uro

MDPI

Article

Use of Kidneys from Anencephalic Donors to Offset Organ Shortage

Dai D. Nghiem

Department of Surgery, Division of Transplantation, Allegheny General Hospital, Pittsburgh, PA 15212, USA; nghiem5000@gmail.com

Abstract: Background: It is well recognized that patient survival and quality of life are superior with renal transplantation than with dialysis. Organ availability is far outweighed by the large number of wait-listed patients. Additional stratagems are sought to expand the donor pool, and kidneys from anencephalic infants can be considered a source of organs, until now unexplored. We plan to assess the feasibility of using the kidneys from anencephalic infants for transplantation. **Material and Methods**: Information about anencephaly, the characteristics of the infant kidneys, the ethical, social and medico-legal aspects raised by the use of these kidneys, their procurement and their transplantation are reviewed. **Conclusions**: En bloc kidney transplants from infants can provide long-term normal renal function after an accelerated catch up growth. They are not subjected to hyperfiltration since they have a full complement of nephrons. They can be transplanted using the techniques currently available.

Keywords: anencephalic donor kidneys; en bloc kidney transplantation; catch-up growth; long term function; infant organ donation

Citation: Nghiem, D.D. Use of Kidneys from Anencephalic Donors to Offset Organ Shortage. *Uro* **2023**, *3*, 10–18. https://doi.org/10.3390/uro3010002

Academic Editor: Tommaso Cai

Received: 25 November 2022
Revised: 22 December 2022
Accepted: 29 December 2022
Published: 5 January 2023

1. Introduction

Kidney transplantation provides extended life expectancy, increased quality of life and is cost effective when compared to dialysis therapy for end stage renal disease. As of 1 January 2022 there were over 100,000 patients on the waiting list for a kidney transplant in the US. Unfortunately, only 6541 living donor kidneys and 13,861 deceased donor kidneys were transplanted last year [1]. As the recipients outstrip the organs by a ratio of 5:1, the median waiting time for a kidney is extended to 3–6 years. Patients with blood group B or O may experience a longer waiting period with up to 47% of patients dying annually. To face this enormous challenge, anencephalic donors can be a source of kidneys, unexplored for nearly fifty-three years since the first successful and long-term transplantation of anencephalic infant en-bloc kidneys [2]. The recipient, 33 years after the original transplantation, was reported to be alive and well with the original kidney transplants [3]. The purpose of this communication is to discuss the problems arising from the use of this infant population as organ donor such as the incidence of the congenital malformations, the characteristics of the kidneys, the ethical, social and medico-legal aspects of the organ donation and procurement, the transplantation techniques, and the long-term results.

2. Material and Methods

2.1. Background of Anencephaly

Anencephaly is the most severe lethal congenital malformation of the neural tube that occurs when the cephalic end of the neural tube fails to close at the base of the skull between the 23rd and the 26th day of pregnancy. The causes are multifactorial: iatrogenic, toxic (ingestion of Fenugreek, a culinary plant found in Morocco known to cause birth defects in humans and animals), metabolic (deficiency of folic acid and zinc during

early gestation, high doses of Vit A in rats), nutritional, bacterial (Mycobacterium avium subspecies paratuberculosis in aerosolized manure in the rural community of Yakima, WA during a cluster of babies with anencephaly), and exceptionally chromosomal [4–9].

The condition is characterized by the absence of the cerebral hemispheres including the neocortex, the meninges, the skull, and the scalp. The exposed brain tissue ultimately transforms into a hemorrhagic and fibrotic mass of neurons and glia. Anencephalic infants are blind, deaf, unconscious, unable to perceive pain, and unable to move or cry. These conditions allow for breathing, cardiac function, and maintenance of body temperature control. Despite the severe brain abnormalities, the facial bones, the base of the skull and the facial aspect are nearly normal. Only 7% of fetuses die in utero. After delivery, infants may live a few hours to one week. One infant survived up to 28 months without life support such as intubation and tube-feeding [10].

Anencephaly accounts for approximately one-half of spinal cord defects. It has an incidence of 1/5000 live births in the United states, which translates to approximately 700 infants born each year with a female predominance ratio of 3:1 to 4:1 [11,12]. It can be recognized on the first prenatal screening ultrasound by a reduced crown-rump-length and the "Mickey Mouse" sign in the coronal view. Second trimester defects include absent calvarium above the level of the orbits in a view of the fetal face [13]. There may be association with Trisomies 13 and 18 and Triploidy [14]. In the 70's, half of the infants were born alive at 35–36 weeks of pregnancy. By 1990, after the diagnosis was made with the combination of polyhydramnios, elevated serum alpha-fetoprotein levels and ultrasound findings, the majority of patients elected to terminate their pregnancy at an average of 19.6 weeks of gestation, although some parents may opt to wait until normal delivery. After delivery, physicians may provide ventilator assistance and other medical therapies that are necessary to sustain organ perfusion and viability until such time as a determination of death can be made [15–19].

