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Renal replacement therapies in neonates: Issues and ethics

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A B S T R A C T

Chronic irreversible kidney disease requiring dialysis is rare in the neonate. Many such neonates are diagnosed following antenatal ultrasound with congenital abnormalities of the kidneys and urinary tract. There is an increased incidence of prematurity and infants that are small for gestational age. Given the natural improvement in renal function that occurs in the neonatal period, some with extremely poor renal function may, with careful management of fluid and electrolytes, be kept off dialysis until the creatinine reaches a nadir when a definitive plan can be made. There is a very high incidence of co-morbidity and this affects survival, which for those on dialysis is about 80% at five years. The multiple and complex ethical issues surrounding the management of these very young children are discussed.

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1. Introduction

The numbers of neonates requiring dialysis for chronic, irreversible kidney disease (CKD) are extremely low. Most registries present data for infants aged <2 years rather than neonates, for which numbers vary from seven to 12 per million age-related population. For example, that would be 20–30 at any time in the UK, with a population of 64 million, and 100–150 in the USA, with a population of 325 million. The European Society for Pediatric Nephrology and European Renal Association–European Dialysis and Transplant Association (ESPN/ERA-EDTA), the International Pediatric Peritoneal Dialysis Network (IPPN), and Australia and New Zealand (ANZDATA) registries have looked to specifically identify neonates within the infant group. A total of 264 neonates started chronic dialysis in 32 countries between 2000 and 2011. They represented around 18% of infants aged <2 years on dialysis in both eastern and western Europe but only 6.8% in Australia and New Zealand. In Japan, neonates were 8.6% of dialysed children aged <5 years [1]. These variations are likely to be related to local attitudes to termination of pregnancy following detection of a life-threatening renal abnormality, to attitudes to acceptance of such infants on to renal replacement therapy (RRT) programmes, and to resources available. Commencement of dialysis is also dependent on local experience and policies.

2. The neonatal kidney

Kidney development commences at five weeks of gestation. By weeks 6–9 the first glomeruli are formed and by week 36 nephrogenesis ceases, by which time there are the definitive numbers of around one million glomeruli in each kidney. Therefore the premature infant's kidneys are especially vulnerable to insult during the period of ongoing nephrogenesis. A bladder is detectable by week 9, and thereafter fetal urine contributes to >90% of amniotic fluid volume.

Ninety percent of infants pass urine within 24 h. Plasma creatinine reflects maternal levels at birth, and may rise in the first three weeks of life in premature infants due to tubular reabsorption. Plasma bicarbonate may be lower than expected as the renal threshold for bicarbonate is 18–20 mmol/L, rising to 24–26 mmol/L by age 1 year.

The neonate is predisposed to acute kidney injury (AKI). Fluid homeostasis is compromised because the kidneys receive only 15–20% of the cardiac output (25% in adults). The glomerular filtration rate (GFR) in the premature infant is 10–15 and 15–20 mL/min/1.73 m^2 in the term infant. These values double over the first two weeks after birth and then rise progressively to adult values of 80–120 mL/min/1.73 m^2 by age 1–2 years. Maximum urine concentrating capacity is also low at birth (up to 600 mOsm/kg) and increases over the first two months of life and then progressively over the first year of life [2].

3. Factors predisposing the neonate with chronic kidney disease to acute kidney injury

The proportion of babies requiring RRT that is premature or small for gestational age (SGA) is higher than that in babies of the

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equivalent gestation without CKD. Up to one-quarter is born prematurely and one-fifth is SGA [3–5] compared to around 8% in otherwise normal pregnancies [6]. These infants are therefore subject to all the complications associated with low birth weight, including chronic lung disease and developmental abnormalities, as well as the potential for insult to the ongoing nephrogenesis that continues up to 36 weeks of gestation.

