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REVIEW

Donor considerations in pediatric kidney transplantation

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Abstract

This article reviews kidney transplant donor options for children with end-stage kidney disease (ESKD). Global access to kidney transplantation is variable. Well-established national policies, organizations for organ procurement and allocation, and donor management policies may account for higher deceased donor (DD transplants) in some countries. Living donor kidney transplantation (LD) predominates in countries where organ donation has limited national priority. In addition, social, cultural, religious and medical factors play a major role in both LD and DD kidney transplant donation. Most children with ESKD receive adult-sized kidneys. The transplanted kidney has a finite survival and the expectation is that children who require renal replacement therapy from early childhood will probably have 2 or 3 kidney transplants in their lifetime. LD transplant provides better long-term graft survival and is a better option for children. When a living related donor is incompatible with the intended recipient, paired kidney exchange with a compatible unrelated donor may be considered. When the choice is a DD kidney, the decision-making process in accepting a donor offer requires careful consideration of donor history, kidney donor profile index, HLA matching, cold ischemia time, and recipient's time on the waiting list. Accepting or declining a DD offer in a timely manner can be challenging when there are undesirable facts in the donor's history which need to be balanced against prolonging dialysis in a child. An ongoing global challenge is the significant gap between organ supply and demand, which has increased the need to improve organ preservation techniques and awareness for organ donation.

Keywords End-stage kidney disease · Graft survival · Kidney transplant

Introduction

The optimal treatment of end-stage kidney disease (ESKD) is kidney transplantation which improves quality of life and patient survival [1, 2]. However, there is an ever-widening gap between supply and demand for kidney transplant donors, which has driven the need for expanding the donor pool [3]. Understanding the factors that need to be considered in assessing the various options for kidney transplant donors in children with ESKD is important for the pediatric nephrologist.

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The first successful kidney transplantation was performed in the 1950s with the donor and recipient pair being identical twins [4]. This evolved with transplantation between dizygotic twins and eventually ABO compatible but genetically non-identical individuals in the late 1950s when immunosuppressive drugs were used to prevent rejection [3, 4]. However, mortality and graft loss in the first year were high. Improvements in pre- and post-transplant care have contributed to improved short-term graft survival since the 1990s [2]. In children under the age of 5 years, 1-year graft survival was 60–70% in the 1980s and has progressively improved since then [5–7]. The disturbing fact is that there has been a worldwide progressive increase in ESKD in the last 20 years.

Access to kidney transplantation is variable globally and even regionally. It is estimated that < 10% of children with kidney failure, actually receive renal replacement therapy [8]. Allocation of health care resources, existence of national networks for waitlist management, and allocation of organs, religious, and cultural biases play a major role in organ donation [9, 10]. According to a survey of the international pediatric nephrology association, pediatric renal replacement therapy registries exist in at least 80% of 94 countries

surveyed [10]. Nevertheless, inequities in access to kidney transplantation exist, particularly in children in many parts of the world. Chronic renal replacement therapy is unavailable in children in 5% of countries [10].

In the USA, there are approximately 90,000 patients on the waiting list for a kidney transplant and approximately 20,000 patients receive a kidney transplant each year [11]. On average, 900–1,000 children < 18 years are added to the kidney transplant waiting list each year, and there are approximately 1,500 prevalent waitlisted children in the USA [11]. However, only a fraction of these children, approximately 750, < 18 years receive kidney transplants each year, with 450–500 being from deceased donors [11]. Congenital anomalies of the kidney and urinary tract is the cause of ESKD in half of all children waiting for a transplant. Pre-emptive kidney transplants occur in only 15–25% of children [7].

Donor source

There are several options for donors in children. Living donors (LD) offer the best long-term survival compared to deceased donors (DD). In the USA, the 1-year conditional half-life of DD transplants (2009–2010) is 12.3 years and that of LD transplants is 15.3 years [12]. The existence of well-established national organizations and aggressive donor management protocols may account for higher DD transplants in some countries [13, 14]. Deceased donor transplantation rate is the highest in Spain, followed by the USA [15]. Developing countries rely more on LD programs [14, 15]. Africa, India, Pakistan, and the Middle East have the lowest organ donation rates [8, 9]. The number of LD transplants have declined in the USA in recent years in children for a variety of reasons including changes in allocation policies [7, 11].

HLA matching, donor age (young donor), and gender (male) appear to have a positive impact on longevity of the kidney transplant [16]. An important consideration in pediatric patients is that they are expected to have greater longevity. Therefore, logically, they should be receiving kidneys that are expected to survive longer. In the USA, and in most countries with established organ donor programs, children are given priority on the waiting list. The average waiting time for a deceased donor kidney transplant in the USA is 6–12 months as compared to 3–5 years in individuals > 18 years of age. Scientific registry for transplant recipients (SRTR) data indicate the main cause of death in donors for pediatric kidney transplant recipients is head trauma followed by anoxia (Fig. 1). Approximately 25% of pediatric kidney transplants are lost within 7 years [17]. An important dilemma that a pediatric nephrologist or transplant surgeon faces is, if there is only one possible living donor, should the first kidney transplant be from a living or a deceased donor [18]. The pros for receiving a deceased organ first are that children get good-quality donors in a relatively short period of time. Therefore, the living donor could be saved for a later time after the age of 18 years, when the waiting time is long. An argument against this would be that later, the potential donor will be older and may have health issues when re-transplantation is considered.