2.2. Characteristics of the Anencephalic Kidneys

The kidneys develop as early as the third week of gestation from the ureteric bud and ascend from a pelvic to the lumbar position, from the pronephros to the mesonephros at 4 weeks, and to the metanephros at 5 weeks, building up the number of nephrons along with its development. Glomeruli formation begins at the 5th week of gestation and urine is produced by the 9th week. Nephrogenesis is completed by 34 weeks [20] although there is evidence of post-natal nephrogenesis at 36 weeks of corrected gestational age [21]. However, postnatal nephrons exhibits abnormal nephron morphology and function [22]. Acceleration of renal maturation may lead to glomerulomegaly. The functional maturity of the kidneys increases rapidly in the first weeks of life due to a combination of increased renal perfusion and glomerular filtration and decreased renal vascular resistance.

The glomerular filtration starts at the rate of 5 mL/min/1.73 m^2, increases from 10–20 mL/min/1.73 m^2 during the first day of life to 30–40 mL/min/1.73 m^2 at the first 2 weeks of life, and slowly reaches 65 mL/min/1.73 m^2 by 2 months. It ultimately reaches adult levels of 120 mL/min/1.73 m^2 at 2 years of age [23]. In the same time renal blood flow increases from 3–7% of the cardiac output during pregnancy to 10% at the first week and 25% of the cardiac output at 2 years [24]. Low renal blood volume and glomerular function cause neonates to have difficulty with increased fluid volume, so intravenous fluid administration should be based on body weight and frequent clinical assessments [25]. Due to their large body surface area, neonates are subjected to greater insensible fluid losses. A transient tubulopathy at birth has also been identified with decreased response to aldosterone, inability to handle free water, electrolytes, small proteins and bicarbonate, resulting in multiple electrolyte imbalance and poor growth [26].

Glomerular counting techniques are performed only on autopsy specimen, and to date there is still no technique allowing in vivo determination of N^{glom}. Using the most accurate and reproducible stereological disector method applied to 11 normal spontaneous second trimester abortions and stillbirths from 15 to 40 weeks gestation, Hinch-

liffe et al. found that the mean glomerular number at 40 weeks is 740,000 [27]. In 78 kidneys from newborn to 84 years, Hoy et al. recorded 210,332 to 1,825,380 glomeruli with a mean of 784,909 ± 314,686 glomeruli, with a slightly higher number in male adults, with 846,386 compared to 720,335 in female patients [28]. N^{glom} is inversely proportional to V^{glom}, with larger glomeruli reflecting compensatory hypertrophy. The terms nephron endowment, nephron number, glomerular number, nephron mass are used interchangeably in the literature. The term nephron mass is used as a clinical term meaning nephron number, kidney weight, kidney size and kidney volume [26]. In a recent study of twenty human fetal kidneys (5 male and 5 female anencephalic fetuses, and 5 male and 5 female normal fetuses at gestational ages 30 to 36 weeks), Kalaycioglu et al. did not find any significant differences between the two groups in terms of kidney volumes, number and height of the glomeruli, and suggested that kidneys from anencephalic infants may be suitable for transplantation [29].

The total kidney volume determined by ultrasound correlates significantly with N^{glom} in infants younger than 3 months [30] and has been used as an in vivo surrogate for N^{glom}. A study of 203 pediatric patients with sonograms yielded one regression equation to determine the renal length in infants under one year as equal to 4.98 cm + 0.155 × age in months [31]. In 307 other children the left kidney measured 50 mm ± 5.8 mm in length, usually longer than the right [32]. Magnetic resonance imaging data on renal size is available in adults only [33].

2.3. Pediatric Organ Donation

Pediatric organ transplantation confers significant benefits to life extending and quality of life for the young recipients. In the United States between 1988 and 2013 there were 130 organ donors under one year of age, annually. In 2020, 1900 children are on the waiting list in the US and 1700 children received transplants from over 850 pediatric donors, of which 121 were babies under one year of age [32].

Pediatric organ donation, faces unique issues compared to adult donation. For instance, even with the best medical, professional and ethical environment it is still very difficult for the bereaved parents and siblings stricken with grief, ethical dilemmas, compassion fatigue, social, cultural and religious issues to understand the concept of brain death when they see their own children resting comfortably under assisted ventilation, with a heart beating on the cardiac monitor [33]. In a survey of 425 parents, of which 65% are willing to donate their children organs, 45% of parents are still believing that children declared brain dead may wake up. Participants in another randomized series of 1072 people from 30 countries are more likely to be certain that the patient was truly dead from "circulatory arrest" with 87.9% ± 19.7% compared to participants exposed to "brain death" with 84.1% ± 22.7% with $p = 0.0004$ [33]. In another study of 131 children eligible for organ donation with 57% of families authorizing donations, multivariate analysis shows that family language, conversation-based characteristic of organ donation and time of referral to Organ Procurement Organization are important aspects in increasing pediatric organ donation [1]. Despite the public support and willingness to donate their child's organs, there is still distrust of health providers regarding the motives of organ donation, especially among minorities and lower social ethnic groups [34].