Premature and term neonates with CKD may have pulmonary hypoplasia, which occurs in association with oligohydramnios or grossly enlarged kidneys and are therefore more prone to birth asphyxia and chronic lung disease over and above the effects of prematurity. They are more likely to develop AKI due to exaggerated tubular electrolyte and water losses and dehydration, accompanying comorbidities, urinary tract obstruction, surgery, sepsis, and the use of nephrotoxic drugs, which are all factors that occur more frequent in the neonate with CKD [7].

4. Frequent diagnoses in neonates requiring long-term renal replacement therapy

The majority of children in whom a need for RRT presents in the neonatal period have congenital abnormalities of the kidneys and urinary tract (CAKUT). Some children may have autosomal recessive polycystic kidney disease (ARPKD), with very large kidneys. Renal tubular dysgenesis is a rare cause. About 50% of these infants are diagnosed antenatally. This offers the benefits of antenatal counseling of families about the potential outcome of the pregnancy, and immediate optimization of medical intervention after birth. On the other hand we are not yet proficient at predicting outcome on the basis of antenatal scans. Clearly the absence of kidneys is going to lead to a very bad prognosis, and such fetuses may not survive or termination may be offered. However, fetal ultrasound and urinary investigations have not consistently been linked to outcome, and even oligohydramnios, which is believed to be a hard sign of poor outcome, is not always predictive [8]. Therefore the family has to live with uncertainty about the future for their infant throughout the pregnancy.

5. When to start dialysis

A clear-cut need to start dialysis is unusual, unless there is renal or tubular agenesis or anuria. Many infants, especially those with CAKUT, have ongoing urine production and, with attention to fluid and electrolyte balance and nutrition, may be kept without dialysis until they have recovered from respiratory complications or show improvement in kidney function, which would be expected in all neonates during the first few weeks of life. Some babies may show a surprising improvement in renal function, and 10% of neonates that have started dialysis are able to stop [1]. The extra time gained enables growth, postponing the technical difficulties associated with small size and allowing easier dialysis access. Indeed some babies may not need dialysis at all. It is widely held that patients in renal failure need fluid restriction. However, for the child with CAKUT, this is rarely the case and is likely to worsen the situation. This is illustrated in case 1.

5.1. Case 1

A male fetus was diagnosed at 22 weeks with a left kidney with increased echogenicity, a right multicystic kidney and a thick-walled bladder (Fig. 1). There was oligohydramnios. He was born by spontaneous delivery at 33 weeks of gestation, with a birth weight of 1.7 kg. He did not require ventilation. He underwent urethral catheterization, and was given intravenous (IV) fluids as 0.45% saline with dextrose, initially at 80 then increasing to 100 mL/kg/day. He was oliguric. His sodium and bicarbonate fell and his creatinine, potassium and urea rose progressively to reach 700 μmol/L (8 mg/dL), 7.0 mmol/L (7 mEq/L) and 40 mmol/L (24,000 mg/dL) respectively by age 2 weeks. Dialysis was not thought to be a possibility by the referring centre. He was referred to another centre for a second opinion. He was found to be dehydrated. He was started on IV normal saline, feeds at full requirement, and sodium and bicarbonate supplements. He began to gain weight and his creatinine fell progressively to 200 μmol/L (2.25 mg/dL), with accompanying improvement in his potassium and urea levels. Dialysis was not necessary.

6. Prognostic indicators

In addition to birth weight, gestation, and pulmonary hypoplasia, there are other factors that impact on outcome and therefore influence the decision of the physician whether or not to recommend dialysis (Box 1). The most important of these is comorbidity. Estimates suggest that this is present in as many as 73% of neonates requiring RRT [1,9] and covers a complete spectrum of disabilities. Studies have linked comorbidity to poor outcome, with a five-fold higher mortality risk over five years of renal replacement therapy in those with neurological disease [1] and an increase in mortality over 20 years of more than seven-fold [9]. Those with CAKUT do better than those with ARPKD, in whom pulmonary hypoplasia and liver disease can cause serious comorbidity. The presence of long-term oliguria is also an adverse factor for outcome, as it is at all ages. Finally, management of infants on RRT is laborious and is not possible without the full commitment of the family and the medical team [10].

