATN), recipient black race, or one or more HLA mismatches. The incidence of DGF was not significantly different between patients receiving rATG and basiliximab. However, the incidence of biopsy-proven acute rejection was significantly lower in patients receiving rATG. Additionally, severe rejection episodes requiring antibody therapy were less frequent in the rATG group.

Marginal donors were initially shown to have worse outcomes than SCD. Several earlier studies demonstrated worse graft survival in kidneys from ECDs [34, 35]. More recent data, however, suggests that ECD kidneys have similar short and intermediate survival as SCD kidneys; instead, allograft function is slightly worse in the ECD group [31]. This finding is not the general consensus as the more recent trend is to match the donor age to the recipient age to optimize outcomes. For example, Chavalitdhamrong et al. demonstrated that recipients over the age of 60 years receiving ECDs from donors over the age of 70 had better survival than recipients aged 41 to 60 years [36].

Numerous studies have also demonstrated an advantage and decreased risk of DGF in marginal donors preserved by HMP compared to static cold storage [37, 38]. However, other factors, such as race, have also been implicated as risk factors for DGF. Several studies have demonstrated that African-American recipients were more likely to develop DGF [39, 40]. Hariharan and colleagues observed lower rates of graft failure in Hispanic recipients and higher graft failure rates in kidneys from Hispanic donors (compared to white) [41].

4. Hepatitis C virus & transplantation

4.1. Introduction

Hepatitis C Virus (HCV) infection is a common condition among ESRD patients and kidney transplant recipients with infection rates between 11% and 49% [42-46]. The best screening test for HCV is nucleic acid testing, or NAT. Because organ transplantation can transmit the hepatitis C virus, the consensus remains that HCV positive donors should only be transplanted into HCV positive recipients [47, 48]. Initial studies suggested that patients with HCV infection have an increased risk of death following kidney transplantation [42, 44, 45]. More recent studies have demonstrated that HCV positive patients who receive a kidney transplant have superior survival than their counterparts who remain on hemodialysis [49, 50]. Thus, kidney transplantation remains the treatment of choice for HCV positive patients with ESRD and preserved liver function without any evidence of cirrhosis.

4.2. Benefits of transplantation

The use of HCV positive donors may have potential benefits to the respective HCV positive recipients. First, HCV positive recipients transplanted with a HCV positive donor have

waiting times that are almost 1 year less than their counterparts who wait for a HCV negative donor [51]. Nevertheless, HCV positive donor kidneys were about 2.6 times more likely to be discarded than HCV negative donors. HCV positive donors could receive high quality organs, especially when the donor is young. As previously discussed, there is a clear survival benefit to transplanting HCV positive recipients with HCV positive donors compared to remaining on the deceased donor waiting list. The use of hypothermic machine perfusion has been shown to decrease the viral load of the allograft prior to implantation [52]. The reported reduction in viral load in the kidney is anywhere from 75% up to 99% if the allograft was perfused for 20 hours and additional flushes were used. Finally, there may be a cost-benefit analysis to using HCV positive donors [53].

4.3. Special transplant considerations

The use of HCV positive donors is not without potential risks. First and foremost, superinfection with a different genotype of HCV could occur with transplantation [54]. This coupled with immunosuppression can lead to a more aggressive HCV infection and increased risk of developing active liver disease [55, 56]. Secondly, recent data suggests that the HCV positive recipient transplanted with an HCV positive donor generally experiences an increase in infectious complications [57]. Moreover, Rao and Ma demonstrated that the HCV positive recipient experienced not only more infectious complications, but also more serious life-threatening infections [56]. The use of induction therapy does not correlate with the level of viremia and has been shown to be safe and efficacious without increasing the risk of infections complications [58, 59]. Finally, HCV positive recipients with ESRD have a higher cardiovascular mortality [60].

4.4. Outcomes following transplantation

The short-term outcomes following transplantation of HCV positive donors into HCV positive recipients have generally been acceptable. Short-term patient survival rates at 1 and 3 years have been reported to be as high as 93% and 83%, respectively, while graft survival rates were 91% and 77%, respectively [51]. The longest study of this cohort of patients comes from Spain with a 10 years total follow-up [61]. Patients had 5- and 10-year survival rates of about 85% and 73%, respectively. The death-censored 5- and 10-year graft survival rates were 69% and 47%, respectively. Graft survival, however, was significantly lower in HCV positive recipients receiving HCV positive donors. The use of a HCV positive donor was not a risk factor for mortality, graft loss or advanced liver disease in this study. Mahmoud and colleagues demonstrated an increased incidence of transplant glomerulopathy among HCV positive renal transplant recipients [62].

5. Kidney paired donation

5.1. Introduction

Up to one-third of all kidney transplant candidates presenting for living donor renal transplantation with a potential living donor will have a blood type or cytotoxic-dependent

cytotoxicity (CDC) crossmatch incompatibility [63]. In the past, these patients would be deemed unsuitable pairs and transplantation would not proceed. Some transplant centers may attempt to use desensitization protocols to overcome the immunologic incompatibility; however, these protocols carry the risk of additional immunosuppression. This added risk does not guarantee successful transplantation and, if successfully transplanted, places the recipient at an increased risk of an acute rejection episode [64, 65].