Donor size

Adult kidneys in pediatric recipients

Size-matched donors are difficult to find in children. Moreover, there is a higher risk of vascular complications, primary non-function, and acute tubular necrosis with the use of size-matched small pediatric donors in children [19]. Use of adult-sized kidneys is a long-established practice and is associated with superior graft outcome [20–22]. However, a large adult kidney which is used to a higher volume of blood flow per minute will be subjected to a relatively low cardiac output and blood volume when transplanted to a young recipient, as demonstrated by Salvetierra et al. [20]. The small child is therefore at a higher risk of hypoperfusion injury when subjected to hypovolemic states and acute illness. Other significant complications that can occur when a large kidney is placed in a small child are abdominal compartment syndrome and respiratory decompensation [23]. There is evidence of a non-immune histological injury over time in children transplanted with adult kidneys which is believed to be from hypoperfusion [24]. Despite these issues, children transplanted under the age of 5 years have the longest graft survival [7]. Generally, the intra-peritoneal placement of the donor kidney is preferred due to a wider exposure of the operative field and better visualization of the blood vessels. However, in selected situations and in experienced centers, the extraperitoneal approach is feasible and preferable, as post-operative recovery is shorter [21, 25]. The minimum weight of children to receive an adult kidney is generally > 10 kg. However, there are centers that would transplant children < 10 kg with an adult living donor kidney with good outcomes [26].

Pediatric kidney donors

According to data published by the organ procurement transplant network (OPTN), 837 donors (8.5% of the total donor pool) were < 18 years of which 300 were < 5 years in 2018. Most kidneys from small pediatric donors are transplanted into adult recipients. There is a higher risk of graft thrombosis when small pediatric donors (< 20 kg) are used and a higher rate of discarded kidneys when the weight of the donor is < 9 kg [27]. Data obtained from SRTR suggest that single kidneys from small pediatric donors had a 78% higher risk of

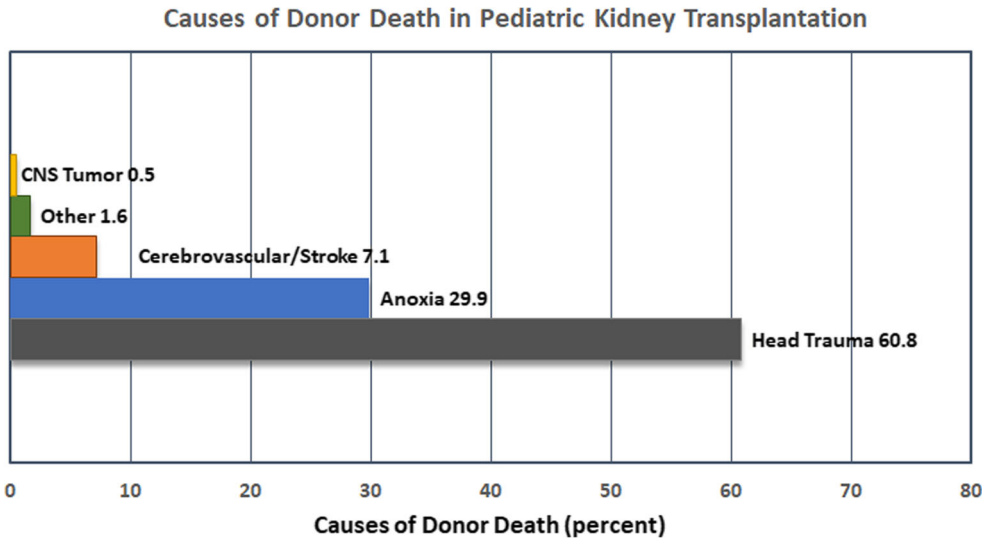

Fig. 1 Head trauma is the most prevalent cause of death in deceased donors that are offered to children followed by anoxia (extracted from SRTR as of March 2019)

graft loss compared to two kidneys being transplanted from a single small donor [27–29]. Some centers therefore have successfully transplanted kidneys from small donors "en bloc" in which both kidneys from a small pediatric donor are transplanted along with a portion of the donor aorta, inferior vena cava, and both ureters into the recipient. Prior to the new kidney allocation system, 1.8% of kidneys were placed "en bloc" from pediatric donors to pediatric recipients compared to 0.53% currently. The long-term graft survival and function were comparable to standard criteria deceased and living donors [31]. However, center experience in performing these transplants is a key factor in pursuing en bloc kidney transplantation as there is a higher risk of vascular thrombosis.