7. Resources

The costs of RRT are substantial, and are particularly high in the infant, both in the short term because of the need for frequent reviews of the dialysis regimen, feeds and medications; and in the long-term because of the requirement for a lifetime of therapy. Such costs inevitably affect a country's ability to treat these infants, depending on available resources. Table 1 shows IPPN data on the number of children taken on to RRT programs according to the gross national income per capita of the country. When this falls

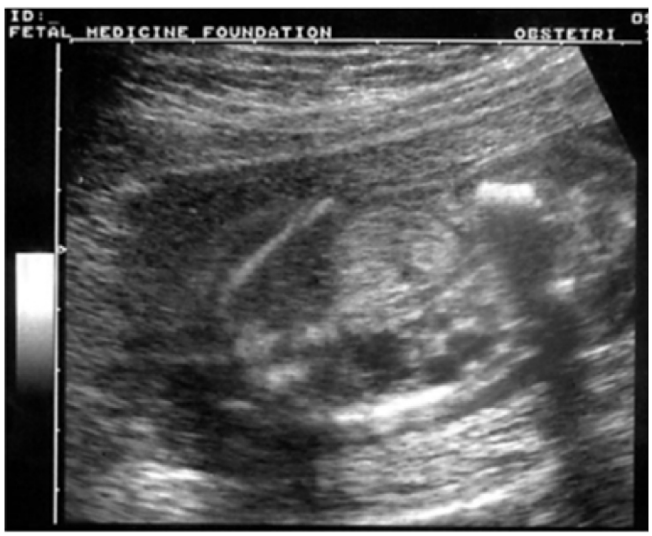

Fig. 1. Antenatal ultrasound of a male fetus with a left kidney with increased echogenicity and a right multicystic kidney.

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Box 1
Factors affecting the prognosis of neonates needing renal replacement therapy.

Birth weight and gestation
Comorbidity
Aetiology of chronic kidney disease
Pulmonary hypoplasia
Oliguria/residual renal function
Family circumstances

below US$12,000, numbers of young children on RRT programmes fall significantly [11].

8. Survival of neonates on renal replacement therapy

Survival of very young children on dialysis is good and similar to that in older children when the effects of comorbidity are removed [9]. Fig. 2 shows the survival to age 5 years for the recent combined registries neonatal data between the years 2000 and 2011 [1], of US neonates and infants aged 1 month to 2 years in the era 1992–2005 [12], and a further analysis over three years in the USA for the era 2000–2012 [13]. The first thing to notice is that the survival of the neonates is similar to that of the infants aged 1 month to 2 years. The second is that the recent cohorts seem to have a better survival than the older ones, being 80% at age 5 years in the combined registries and also 80% at age 3 years in the USA. This had been 60% at age 5 years between 1992 and 2005, and this improvement is statistically significant [13]. However, the data should be viewed in the context that, like all registries, we do not know its completeness. It is likely that not only have the sickest children been excluded, but also that others with equally poor renal function may not have been included because of purposeful delay in initiating dialysis. The importance of this is that the missing data will influence the survival and causes of death in the cohorts that have been treated. Despite that, these data are helpful when counseling families about the prognosis for their child.

9. Heath-related quality of life

The outcome for the future quality of life for the newborn is another important question that families want answered. In a follow-up study of 41 young adults who had CKD stage 4/5 from infancy, 13% were on dialysis and 87% had a transplant at the time of the analysis; 54% had comorbidities. Lower health-related quality of life (HRQoL) scores were associated with comorbidities, being on dialysis, more than one treatment modality change, and being of short stature. Compared to a healthy, age-matched population, employment rates and educational were levels similar although HRQoL was lower in physical and social role limitation and general health perception. The scores were comparable to those needing RRT in later childhood [14]. Again, these data are very helpful when counseling families about the prognosis for their child.