Because of the cephalic anatomic consideration and the precarity of survival, death by circulatory arrest declared by medical and legal standpoint is the most likely event, and organs can be recovered for transplantation afterwards. This is known as Donation after Circulatory Determination of Death, or simply Donation after Cardiac Death (DCD) or Non-Heart Beating Donation [35,36]. Discussions regarding DCD can occur only after the family and the medical team have made the decision to withdraw support or terminate care. There should also be no conflict of interest between a dying child and a potential organ recipient, and the transplant team should not be involved until after the death declaration. In the U.S., pediatric donation has increased from <5% in 2004 to nearly 20% in 2014 [37–42]. Concerns regarding prolonged warm ischemia and ensuing pediatric organ dysfunction

have been raised, studied and found of no significance in 1–5 year graft survival using general data available [41,42].

The first use of anencephalic kidneys was reported by Martin et al. who transplanted successfully the kidneys from an anencephalic baby to a 17-pound boy in 1969 [2] and subsequently in 1978 with 7 en bloc kidneys [43]. Since then, there have been multiple reports on the subject with a few cases each [41–52].

The use of anencephalic organs for transplantation gained widespread publicity in the late 1980's with the successful newborn cardiac transplant from a Canadian anencephalic infant by Bailey et al. [53] Subsequently Loma Linda Medical Center reported a study of 12 anencephalic infants who were supported with intensive care measures to allow the declaration of brain death. None of the infant became organ donor [51].

Recently, there is renewed interest in the use of neonatal organs to close the gap in organ shortage with the report on the use of kidneys from a 7-week old DCD donor weighing 5 kg to a 22-year old woman with 1-year follow-up [54], another from 3 organ procurement organizations with 2 kidneys transplanted [55] and a larger series of 10 en bloc neonatal kidneys including 2 with anencephaly accepted for donation while still in utero. Of these, 2 pairs of en bloc kidney thrombosed and 2 single kidneys clotted off, with the remaining kidneys providing one year eGFRs of 48.1 and 81.1 mL/min/1.73 m^2 [56].

2.4. Procurement and Transplantation

The organ procurement and transplantation are the most important technical steps to be undertaken with utmost care to avoid post operative thrombosis, the "bête noire" of the transplant surgeon [56,57].

At the time of recovery, cold perfusion was administered via the distal right iliac artery through a 1 mm cannula and the kidneys were removed en bloc, with proximal transection of the aorta and the vena cava below the level of the celiac trunk which supplies the liver, and the common iliac arteries bifurcation. The hilum was not dissected to avoid injuries to the renal vessels, the excretory system and post operative torsion. The ureters were removed with a bladder segment to provide maximal ureteral length. At the recipient center, on the back table and under 2.5 magnification loupes, the proximal aortic and cava end were closed transversally. All non-renal vessels were suture-ligated with very fine suture material [56]. No attempt was made to reconstruct the missing cuffs of the renal arteries or the renal veins to avoid postoperative thrombosis encountered in the early experience of en bloc pediatric kidney transplants in adult recipients [57]. When injuries to the kidneys were suspected, the aorta was injected, at very low pressure, with 10 cc of fresh preservative solution stained with 1/3 ampule of indigo carmine. Failure to stain blue *immediately* on any part of the kidneys and the ureters denoted the presence of ischemic damage and led to organ discard. Delayed staining is secondary to diffusion of the dye and gave false information. The dye was then flushed out with fresh perfusate to avoid particulate embolization [58]. The adrenal glands were dissected partially and tied together with 3-0 silk sutures left long to serve as handles of the en bloc kidneys and facilitate their orientation and manipulation.

Classic transplantation using living donor kidney can be accomplished in infants weighing at least 15 pounds to allow technically sound anastomosis of the renal vessels to the recipient's aorta and vena cava [59]. Conversely, transplantation of the pediatric kidneys into pediatric recipients has always been poor due to technical difficulties [60,61]. Pelletier et al. using the data from the Scientific Registry of Transplant Recipients reported that of the 1287 en bloc kidneys, 4.3% were transplanted into pediatric recipients and 90.2% transplanted into adults, whereas among 1162 single kidneys, 9.3% of kidneys were transplanted into pediatric recipients and 85.3% transplanted into adult recipients [62]. Hence, the transplantation technique in adult recipients is described. At the time of transplantation, an extraperitoneal approach to the right iliac fossa was used because more room is available compared to the opposite iliac quadrant, allowing the kidneys to catch-up grow without vascular kinking. The en bloc kidneys were inverted 180 degrees

to allow donor cava-recipient iliac vein concordance at the pelvic level to avoid venous thrombosis from vascular scissoring. The distal aorta and vena cava were copiously spatulated posteriorly to maximize the size of the vascular anastomosis to accommodate the high flow of the full-grown kidneys. A small aortic punch was used to enlarge the arteriotomy. The anastomoses were performed end to side to the external iliac artery and vein, respectively. The ureters were anastomosed directly to the bladder over small 2 F stents using a no-touch technique [63,64]. The use of the bladder segment described originally by Carrel in 1908 in a canine model [65] and used by Gutierrez-Caldaza et al. in humans [46] is not necessary and may lead to urinary leakage from ischemic necrosis [66]. Anticoagulation was not used after the operation. Triple immunosuppression with low dose tacrolimus trough levels, mycophenolate mofetil and 4 days of methylprednisolone was used. Anti-thymocyte globulin was given for 5 days to mitigate dreadful rejection with ensuing tissue loss of the tiny kidneys. Clinical rejection episodes were treated with 5 days of 250 mg of intravenous methylprednisolone. No needle biopsies were performed to avoid injuries to the hilar structures of the very small kidneys during the first 3 months. Regardless of urine output, a technetium diethylene-triamine-penta-acetic scan was performed on day 1, and every 6 months as indicated. Ultrasound examination was performed at bedside to assess complete bladder emptying before discharge and repeated every six months as necessary. The patient was instructed to void every hour and the stents were removed by flexible cystoscopy during a clinic visit at 6 weeks.