Living donation kidney transplantation in children

Younger recipients have a greater likelihood of having a living donor [6, 7]. However, in the USA, the number of LD has decreased to < 40% from the year 2005, in comparison to > 60% in prior years [30]. This was observed after implementation of a policy known as Share-35, whereby priority was given to children < 18 years for deceased donors (DD) younger than 35 years [32]. Globally, the highest living donation to children occurs in the USA, UK, Netherlands and Denmark [33, 34]. In certain European countries, LD kidney transplants occur in < 20% [34]. There are several barriers to living donation such as single caregiver, cultural biases, healthcare policies, gross domestic product and medical issues in potential donors [32–36]. Laws regarding donation after brain death (DBD) were enacted only in recent years in Japan where the rate of LD transplantation is higher compared to other countries [37]. The rate of LD transplantation is also higher in some developing countries where there is no national organized deceased donor policy [14].

In the USA, most living donors for children are parents, with mothers constituting 55%. Zero mismatches in 6 HLA A, B, and DR alleles occurred in 5.5% of LD transplants and 6 mismatches occurred in 2.7% of the total LD pool [7]. In recent years, the living unrelated donor pool in children has increased to 13.3 per 100 LD transplants [7]. Despite poor HLA matching, outcomes remain superior to DD kidney transplants. Living unrelated donors are an important source of organs in other countries and increase the donor pool [38]. Better HLA matching and shorter cold ischemia time with less time exposure to ischemia-reperfusion injury are some of the major factors that differ between LD and DD donors, translating into better long-term graft survival [12].

A kidney graft survival calculator based on age, sex, HLA match, and body size has been proposed in living donor kidney transplantation. The algorithm allows physicians to estimate long-term outcomes based on donor and recipient characteristics, and choose between multiple living donors in a given recipient. Male donors, better HLA match, and less disparity in donor-recipient size are associated with greater longevity [39, 40].

Paired exchange donors The demand for kidney donors far exceeds the supply. Increasing the living donor pool among genetically unrelated donor-recipient pairs offers a viable solution and improves the outcome of recipients. Paired donor exchange offers a suitable alternative to patients with ESKD who are medically fit and willing, but incompatible living donors. HLA or ABO incompatible donor-recipient pairs would be situations in

which paired donor exchange can be considered [41–43]. Swapping an older donor for a younger donor, for a young recipient, is another instance where this can be considered. Living unrelated donor kidney transplantation can be considered in patients with dominantly inherited diseases such as polycystic kidney disease which precludes living related kidney transplantation. Highly sensitized patients with incompatible donors must wait much longer on the deceased donor waiting list, often have to undergo desensitization prior to transplantation, and receive more potent immunosuppressive protocols after transplantation. Paired exchange offers an opportunity to match with a donor of lesser immunological risk. Two-way, three-way, and chain exchanges are strategies that have been employed. A domino exchange is characterized by an altruistic donor providing a non-directed donation [44] (Fig. 2). Both single-center and national registries participate in paired donor exchange. Internationally, paired donor exchange programs are also available in the Netherlands, South Korea, UK, Canada, and India [45].

Pediatric living donors Pediatric living donors were seldom used in the past. In an analysis done by Harmon et al., 12% of pediatric living kidney donors were identical twins [46]. In a survey of physicians in the USA, one third would consider using a twin donor who is a minor, as justifiable [47]. In monozygotic twin donor transplantation, despite complete HLA homology, there can be a heightened immune response to trauma and ischemia at the time of transplantation. Therefore, immune suppression may be considered for a short period of time [48]. Monozygosity has to be established by appropriate genetic testing [48]. Under exceptional circumstances, when the child donor is able to understand the implications of donation, kidney transplantation can be considered after due process. An identical twin could derive emotional and psychological satisfaction from donating to a twin. The American Academy of Pediatrics has developed guidelines that emphasize 4 conditions need to be met to consider a pediatric living kidney donor: (1) both donor and recipient are highly likely to benefit, (2) surgical risk to the donor is extremely low, (3) all other living and deceased donor options have been exhausted, (4) the donor freely assents to donation without coercion (established by an independent advocacy team), (5) emotional and psychologic risks to the donor are minimized [49] (Fig. 3).

Deceased donor kidney transplantation

Spain has the highest deceased donation rate because of their "opt out" organ allocation policy of presumed consent where all citizens are potential organ donors unless the donor family opts out. France, Greece, Norway, Sweden, and Wales in England have "opt out" policies [15]. The US has an "opt in" policy in which the wish to be an organ donor is expressed during a person's lifetime, or after death when the family opts to donate. Despite the opt-in policy, the DD organ donation rate is high in the USA compared to other countries [15]. UK and the Netherlands have some of the lowest deceased donor rates [15].