Table 1
Decreasing gross national income per capita adversely affects the number of children aged <3 years accepted on to renal replacement therapy programmes [11].

Age at start of dialysis	Gross national income in US$000s per capita			
	>28	18–28	12–18	<12
<1 year	19	18	16	2
1–3 years	11	15	11	6

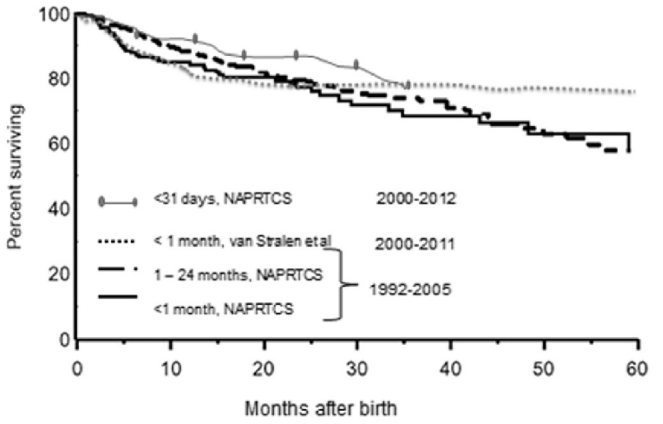

Fig. 2. Survival of neonates and infants during two different eras in the USA (NAPRTCS: North American Pediatric Renal Trials and Collaborative Studies) and European Society for Pediatric Nephrology and European Renal Association–European Dialysis and Transplant Association (ESPN/ERA-EDTA), Australia and New Zealand (ANZDATA), and Japanese registries.

10. Ethical aspects of renal replacement therapy in infants

The decision as to whether to start RRT in the neonate can be fraught with complex ethical issues, especially in the child with comorbidities that also affect their survival and quality of life, and in parts of the world with limited resources. The European Paediatric Dialysis Working Group Guidelines, drawn up in 2014, state that when deciding whether to start RRT in the infant, comorbidities, predicted quality of life for the child and family, availability of resources (both medical and those of the family support structure), and the prognosis and possibility for future transplantation should be taken into consideration. The guidelines also recommend that parents of the affected child should be actively involved in the decision-making process [15]. Even with these guidelines it may be difficult to decide whether RRT is the best and most appropriate next step, and agreement between the parents and the medical team is not always achieved.

11. Views of pediatric nephrologists and the multidisciplinary team on starting renal replacement therapy in neonates and infants

Even in well-resourced countries there differences of opinion among pediatric nephrologists as to whether RRT is justified in all newborns who require it, and especially so in those with comorbidity [16]. In a survey of pediatric nephrology teams in Canada, Germany, Japan, the UK, and the USA in 2010, only 30% of pediatric nephrologists said that they would offer RRT to all neonates and 50% to all infants aged 1–12 months. The most influential factor in rejecting RRT for infants was comorbidity, which was the most frequent cause given for the reason not to treat. Fifty percent believed that parents should never refuse RRT for children aged 1–12 months, compared with 27% for neonates. Interestingly, nurses were more likely to believe that parents have the right to refuse RRT for infants [16].

In a more recent survey of pediatric nephrologists undertaken at the ESPN annual meeting in 2012, 12% said they would recommend RRT to all neonates with end-stage kidney disease (ESKD) and 5% said they would not offer it at all. However, for infants aged 1–12 months, opinions changed such that 31% would recommend RRT for all and no one stated that they would not offer it at all to any infant. Seventy-two percent thought it was usually acceptable for parents to refuse treatment for their newborn, whereas only 50% thought this is acceptable for those aged 1–12 months. The reasons

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for this difference in attitude to neonates in comparison to infants are not clear, and are in contrast to a recent eloquent discussion of ethical issues in the neonate, which makes very forcefully the argument that a decision to treat a neonate differently from an older child is unjustified [17]. Factors affecting the decision-making process were ranked in order of importance as follows: coexistent serious medical abnormalities the highest, followed by anticipated morbidity for a child, the family's right to decide, the doctor's/medical staff's right to decide, the presence of oliguria, family socio-economic status, and finally hospital/government budget constraints (personal data, F. Emma, L. Rees).