2.5. Long Term Function and Growth of the En Bloc Kidneys

After a follow up period of 25.6 $\pm$ 14.2 months of 78 infant kidneys from donors weighing 10.8 $\pm$ 3.6 kg Nghiem et al. reported a graft survival of 79% with serum creatinine of 0.8 mg/dL, creatinine clearance of 88 mL/min/1.73 m^2 (34–188) and 24 h-proteinuria of 146 mg (normal range 1–150 mg) [67]. The total volume of both kidneys during the 3 study periods 1–3 months, 3–6 months and over 6 months rose significantly from 132 $\pm$ 69 cc to 209 $\pm$ 69 cc and to 325 $\pm$ 106 cc, respectively with $p < 0.001$. For comparison, the volume of 12 single standard criteria adult donors kidneys was 260 $\pm$ 110 cc and the GFR was 67 $\pm$ 25 mL/Mn/1.73 m^2. The total glomerular filtration rates of the en bloc kidneys during the same periods rose from 22.5 $\pm$ 14.2 mL to 85.4 $\pm$ 52.3 mL and to 120 $\pm$ 45 mL, significantly with $p < 0.001$, translating into a 4–6 fold increase of initial glomerular filtration rate with time. The intra renal hemodynamics in both kidneys remained normal with resistive indices between 0.60 to 0.93. These findings reflected in the normalcy of the recipient's blood pressure. Growth and function of these pediatric en bloc kidneys are summarized in Table 1. These findings persisted at a 12–24 months follow-up [68]. Sureshkumar et al. comparing all en bloc kidneys to living donor kidney transplants performed at a single center between 1990 and 2010 reported earlier detection of proteinuria in living donor kidneys recipient compared to en bloc recipients. Modifications of Diet in Renal Disease Glomerular Function Rates are higher than in living donor kidneys with 70.7 $\pm$ 27.1 mL/min/1.73 m^2 vs. 43.3 $\pm$ 16.9 mL/min/1.73 m^2, $p < 0.001$ [69]. Hirukawa et al. in the follow-up biopsies at 1-hr post-reperfusion, 6 months and at 3.5 years post transplant in a pair of en bloc kidneys from a 9 months old child, demonstrated a growth in glomerular area and volume, respectively, from 5.9 $\times$ 10^3 micron^2 and 0.34 $\times$ 10^6 micron^3 at 1-hr post- reperfusion to 14.9 $\times$ 10^3 micron^2 and 1.27 $\times$ 10^6 micron^3 at 3.5 years post transplant. On 1-hr post-reperfusion, the podocytes were structurally immature. At 6 months, podocyte immaturity was still present, but at 3.5 years podocytes were mature [70]. Taken all together, these data demonstrate that renal hyperfiltration seen in a model of 5/6 nephrectomized rats [71] has not been observed during the long term experience because the infant kidneys were able to adapt rapidly well to the high metabolic demand of their large hosts [72].

Table 1. Growth and function of en bloc infant kidney transplants.

	1–3 Months	3–6 Months	>6 Months	2-Tailed Measures
Volume (cc)	132 ± 69	209 ± 69	325 ± 106	$p < 0.001$
S.Creatinine (mg/dL)	1.76 ± 0.13	1.50 ± 0.33	1.25 ± 0.26	$p < 0.001$
GFR (mL/Mn/1.73 m^2)	22.5 ± 14.2	85 ± 52.3	120.7 ± 45.1	$p < 0.001$

All values are Mean ± SD. RI = Resistive index = peak systolic velocity- min end diastolic velocity/peak systolic velocity is 0.60–0.93 (normal range). For comparison, the mean volume and mean GFR determined in 12 standard criteria adult kidneys were 260 ± 110 cc and 67 ± 25 mL/Mn/1.73 m^2, respectively. 24 h proteinuria was 146 mg (normal 1–150 mg).

2.6. Donor Selection, Organ Procurement and Allocation

Donors older than 36 weeks of gestation with evidence of urine production after birth, a normalizing serum creatinine [23,24], a kidney length of 4.5–5.0 cm on ultrasonic view with absence of renal anomaly [29,31,32], absence of congenital metabolic and genetic diseases, normal levels of AFP in addition to regular criteria of a kidney donor are candidates for organ donation. For donors considered in utero, normal fetal growth, absence of oligohydramnios, presence of urine in the bladder, and absence of congenital anomaly of the kidneys should be confirmed [13,27,29,54,56,63].