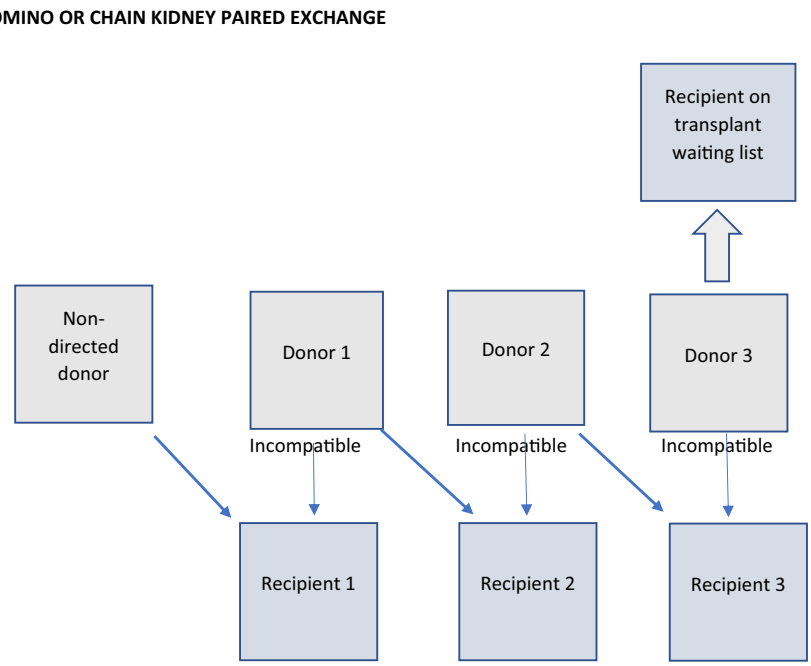

Fig. 2 Kidney paired exchange can occur in a simple two-way donor-recipient paired exchange or in a chain which starts with a non-directed or altruistic donor and the final donor in the chain will give to a recipient on the deceased donor list and close the chain. Chain donation has the advantage of improved matching and increasing the donor pool. However, it can be logistically challenging

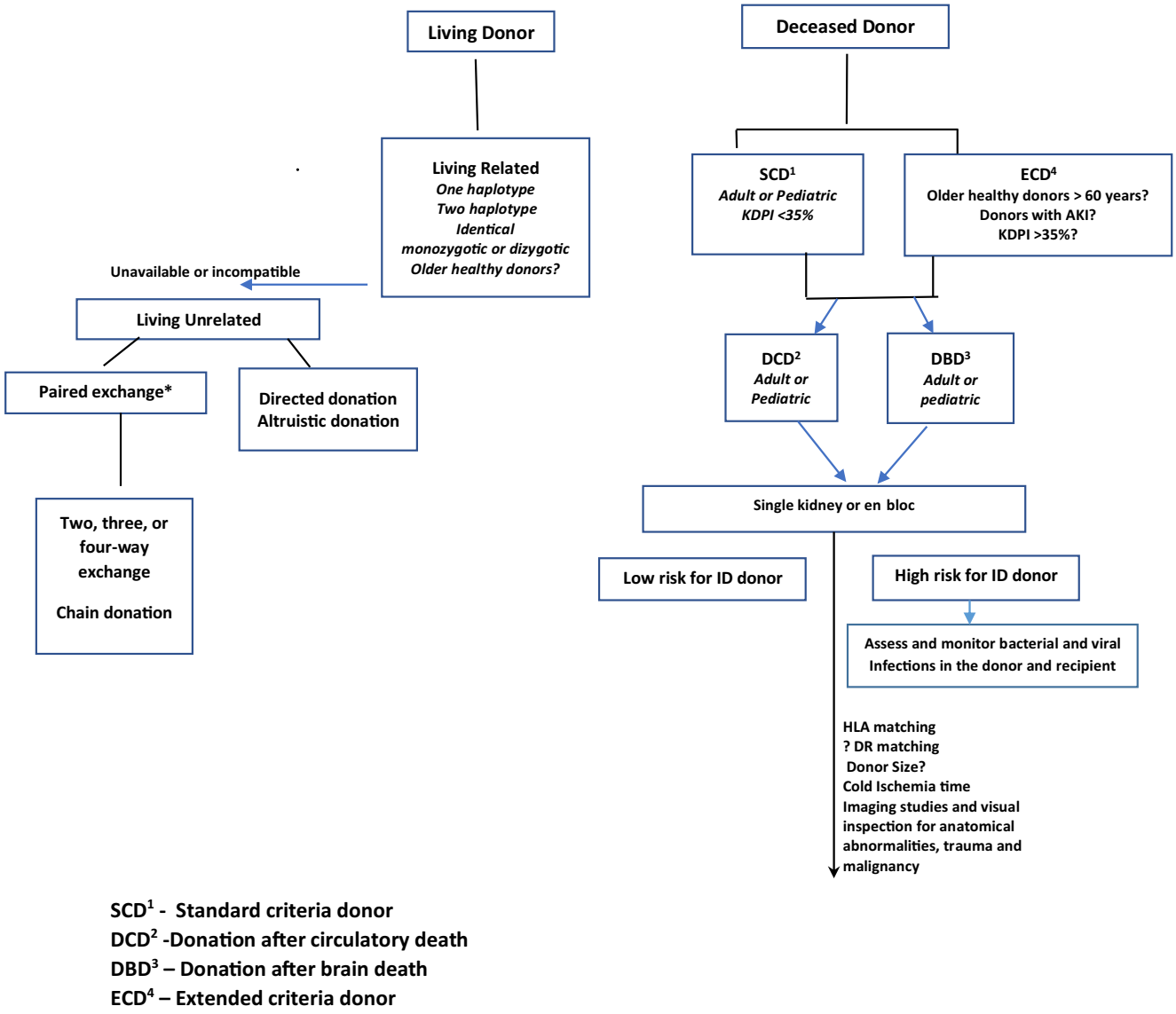

Fig. 3 Donor options in children with ESKD. Despite several choices, social, cultural, religious, and medical factors play a major role in both living and deceased kidney transplant donation. In addition, logistical factors such as national organizations for organ procurement and allocation, and donor management policies play an important role in deceased donation

