Seminars in Fetal & Neonatal Medicine xxx (2016) 1–5

Contents lists available at ScienceDirect

Seminars in Fetal & Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Renal replacement therapies in neonates: Issues and ethics

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Keywords:
Neonate
Kidney
Chronic kidney disease
Dialysis
Survival
Renal replacement therapy
Ethics

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.

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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http://dx.doi.org/10.1016/j.siny.2016.11.001
1744-165X/

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

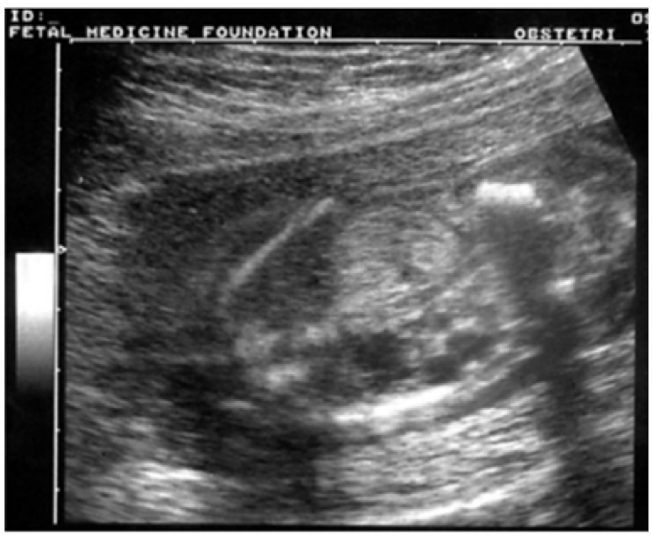

Fig. 1. Antenatal ultrasound of a male fetus with a left kidney with increased echogenicity and a right multicystic kidney.

Please cite this article in press as: Rees L, Renal replacement therapies in neonates: Issues and ethics, Seminars in Fetal & Neonatal Medicine (2016), http://dx.doi.org/10.1016/j.siny.2016.11.001