During procurement, surgical teams should be working together with collegiality and professionalism to assure the maximum number of organ transplants. The kidneys should be removed en bloc with a bladder segment, with as much aorta and vena cava as possible, and packed en bloc with extra carotid arteries for future reconstruction, to be assessed only by the few recipient transplant centers [57,62,68]. A list of such centers performing the infant kidneys transplantation should be drafted in advance to speed up the organ allocation and to avoid a long cold ischemia time. Efforts to develop surgical training and exchange among transplant centers should be promoted to optimize the use of such scarce resources.

3. Conclusions

The severe organ shortage can be improved with the use of kidneys from anencephalic donors. There is ample evidence that these kidneys have a rapid catchup growth, provide long term excellent results and can be transplanted safely with currently available techniques. Policies should be developed to promote and implement the use of this special donor by early referral by the medical and nursing teams.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The author declares no conflict of interest.

References

1. Health Resources & Services Administration. Organ Donation and Transplantation Statistics. Available online: https://data.hrsa.gov/topics/health-systems/organ-donation#:~{}:text=HRSA\T1\textquoterights%20Health%20Systems%20Bureau%20manages,the%20most%20appropriate%20therapeutic%20treatment (accessed on 20 March 2022).
2. Martin, L.W.; Gonzalez, L.L.; West, C.D.; Swartz, R.A.; Sutorius, D.J. Homotransplantation of both kidneys from an anencephalic monster to a 17-pound boy with Eagle-Barrett syndrome. *Surgery* **1969**, *66*, 603–607. [CrossRef] [PubMed]
3. United Network for Organ Sharing Meeting in Philadelphia USA; UNOS, Philadelphia, PA, USA. Personal communication, 2002.
4. El-Moussaoui, K.; Bakkali, S.; Ghrab, J.; Baidada, A.; Kharbach, S.A. Anencephaly: A Case Report and Literature Review. *Gynaecol. Obstet. Case Rep.* **2021**, *7*, 005–007.
5. Coffey, V.P.; Jessop, W.J. A Study of 137 Cases of Anencephaly. *Brit. J Prev. Soc. Med.* **1957**, *11*, 174–183. [CrossRef] [PubMed]
6. Coffey, V.P.; Jessop, W.J. A three years study of anencephaly in Dublin. *Irish J. Med. Sci. (1926–1967)* **1953**, *33*, 391–413. [CrossRef]