A donor is considered standard criteria (SCD) when the organ is procured after brain death, the donors have no prior significant co-morbidities such as hypertension or diabetes, serum creatinine is < 1.5 mg/dl and the age of the donor is < 50 years [50]. Usually, the cause of death is related to trauma. Children are given priority to receive these organs which have better longevity. A donor is considered extended criteria if the donor is > 60 years, or between the ages of 50–59 and has 2 of 3 features: hypertension, terminal serum creatinine of > 1.5 mg/dl, or death by cerebrovascular accident [50].

Donation after brain death Most children receive deceased organs from standard criteria donors which are procured from brain dead donors, where irreversible loss of function of the brain and brainstem has been determined by neurologic criteria. However, the heart continues to function, and respiratory status is maintained with a ventilator. The functioning heart helps to maintain perfusion of essential organs. An ideal donor is one with no pre-morbid conditions, whose organs are recovered after brain death and cause of death is isolated head trauma [51]. Ninety percent of deceased donors in the USA are DBD [15].

Donation after circulatory death Although DBD donors are preferred for better long-term outcomes, donation after circulatory death (DCD) donors are an important source of organs and help to expand the donor pool. There are several categories of donation after circulatory death. These are described in the Maastricht classification [52] (see Table 1). It is preferable that death occurs in a controlled situation as this improves viability of organs and warm ischemia time may be shorter. Categories 3 and 4 are controlled and there is planned withdrawal of life-sustaining therapies when further treatment is considered futile as agreed upon by the family and health care team. Life-sustaining measures are withdrawn in a controlled setting, typically in an operating room after consent is obtained from the next of kin. The time from withdrawal of support to cessation of circulatory activity (defined as a systolic BP ≤ 50 mm Hg or ≤ 60 mmHg depending on local laws) can vary and contributes to the total warm ischemia time [52]. There is a mandatory observation time from cessation of circulatory activity to declaration of death. In the USA, this observation period is usually 5 min but can vary in other countries [52]. The interval from withdrawal of support to initiation of perfusion of cold preservative solution (total warm ischemia time) can range from 10 to > 170 min with the 50th, 75th, and 90th percentile being 26, 34, and 48 min respectively [52]. There is a higher risk of DGF if the warm ischemia time is > 48 min [53]. A cold ischemia time of > 12 h in kidneys from DCD donors increases the risk of graft loss. In general, there is a higher rate of non-function and DGF in DCD kidneys [53]. However, if the warm ischemia time is short, DCD kidneys could be a valuable component of the donor pool in children [54, 55].

Approximately 4% of children in the USA received DCD kidneys each year since 2015 (SRTR data as of March 2019).

In the UK, 1.2% of pediatric kidney transplant recipients receive DCD kidneys [56]. Delayed graft function occurred in 25% and primary non-function in 5% of DCD kidneys, but if the graft recovered function after implantation, 1- and 3-year graft survivals were comparable with DBD donors [56]. Registry data from the USA reveal a significant increase in graft loss starting 4 years after transplantation in DCD versus DBD donors [57]. Furthermore, in the USA, concerns regarding hypoxic ischemic injury before organ recovery limits the use of DCD kidneys in children. However, they may be an important source of donors in children who have been on the waiting list for a long time. Improvement in organ preservation techniques and formulating guidelines for maximum allowable warm ischemia times can increase the use of DCD kidneys.

Other non-SCD donors Consideration may need to be given to the use of donors with acute kidney injury and creatinine > 1.5 mg/dl, who were known to be previously healthy, in children who have been on the waiting list for a long time. If the donor did not require dialysis, the chances of complete recovery of these kidneys is 70–75% [55]. Although, living donors 35–49 years of age provide the best transplant survival, older healthy living or deceased donors (if the cold ischemia time is short) > 60 years could also be considered if options are limited [55].