Kidney paired donation (KPD) was introduced as an effective tool to overcome immunologic barriers, such as blood type or CDC crossmatch incompatibility among donor/recipient pairs [66-68]. This initially began as a concept of swapping living donors in individual transplant centers with two or three paired donor exchanges to permit transplantation [69]. This has expanded to various nationwide registries of incompatible donor/recipient pairs of major transplant centers, including our own in the National Kidney Registry [66].

5.2. Living donor chains

An important element of maximizing the benefits of KPD is the addition of an altruistic, or non-directed, donor. These donors wish to donate their kidney, however they do not have an intended recipient. Utilizing these altruistic donors in KPD registries permits the creation of transplant chains with an extra donor to spare. This extra donor is called a bridge donor and is able to donate at a later time (Figure 4). This potentially can create non-simultaneous extended altruistic donor (NEAD), or in other cases the bridge donor can even donate to the deceased donor waitlist [70].

Many different registries exist in the United States and these registries have facilitated the majority of KPD transplants performed to date. One of the important practical lessons learned over time is that it may be more beneficial to have bridge donors donate to a candidate on the deceased donor waiting list [66]. Sometimes it may take longer than expected to find a suitable recipient entered into a registry to match with a bridge donor. The bridge donor's circumstances could change while awaiting donation, such as work or professional changes, economic inability to donate or the donor might renege on their decision to donate. Ultimately this would result in loss of the bridge donor and any future transplant generated by the bridge donor. The exception to this rule is blood type 'O' bridge donors who may be kept within the registry due to their ability to generate future transplant chains [71].

In order for chains to be successful, many logistical aspects need to be addressed. For example, only major transplant centers with operating room availability 24 hours a day should participate, as acute changes can occur regarding scheduling and require flexibility on the donor and recipient hospitals parts. Transplant coordinators with sound understanding of the KPD process are necessary to manage the complex logistical problems that may arise, and to manage entry of donors and recipients into the registry, obtain match offers, and participate in conference calls to coordinate and facilitate continuation of chains[66]. Transplant coordinators need to have GPS access to track organs shipped from other transplant centers.

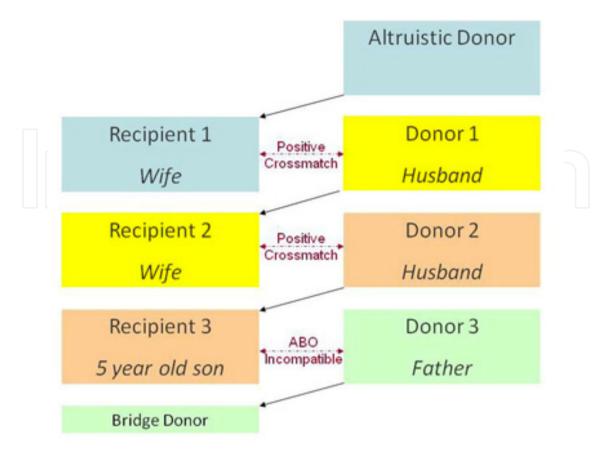


Figure 4. Bridge Donor. The following figure depicts a chain of incompatible donor/recipients who are a part of a chain, beginning with an altruistic donor and ending with a bridge donor who may facilitate another chain.

5.3. Benefits of kidney paired donation

Kidney paired donation offers multiple benefits. First, transplant candidates are removed from the UNOS waiting list. These patients avoid the morbidity and mortality of initiating or remaining on hemodialysis as well as enjoying a survival benefit (U.S. Renal Data System, USRDS 2010 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2010). These patients benefit from receiving a living donor renal transplant, which has better graft survival than a deceased donor allograft. Moreover, these patients, who may undergo various desensitization protocols, avoid the added immunosuppression and risks involved in blood group incompatible transplants. These highly sensitized patients benefit from receiving a living unrelated transplant via a bridge donor. Furthermore, those candidates without a living donor would benefit from having additional patients removed from the deceased donor waiting list.

In general, allografts from living donors have better outcomes than allografts from deceased donors. First, graft half-life is significantly longer in living donor allografts than deceased donors [72]. Second, the incidence of DGF is significantly lower in living donors, thus

recipients are receiving a better quality allograft. Even if allografts are shipped across the country with cold ischemia times that may exceed 12 hours, outcomes remain superior to deceased donors [68]. The benefits of higher quality organs could translate into improvements in quality of life for the recipient [73]. KPD maximizes opportunities for transplantation for all transplant candidates.

6. Summary

The supply of available allografts for kidney transplantation does not meet the demands of the growing number of patients listed for transplantation. Thus, other sources of available allograft must be sought to alleviate the burden of the deceased donor waiting list. The use of pediatric donors, en-bloc, or even better as single organs that can be split for two recipients represents a potential source of allografts. Marginal donors are also being increasingly used with respectable graft survival rates. The use of HCV positive donors for HCV positive recipients leads to the transplantation of HCV positive patients significantly faster than waiting for an HCV negative donor, which lessens the burden of those awaiting HCV negative organs. Finally, successful implementation of KPD transplant registries has lead to the transplantation of high quality organs with considerable graft life into patients with blood type incompatible or crossmatch positive donors. Finding a solution to the shortage of suitable organs remains a challenge that must continue to be addressed in the field of transplantation.

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