12. The role of ethics in decision-making

So, can ethics help us when faced with these circumstances? Ethics are a set of principles that distinguish between right and wrong. However, rarely is there one single 'right' way to do something. Ethics therefore provide a means of evaluating and choosing between different, often competing, options and are about analyzing values rather than facts.

The UK Royal College of Paediatrics and Child Health has produced guidelines on withholding and withdrawing life-saving treatment. The guidelines state that treatments, now and in the future, must be "in the child's best interests". They also state that "It is ethically acceptable to limit treatment that is not in a child's best interests" [18]. An action or intervention is defined as being in the child's best interests if the benefits outweigh burdens, if there is acceptable minimization of harm, if the child is treated fairly and justly, and, in the case of older children, if there is respect for as much autonomy (capacity for self-directed, informed choice) as the individual is capable of exercising. However, sources of ethical conflict are rarely that simple to resolve.

The French Neonatal Society states that assessment of the child's future quality of life, rather than its chances of survival, is the determinant of whether life-saving treatment is reasonable or unreasonable, i.e. in the child's best interests [19]. The Nuffield Council on Bioethics (UK) definitions of quality of life include survival without life support, life outside of hospital, ability to develop relationships, and ability to gain pleasure from life [20].

13. Sources of ethical conflict

As well as withholding or withdrawing life-sustaining therapies, there are additional situations when ethical conflicts may arise. Among these are: when application of clinical facts alone cannot determine what should be done; when there is disagreement about the right course of action; and when application of moral principles leads to conflict. Below are some examples of such ethical conflicts.

13.1. Case 2: application of clinical facts alone cannot determine what should be done

Failure of peritoneal dialysis (PD) access has made PD an impossibility for the future, and the only option is hemodialysis (HD).

A baby with an antenatal diagnosis of posterior urethral valves with severe oligohydramnios at 22 weeks was delivered following spontaneous onset of labor at 32 weeks. The birth weight was 2.4 kg. A PD catheter was inserted on day 3 of life due to anuria. There was leakage around the catheter and it had to be changed on day 5 of life. The baby developed necrotizing enterocolitis with gangrenous gut and severe peritonitis, requiring catheter removal. The only option was HD in this small infant whose peritoneum was unlikely to recover for use in the future. Should HD be recommended or should treatment be withdrawn at this stage?

13.2. Case 3: there is disagreement about the right course of action

Removal of kidneys in a child with congenital nephrotic syndrome or ARPKD, considered to be life-saving by the medical team, conflicts with parental views.

Termination was recommended following an antenatal diagnosis at 20 weeks of gestation of bilateral, large, bright kidneys with oligohydramnios due to ARPKD. The parents rejected termination. The infant was delivered at 36 weeks of gestation with a birth weight of 2.8 kg. He required resuscitation and high frequency oscillation. The kidneys filled the abdomen but the urine output was good (Fig. 3). The baby could not be maintained without ventilation because of diaphragmatic compression by the kidneys. The parents refused the doctors' recommendation for nephrectomies.

13.3. Case 4: application of moral principles leads to conflict – treatment of the child with severe comorbidity

An infant was born with multiple complex abnormalities including abnormal vision and hearing, cardiac abnormalities, microcephaly, and bilateral renal abnormalities. The child needed dialysis but the medical staff believed that this would not be appropriate. The parents wanted all possible treatments to proceed.

The law may be unhelpful in these situations. Although deliberate intention to cause or hasten a patient's death (euthanasia) is illegal, decisions about withholding or withdrawing treatment are less black and white, and ethical conflicts require professionals to make value judgments to resolve them. Many hospitals have "ethical committees" whose purpose is to lead and aid discussions about difficult cases, but they are for guidance only rather than formal decision-making.