Waitlist and allocation policies in the USA

Balancing equity (every patient has a fair opportunity to receive a kidney transplant) and utility (transplanting kidneys that are expected to last the longest, to patients who are expected to live the longest) is challenging in organ transplantation [58]. In December 2014, a new kidney allocation system came into effect in the USA (https://optn.transplant.hrsa.gov/news/introduction-to-the-new-kidney-allocation-system/). The major change from previous years was that the waiting time on the list was calculated from the time on dialysis rather than from the date of being placed on the list. In addition, allocation of kidneys was based on a kidney donor profile index or KDPI which is derived from a Kidney Donor Risk Index (KDRI—see Table 2) [60]. KDRI estimates the relative risk of post-transplant kidney graft failure in a given deceased donor. In the new allocation

Table 1 Modified Maastricht classification. Adapted from [52]

Category I Uncontrolled	Found dead IA. Out-of-hospital IB. In-hospital	Sudden unexpected cardiac arrest with no resuscitation
Category II Uncontrolled	Witnessed cardiac arrest IIA. Out-of-hospital IIB. In-hospital	Sudden unexpected cardiac arrest with unsuccessful resuscitation
Category III Controlled	Withdrawal of life-sustaining therapy	Planned withdrawal of life-sustaining therapy; expected cardiac arrest
Category IV Uncontrolled Controlled	Cardiac arrest while brain dead	Sudden cardiac arrest after brain death diagnosis during donor management but prior to planned organ recovery

Table 2 Donor characteristics for calculation of Kidney Donor Risk Index which is used to calculate KDPI

Characteristics	Reference donor characteristics	Factors that increase KDRI
Donor age (years)	40	Age > 60 Age 50–60 in the presence of a co-morbidity
Height (cm)	170	Donor-recipient size mismatch
Weight (kg)	80	Pediatric donor
Ethnicity	Non-African American	African American
History of hypertension	No	Decreases quality of kidney
History of diabetes	No	Decreases quality of kidney
Cause of death	Not cerebrovascular accident	Cerebrovascular accident
Serum creatinine (mg/dl)	1	> 1.5
Hepatitis C status	negative	Hepatitis C positive
Donation after circulatory death	no	yes

system, all adult candidates (> 18 years) receive an expected post-transplant survival score which takes age, time on dialysis, presence of diabetes, and history of previous transplant to estimate the expected longevity of a recipient. The KDRI of the deceased donor and the expected longevity of the recipient are then factored into an algorithm whereby adult transplant candidates with longer expected post-transplant survival will receive high-quality kidneys which have a low KDPI. Previously pediatric priority was given for organs from deceased donors < 35 years after this was offered to highly sensitized patients and former living donors. In the new system, pediatric recipients receive priority for KDPI < 35%. However, since the transition to the new allocation system, younger children are experiencing longer waiting times, less pediatric donor offers, and an increased incidence of delayed graft function (DGF) [61–63]. An explanation for this is that pediatric donors < 10 years of age are assigned a higher KDPI and therefore are not offered to the youngest recipients [61]. In addition, a higher proportion of donors with a KDPI < 35% have history of opioid addiction and are considered public health service (PHS) high risk for transmission of HIV, or hepatitis B or C [64]. In the new allocation system, although there has been an increase in high-risk donors for children, many centers have reservations in accepting these donors [61]. It is important to note that anatomical abnormalities, trauma or malignancy in the donor kidney, are not considered in calculating KDPI, and need to factor into the decision-making process by the individual transplant center when evaluating donor offers.

Characteristics of deceased donors

Allocation of a deceased donor is based on several donor and recipient factors determined by a computerized algorithm, which includes time on the waiting list, blood group compatibility, tissue type, and pediatric status (https://optn.transplant.hrsa.gov/news/introduction-to-the-new-kidney-allocation-system/) [65]. In certain European countries and in Australia, greater emphasis is given to HLA matching in deceased donor kidneys with less weight given to time on dialysis, ischemia time, and degree of sensitization [66]. In the USA, a point system is used in assigning priority as seen in Table 3 (https://optn.transplant.hrsa.gov/news/introduction-to-the-new-kidney-allocation-system/). The decision to accept or reject a deceased donor offer relies on a center's transplant team and approximately 15–20% of DD offers are rejected in the USA [67, 68]. Donor offer refusals are most often due to increased donor age and quality of the organ. Practice patterns vary between transplant centers [67, 68].

Deceased donor selection in children

Figure 1 shows the cause of death in donors from whom kidneys were recovered for pediatric kidney transplantation between the years 2015–2018 based on data obtained from the OPTN. Donors with multi-organ failure, sepsis, meningitis, unexplained altered mental status, and surgically manipulated CNS tumors should be viewed with caution. A thorough history from the family may be helpful but unreliable, since they may not be aware of all aspects of the donor's health. History of high-risk behavior such as use of intravenous illicit drugs and jail time should be noted to assess the infectious risk to the recipient. Hospital records of the donor's urine output, urine analysis, and trends in serum creatinine should be reviewed as this will determine the extent of acute or chronic renal injury and the likelihood of delayed graft function in the recipient. Cardio-pulmonary resuscitation (CPR) time and the average amount of vasopressors used should be noted [51]. Notation should also be made regarding massive transfusions of blood and blood products as these could dilute serologic tests and give a false negative reading of underlying infections such as hepatitis B or C or HIV.