7. Pierce, E.S. Could zoonosis cause some cases of anencephaly? Mycobacterium avium subspecies paratuberculosis inhaled from aerosolized dairy cow manure and the Washington State rural anencephaly cluster. *Dly. Herds Wash.* **2018**, 1–23. [CrossRef]
8. Welch, G.W.; Stumpf, D.A. The Infant with anencephaly. *N. Engl. J. Med. Aug.* **1990**, *323*, 615.
9. Taloubi, L.M.; Rhouda, H.; Belachcen, A. An overview of plants causing teratogenicity: Fenugreek (Trigonellafoenum-graecum). *Intern. J. Pharm. Sci. Res.* **2013**, *4*, 516–519.
10. Dickman, H.; Fletke, K.; Redfern, R.E. Prolonged unassisted survival in an infant with anencephaly. *BMJ Case Rep.* **2016**, *2016*, bcr2016215986. [CrossRef]
11. Chescheir, N. ACOG Committee on Practice Bulletins. Neural tube defects. *Int. J. Gynaecol. Obst.* **2003**, *83*, 123–133.
12. Parker, S.E.; Mai, C.T.; Canfield, M.A.; Richard, R.; Wang, Y.; Meyer, R.Y.; Anderson, P.; Mason, C.A.; Collins, J.S.; Kirby, R.S.; et al. Updated national birth prevalence estimates for selected birth defects in the United States 2004–2006. *Birth Defects Res. A Clin. Mol. Teratol.* **2010**, *88*, 1008–1016. [CrossRef]
13. Goldstein, R.B.; Filly, R.A. Prenatal diagnosis of anencephaly: Spectrum of sonographic appearance and distinction from amniotic fluid syndrome. *Am. J. Roentgenol.* **1988**, *151*, 547–550. [CrossRef] [PubMed]
14. Melnick, M.; Myrianthopoulos, N.C. Studies in neural tube defects. II. Pathologic findings in a prospectively collected series of anencephalic. *Am. J. Genet.* **1987**, *16*, 797–810. [CrossRef] [PubMed]
15. UK Donation Ethics Committee; Academy of Medical Royal College. Organ Donation from Infants with Anencephaly Guidance from the UK Donation Ethics Committee Feb 2016. Available online: http://www.aomrc.org.uk/wp-content/uploads/2016/06/Organ_Donation_-infants_anencephaly_020316-2.pdf (accessed on 10 November 2022).
16. Lagay, F. Considering Organ Donation by Anencephalic Neonates. *JAMA J. Ethics* **2004**, *6*, 364–367.
17. Shewmon, D.A.; Capron, A.M.; Peacock, W.J. The use of anencephalic infants as organ source. A critique. *JAMA* **1989**, *26*, 1773–1781. [CrossRef]
18. Shinnar, S.; Arras, J. Ethical issues in the use of anencephalic infants as organ donors. *Neurol. Clin.* **1989**, *7*, 729–743. [CrossRef] [PubMed]
19. Harrison, M.R. Organ procurement for children: The anencephalic fetus as donor. *Lancet* **1986**, *2*, 1383–1386. [CrossRef]
20. Zapitelli, M.; Ambalavanan, N.; Askenazi, D.J.; Moxey-Mims, M.M.; Kimmel, P.L.; Star, R.A. Developing neonatal acute kidney injury research definition: A report from the NIDDK neonatal AHI workshop. *Pediatr. Res.* **2017**, *82*, 569–573. [CrossRef]
21. Sutherland, M.R.; Gubhaju, L.; Moore, L.; Kent, A.L.; Dahlstrom, J.E.; Horne, R.S.; Hoy, W.E.; Bertram, J.F.; Black, M.J. Accelerated maturation and abnormal morphology in the preterm neonatal kidney. *J. Am. J. Soc. Nephrol.* **2011**, *22*, 1365–1374. [CrossRef]
22. Rodriguez, M.M.; Gomez, A.H.; Chandar, J.I.; Duara, S.; Abithol, C.L.; Zillerruelo, G.E. Histomorphometric analysis of post natal glomerulosclerosis in extremely preterm neonatal kidney. *Pediatr. Dev. Pathol.* **2004**, *7*, 17–25. [CrossRef]
23. Vieux, R.; Hascoet, J.M.; Merdariu, D.; Fresson, J.; Guilermin, F. Glomerular filtration rate reference values in very preterm infants. *Pediatrics* **2010**, *125*, e1186–e1192. [CrossRef]
24. Mulhari-Stark, E.; Burkharaat, G.J. Glomerular filtration Rate Estimation Formula for Pediatric and Neonatal Use. *J. Pediatr. Pharmacol. Ther.* **2018**, *23*, 424–431.
25. Branagan, A.; Costigan, C.S.; Stack, M.; Slagle, C.; Molloy, E.J. Management of Acute Kidney Injury in Extremely Low Birth Weight Infants. *Front Pediatr.* **2022**, *19*, 867715. [CrossRef] [PubMed]
26. Sulemanji, M.; Vakili, K. Neonatal renal physiology. *Semin. Pediatr. Surg.* **2013**, *22*, 195–198. [CrossRef] [PubMed]
27. Hinchliffe, S.A.; Sargent, P.H.; Howard, C.V.; Chan, Y.F.; van Veltzen, D. Human intrauterine renal growth expressed in absolute number of glomeruli assessed by the disector method and Cavalieri principle. *Lab. Investig.* **1991**, *64*, 777–784.
28. Hoy, W.E.; Douglas-Denton, R.; Hughson, M.D.; Cass, A.; Johnson, K.; Bertram, J.F. A stereolological study of glomerular number and volume: Preliminary findings in a multiracial study of kidneys at autopsy. *Kidney Int. Suppl.* **2003**, *63*, S31–S37. [CrossRef] [PubMed]
29. Kalaycioglu, A.; Karaca, M.; Can, I.; Nuri Keles, O.; Ucuncu, Y.; Gungogdu, C.; Uyanik, A.; Unal, B. Anencephalic fetuses can be an alternative for kidney transplantation: A stereological and histological investigation. *Histo. Histopathol.* **2010**, *25*, 413–422.
30. Nyengaard, J.R. Stereologic methods and their application in kidney research. *Am. J. Nephrol.* **1999**, *10*, 110–112. [CrossRef]
31. Rosenbaum, D.M.; Korngold, E.; Teele, R.L. Sonographic Assessment of Renal Length in Normal Children. *AJR* **1984**, *142*, 467–469. [CrossRef]
32. Konug, O.L.; Ozdemir, A.; Akkays, A.; Erbas, G.; Celik, H.; Isik, S. Normal Liver, Spleen and Kidney Dimensions in Neonates, Infants and Children: Evaluation with sonography. *AJR* **1998**, *171*, 1693–1698.
33. Cheong, B.; Muthupillai, R.; Rubin, M.; Flamm, D. Normal values for Renal Length and Volume as Measured by Magnetic Resonance Imaging. *Clin. J. Am. Soc. Nephrol.* **2007**, *2*, 38–45. [CrossRef]
34. Brain Injury Association of America. Available online: www.biusa.org/brain-injury/about-brain-injury/children-what-toexpect/incidence (accessed on 21 September 2022).
35. Jones, A.; Jacovi, M.; Dizon, Z.; October, T. Public perception of pediatric organ donation and brain death using crowdsourcing. *Crit. Care Med.* **2019**, *47*, 192. [CrossRef]
36. Rodrigue, J.R.; Cornell, D.L.; Howard, R.J. Pediatric organ donation: What factors most influence parents' donation decisions? *Pediatr. Crit. Care Med.* **2008**, *9*, 180–185. [CrossRef] [PubMed]
37. Manara, A.R.; Murphy, P.J.; O'Callaghan, G. Donation after circulatory death. *Brit. J. Anaesth.* **2011**, *108*, 1108–1121. [CrossRef] [PubMed]