14. Is withholding or withdrawing life-sustaining treatments ever acceptable?

The French Neonatal Society Recommendations state that "Withholding or withdrawing life-sustaining treatment may be acceptable, and unreasonable therapeutic obstinacy is condemned. To withhold or withdraw a life-sustaining treatment can be justified when the intention is to cease opposing, in an unreasonable manner, the natural course of a disease" [19]. A particularly difficult concept for affluent areas is the role of resources in the decision making process. Clearly there are countries that do not have the resources to support such expensive treatments. In 1995 UK

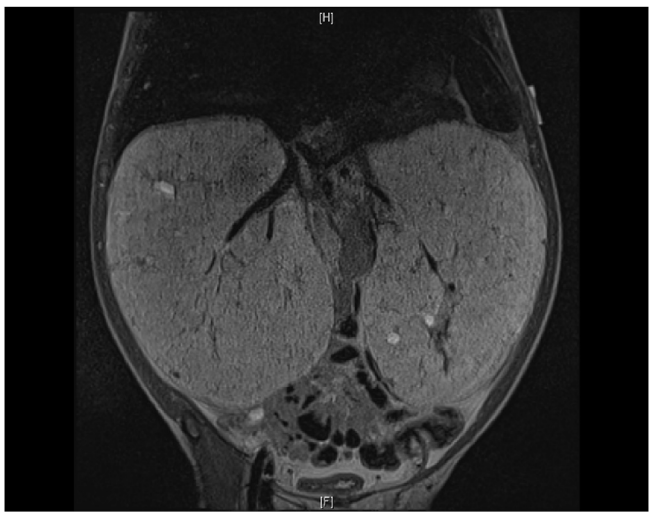

Fig. 3. Nephromegaly in a child with autosomal recessive polycystic kidney disease, causing respiratory depression (case 3).

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neonatologists wrote that "It may well be ethical to withdraw [or withhold or limit] treatment on the grounds that greater benefit could be achieved by using the resources in other ways" [21]. Nearly 20 years later the debate continues, but there is no country in the world that does not have to ration treatments in some ways.

15. Conflicts in decision-making responsibilities

There is no international concordance about who should be responsible for decision-making in ethical disputes, and opinions vary between countries. The US Presidential Commission for the Study of Bioethical Issues is an advisory panel of the nation's leaders in medicine, science, ethics, religion, law, and engineering. The Bioethics Commission seeks to identify and promote policies and practices that ensure scientific research, health care delivery, and technological innovation are conducted in a socially and ethically responsible manner. The commission has divided ethical issues about treatment management into three neat categories: those that are clearly beneficial, when treatment should be provided even if the parents do not consent; those that are clearly futile, when treatment should not be provided, even if parents want it; and those when outcomes are ambiguous or uncertain, when parents should be the final determiners of course of action [22]. Unfortunately, although these guidelines are very neat they are over-simplistic and it is rarely possible to make such distinctions. The French Neonatology Society recommends that although the parents must be involved in the decision process so that they form an alliance with the health care team, any important decision affecting the patient's life calls for individual medical responsibility [19].

16. Are neonates treated differently from infants, older children or adults?

In 1995 it was written that "Clinicians frequently give young patients more chances to revive from and survive their illnesses than they offer to older, particularly elderly, patients. Clinicians also seem more willing to impose greater burdens on children with fewer chances of success than adults" [23]. Conversely, a more recent review stated that "Dialysis is not a therapy that doctors feel to be morally obligatory in most cases. Whereas many doctors recommend dialysis for most infants with ESKD, most are willing to provide only palliative care if that is what the parents want" [17]. The conflicting nature of these statements reflects the individuality of each case such that generalizations are neither possible nor appropriate.

17. Conclusion

The number of neonates requiring RRT is small. However, their outcome is good, and equal to that of infants, providing that they do not suffer from comorbidities. Ethical issues are complex and every chosen pathway must be in the child's best interests.

Conflict of interest statement

None declared.

Funding sources

None.

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