Table 3 Allocation of points for transplantation. Adapted from OPTN/SRTR

Recipient variables	Points
Waiting time on list	1 per year
Pediatric candidate with zero mismatch	4, if 0–10 years; 3, if 11–17 years
Pediatric candidate	1
Prior living donor	4
Single HLA DR mismatch with donor	1
Zero HLA DR mismatch with donor	2
Calculated panel reactive antibody (cPRA)	
80–84%	2.5
85–90%	4
91–98	5–17
99%	50
100%	202

Since the new kidney allocation system (from 2015 to 2018), the most recent data from the OPTN reveals that 45% of DDs for children had a median CPR time of 20 min. In this time period, the median donor age for pediatric recipients was 22 years and that of the recipient was 13 years. The median terminal creatinine of the donor was 0.8 mg/dl. Male donors constituted 69% and 61% were Caucasian. Only a small proportion of children (6.3%) received deceased donors with a KDPI of 35–85%, while most children have generally received good-quality kidneys.

Although the 1-year survival graft survival is 97.8%, the estimated long-term graft survival probabilities of DD kidneys in children is 63% as compared to 77% at 7 years with LD transplants [7]. This difference in survival with DD is explained by increased cold ischemia time, ischemia reperfusion injury, catastrophic events in the donor prior to brain death that impact kidney function, and unknown medical issues in the donor. The impact of CPR time in the donor on long-term graft survival in the recipient is also not known.

Donor-derived infections

Infectious diseases can be transmitted through organ donation and have been reported in children [69, 70]. Pre-transplant screening of potential donors and recipients is essential to implement a preventative approach. All children should be immunized prior to transplant with the recommended childhood vaccination series. Additional immunizations against 23 and 13 valent pneumococcal, meningococcal, and human papilloma virus (in older children) and influenza should be instituted. Risk evaluation for CMV and EBV infections should be routinely performed. In addition, screening tests should be performed for tuberculosis; syphilis; hepatitis A, B, and C; and diseases that may be endemic in the local population. From 2005 to 2012, there has been an increase in donor-derived infections [71]. Bacterial, viral, fungal, and parasitic infections have been reported. Rabies, lymphocytic choriomeningitis, and West Nile virus have been notable donor-derived infections which carry a high degree of morbidity and mortality [71]. CNS infection in the donor may not be recognized at the time of organ procurement and the diagnosis in the donor may be made several days after transplantation, or if the recipient manifests clinical symptoms and signs of CNS disease [72]. Identified cause of death at the time of organ procurement may be unrelated events such as anoxia, intra-cerebral hemorrhage, or gunshot wound to the head [73]. There should be a high index of suspicion for encephalitis when a donor has altered mental status without obvious explanation. All deceased donors routinely have blood, urine, and sputum cultures done. If the potential donor has a bacterial infection, documentation of treatment is important prior to organ donation. It is important to continue to follow donor cultures in the peri-operative period and the recipient should have cultures sent and treated. Certain infections take longer to manifest in the recipient and unsuspected bacterial infections can occur in the donor. Bacterial sepsis and mycotic aneurysms can occur in the recipient as a result of donor-derived bacterial infection. Recipient risk factors for infection such as a past history of blood stream, and peritoneal or urinary tract infections, especially with multi-drug-resistant organisms could potentially augment the risk of a serious infection in a child exposed to a donor-derived infection. Certain donor-derived infections such as influenza and strongyloides (as observed by our group) can be associated with high mortality in the recipient [74]. Other infections that have been known to be transmitted through organ donation are varicella and dengue [75, 76].

Increased risk for infectious disease donors This is a terminology used for donors who are at risk for transmitting blood-borne viral infections such as hepatitis C, HIV, and hepatitis B. There is a higher prevalence of these diseases

in certain homeless populations and intravenous drug users [77–79]. Public Health Service definition of donors at increased risk for infectious diseases in the USA are listed in Table 4 [64].

Typically, there is a window of time from transmission of infection, to the time these infections may be detectable by standard diagnostic tests. Enzyme-linked immunosorbent assays have a longer diagnostic window of time compared to nucleic acid amplification testing (NAT) [80]. The availability of NAT testing for hepatitis B and C and HIV infection has shortened the time to detect these infections. However, availability of test results within a 12-h time frame varies between organ procurement organizations and there are false positive results [81, 82]. False negative results can occur if the donor acquired the infection in the recent past and if the donor's blood has low viral titers [81, 82]. The latter can also occur if the donor had multiple transfusions of blood products prior to death. Approximately 20% of deceased donors fall into the category of being at risk for transmission of hepatitis B or C or HIV. Donor's past history may not be available soon after the catastrophic event leading to the donor's death, and/or the family may not be aware of all aspects of the donor's history. Therefore, a high degree of vigilance is required even after organ procurement. Following cultures and serological tests over a period of time in both the donor and the recipient is key to prevention and treatment of serious infections in the recipient.

Donors who are at higher risk for transmitting infections are more likely to be male and die from anoxia and less likely to have diabetes or hypertension. Therefore, the quality of the organs is typically high [83]. However, there is resistance in organ acceptance because of the potential risk of transmission of infections from the donor to the recipient. Use of high-risk donors in children does not offer a survival benefit when compared to adults. However, declining donors at high risk for infection increases waiting time in children [84]. The risk of transmission of viral diseases is < 1% and given the recent advances in treatment of hepatitis B and C, consideration can be given to accepting donors at high risk for these infections on a case by case basis.