38. Thuong, M.; Ruiz, A.; Evrard, P.; Kulper, M.; Boffa, C.; Ahktar, M.Z. New classification of donation after circulatory death donors definitions and terminology. *Transpl. Int.* **2016**, *29*, 749–759. [CrossRef] [PubMed]
39. Hart, A.; Smith, J.M.; Skeans, M.A.; Gustafson, S.K.; Stewart, D.E.; Cherikh, W.S. OPTN/SRTR 2014 annual data report. *Am. J. Transplant.* **2016**, *16*, 11–46. [CrossRef]
40. Nakagawa, T.S.A.; Mou, S.S. The process of Organ Donation and Pediatric Donor Management. In *Pediatric Critical Care*; Elsevier Inc.: Amsterdam, The Netherlands, 2016.
41. Curley, M.A.; Harrison, C.H.; Craig, N.; Lillehei, C.W.; Mitchell, A.; Laussen, P.C. Pediatric staff perspectives on organ donation after cardiac death in children. *Pediatr. Crit. Care Med.* **2007**, *8*, 212–219. [CrossRef]
42. Summers, D.M.; Johnson, R.J.; Allen, J.; Fugle, S.V.; Colbert, D.; Watson, C.J.; Bradly, J.A. Analysis of factors that affect outcome after transplantation of kidneys donated after cardiac death in the UK: A cohort study. *Lancet* **2010**, *376*, 1303–1311. [CrossRef]
43. Litaka, K.; Martin, L.W.; Mc Enery, P.T.; West, C.D. Transplantation of cadaver kidneys rom anencephalic donors. *J. Ped.* **1978**, *93*, 216–220.
44. Kinnaert, P.; Vereerstraeten, P.; Van Asperen de Boer, F.; Struyven, J.; Frederic, N.; Verhas, M.; Schoutens, A. Transplantation of both kidneys of an anencephalic newborn to a 23-year-old patient. *Euro. Urol.* **1981**, *7*, 373–376. [CrossRef]
45. Ohshima, S.; Ono, Y.; Kinukawa, T.; Matsuura, O.; Tsuzuki, K.; Itoh, S. Kidney transplantation from an anencephalic baby: A case report. *J. Urol.* **1984**, *132*, 546–547. [CrossRef]
46. Gutierrez Caldaza, J.L.; Baena, M.V.; Laguna, G.; Arrieta, J.; Rodrizuez, J.; Moncada, A. En bloc kidney and bladder transplantation from an anencephalic donor into an adult recipient. *J. Urol.* **1987**, *138*, 125–126.
47. Holzgreve, W.; Beller, F.K.; Buchholz, R.; Hansmann, M.; Kohler, K. Kidney Transplantation from Anencephalic Donors. *N. Engl. J. Med.* **1987**, *316*, 1069–1070. [CrossRef] [PubMed]
48. O'Rourke, K. Kidney transplantation from anencephalic donors. *N. Engl. J. Med.* **1987**, *317*, 960–961. [PubMed]
49. Nezamuddin, N.; Adiku, W.; Farsi, H.; al-Fayez, S.; Shaheen, F.; Bayrakdar, A.; Haddad, R. En-bloc anencephalic cadaver donor renal transplantation. *Transpl. Proc.* **1989**, *21*, 1934–1935.
50. Gutierrez-Carreno, R.; Lehne-Garcia, C.; Ohjeda-Duran, S.; Mendieta-Hernandez, M.; Vasquez-Salas, L.; Moreno-Aranda, J.; Trejo-Bellido, J.; Vargas-Rosendo, R.; Gutierrez-Carreno, A. Renal transplants from anencephalic donors. *Bol. Med. Hosp. Infant. Mex.* **1989**, *46*, 808–811. [PubMed]
51. Peabody, J.; Emery, J.R.; Ashwal, S. Experience with Anencephalic Infants as Prospective Organ Donors. *N. Engl. J. Med.* **1989**, *321*, 344–350. [CrossRef]
52. Gomez-Campdera, F.J.; Robbles, N.R.; Anaya, F.; Rengel, M.; Albertos, J.; Luque, A.; Vallejo, J.L.; Valderrabano, F. Kidney transplantation from anencephalic donors. Report of 5 cases and a review of the literature. *Child Nephrol. Urol.* **1990**, *10*, 143–149.
53. Bailey, L.L.; Nehlsen-Cannarella, S.L.; Doroshow, R.W.; Jacobson, J.G.; Martin, R.D.; Allard, M.W.; Hyde, M.R.; Bui, D.; Petry, E.L. Cardiac Allotransplantation in Newborns as Therapy for Hypoplastic Left Heart Syndrome. *N. Engl. J. Med.* **1986**, *315*, 949–951. [CrossRef]
54. Wijetunga, I.; Pandanaboyana, S.; Farid, S.G.; Ecuyer, C.; Lewington, A.; Hostert, L.; Attia, M.; Ahmad, N. Neonatal kidney donation and transplantation: A realistic strategy for the treatment of end-stage renal disease. *Arch. Dis. Fetal. Neonatal. Ed.* **2014**, *99*, F518–F519. [CrossRef]
55. Nakagawa, T.; Zollinger, C.; Chao, J.; Hill, R.; Angle, S.; Pilot, M. Anencephalic Infants as Organ Donors After Circulatory Death. *Transplantation* **2017**, *101*, S60. [CrossRef]
56. Wijetunga, I.; Ecuyer, C.; Martinez-Lopez, S.; Jameef, M.; Baker, R.J.; Welberry Smith, M.; Pater, C.; Weston, M.; Ahmad, N. Renal transplant from infants and neonatal donors is a feasible option for the treatment of end-stage renal disease but is associated with increased early graft loss. *Am. J. Transplant.* **2018**, *18*, 2679–2688. [CrossRef] [PubMed]
57. Nghiem, D.D. En bloc transplantation of kidneys from donors weighing less than 15 kg into adult recipients. *J. Urol.* **1991**, *145*, 14–17. [CrossRef] [PubMed]
58. Nghiem, D.D. Role of bench angiography in the assessment of pancreaticoduodenal (PD) graft blood supply. *Transplant Proc.* **2018**, *30*, 256–258. [CrossRef] [PubMed]
59. Miller, L.C.; Lum, C.T.; Bock, G.H.; Simmons, R.L.; Najarian, J.S.; Mauer, S.M. Transplantation of the adult kidney into the very small child. Technical considerations. *Am. J. Surg.* **1983**, *145*, 243–247. [CrossRef]
60. Markus, B.H.; Hakala, T.R.; Tzakis, A.; Mitchell, S.; Marino, I.; Gordon, R.; Duquesnoy, R.J.; Starzl, T.E. Kidney transplantation in Pittsburgh: Experience and innovations. In *Clinical Transplants*; Terasaki, P., Ed.; UCLA Tissue Typing Laboratory: Los Angeles, CA, USA, 1987; Chapter 14; pp. 141–154.
61. Opelz, G. Influence of recipient and donor age in pediatric renal transplantation. Collaborative Transplant Study. *Transpl. Int.* **1988**, *1*, 95–98. [CrossRef] [PubMed]
62. Pelletier, S.J.; Guidinger, M.C.; Merion, R.M.; Englesbe, M.J.; Wolfe, W.A.; Magee, J.C.; Sollinger, H.W. Recovery and Utilization of Deceased Donor Kidneys from Small Pediatric Donors. *Am. J. Transplant* **2006**, *6*, 1646–1652. [CrossRef]
63. Swift, E.; Parthasarathy, P.; Redjepova, O.; Satodia, P. The Challenge to Fetal Organ Donation. A Case Report. Available online: https://fetalmedicine.org/abstracts/2018/var/pdf/abstracts/2018/2936.pdf (accessed on 18 July 2022).
64. Nghiem, D.D. Pull-Through Ureteroneocystostomy for Very Small En Bloc Kidney Transplants from Donors Weighing $\leq$ 5 kg. *Uro* **2022**, *2*, 102–108. [CrossRef]
65. Carrel, A. Transplantation in mass of the kidneys. *J. Exp. Med.* **1908**, *1*, 98–140. [CrossRef]