Cold ischemia time and machine perfusion

After organs are procured from a donor, the organ is preserved in a cold physiologic solution until implantation in a recipient. However, cold preservation and ischemia cannot prevent noxious injury to the graft. Additionally, inflammatory and immune injury occurs with reperfusion of the organ resulting in ischemia-reperfusion injury. Longer cold ischemia times, particularly over 30 h, increase the risk of mid-term graft failure [85]. In children, a cold ischemia time of > 24 h increases the risk of acute tubular necrosis by 25% in the immediate postoperative period and affects long-term graft survival [6].

Hypothermic machine perfusion is a technique which uses a continuous and pulsatile flow of cold physiologic solution to improve viability of the DD kidney. Pulsatile perfusion parameters such as flow and vascular resistance are used in the evaluation of the donor kidney and to predict outcome [86–88]. Use of this technique is associated with a reduced risk of delayed graft function and improved graft survival [86, 87]. Most recent data from the OPTN indicates that machine perfusion is used in 31% of deceased donor kidneys in pediatric recipients. At our center, hypothermic machine perfusion is used for all deceased donor kidney transplants and in addition to decreasing the incidence of DGF, it appears to mitigate the effect of prolonged cold ischemia in the explanted kidney.

HLA matching

Sibling donors have a greater likelihood of being a one or two haplotype match. Parent donors are usually a one haplotype match. The current allocation system in the USA favors

Table 4 Sex refers to any method of contact including vaginal, anal, or oral

Public health high-risk categories for transmission of HIV or hepatitis B or C from the organ donor in the USA
Men who have had sex with other men (MSM) in the preceding 12 months
Women who have had sex with a man with history of MSM in the preceding 12 months
People who have had sex with a person who is known to have HIV or hepatitis B or C in the preceding 12 months
Parenteral non-medical use of illicit drugs in the preceding 12 months or sex with a person known to use parenteral illicit drugs in the preceding 12 months
Persons (women or men) who have engaged in sex in exchange for money or drugs in the preceding 12 months
Inmates of correctional systems or jail time > 72 h in the preceding 12 months
People diagnosed with and treated for syphilis, gonorrhea, chlamydial infection, or genital ulcers in the preceding 12 months
Child ≤ 18 months of age who is born to a mother known to have or is at increased risk of hepatitis B or C or HIV infections
Child who has been breast-fed within the preceding 12 months and the mother is known to have or at increased risk for HIV infection
At risk for HCV infection only: people who have had hemodialysis in the preceding 12 months

prioritization of younger deceased donors to children. Therefore, there is less emphasis on HLA matching which increases the risk of sensitization, thus making it potentially difficult for re-transplantation. Given the limited half-life of a kidney transplant, the chances of having a second or third transplant in individuals who have had a kidney transplant as a child are very high. Several studies reinforce the fact that higher HLA mismatches limit long-term graft survival [89]. HLA B and DR mismatches are associated with decreased longevity even among living donor kidney transplants [89]. Most concerning is the fact that two HLA DR mismatches increase the risk for non-Hodgkin's lymphoma in children [90].

Greater emphasis is given to HLA matching in deceased donor kidneys in some countries [66]. This may be disadvantageous in ethnic minorities who have uncommon HLA phenotypes and those who are highly sensitized. These patients can benefit from epitope matching which takes into consideration the fact that HLA antigens comprise multiple serologic epitopes, the structure and position of which determine recognition, accessibility, and reactivity to an antibody [91]. Some epitopes are shared across multiple HLA alleles. Identification of these epitopes can result in acceptable HLA mismatches that could be compatible at a structural or functional level. Acceptable HLA mismatches are identified using the HLA Matchmaker or Luminex platform and this technology allows transplantation in individuals who are otherwise difficult to transplant [91].

Conclusions

The survival of children after kidney transplantation has considerably improved in recent decades, although recipients of LD kidney transplants have better patient and graft survival than those who receive a DD transplant. However, social, cultural, religious, and medical factors play a major role in both LD and DD kidney transplant donation. In addition, logistical factors such as national organizations for organ procurement and allocation, and donor management policies play an important role in deceased donation. The survival of the transplanted kidney is limited and children who require renal replacement therapy from early childhood will probably have 2 or 3 kidney transplants in their lifetime. The choice of donor will need to be evaluated on an individual basis and will have to take into consideration social and medical characteristics of both donor and recipient. Although there are multiple donor options for kidney transplantation in children, ongoing challenges are preservation of long-term graft function and the organ shortage from the increasing burden of chronic kidney disease across the globe. Furthermore, the need for life-long immune suppression increases the risk of infection and malignancies which also impose limitations in the transplant recipient's life span. Increased awareness for organ donation, improved organ preservation techniques, targeted immunosuppressive therapies, and regenerative techniques might hold promise for the future and improve the lives of children with ESKD.

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Compliance with ethical standards

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