66. Kato, T.; Selvaggi, G.; Burke, G.; Giango, G.; Hattorld, M.; Cosalbeze, R.; Tsakis, A. Partial bladder transplantation with en bloc kidney transplantation-the first case report of a "bladder patch technique" in a human. *Am. J. Transplant.* **2008**, *8*, 1060–1063. [CrossRef]
67. Nghiem, D.D.; Schlosser, J.D.; Nghiem, H.G. En bloc Transplantation of Infant Kidneys: Ten-Year Experience. *J. Am. Coll. Surg.* **1998**, *186*, 402–407. [CrossRef]
68. Nghiem, D.D.; Hsia, S.; Carpenter, B.J.; Chao, S.H.; Marcus, R.J.; Palumbi, M.A.; Paul, C.L.; Kijanka, B.A.; Breckenridge, M.A.; Meleason, D.F.; et al. Renal Transplantation at Allegheny General Hospital General Hospital with Special Reference to the Use of Extreme Age Cadaveric Donor Kidneys. In *Clinical Transplant Chapter 19*; Terasaki, P.I., Cecka, J.M., Eds.; UCLA Tissue Typing Laboratory: Los Angeles, CA, USA, 1994; pp. 213–218.
69. Sureshkumar, K.K.; Reddy, C.S.; Nghiem, D.D.; Sandroni, S.E.; Carpenter, B.J. Superiority of pediatric en bloc renal allografts over living related donor kidneys. A long-term functional study. *Transplantation* **2006**, *82*, 348–353. [CrossRef] [PubMed]
70. Hirukawa, T.; Suzuki, H.; Nijimura, F.; Fukagawa, M.; Kakuta, T. En bloc Cadaver Kidney Transplantation From a 9 month-old donor to an Adult Recipient: Maturation of Glomerular Size and Podocyte in the Recipient. *Transplant. Direct* **2017**, *3*, e130–e142. [CrossRef] [PubMed]
71. Shimamura, J.; Morrison, A. A progressive glomerulosclerosis occurring in partial five-sixths nephrectomized rats. *Am. J. Pathol.* **1975**, *79*, 95–102. [PubMed]
72. Brenner, R.M.; Cohen, J.A.; Milford, E.L. In renal transplant, one size may not fit all. *Am. Soc. Nephrol.* **1992**, *33*, 162–169. [CrossRef]