

ORIGINAL ARTICLE

Outcome of reaching end stage renal failure in children under 2 years of age

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Aims: To determine the outcome of children who reach end stage renal failure before the age of 2 years.

Methods: Using a retrospective questionnaire, 10 years' data were collected from the paediatric nephrology units in Britain and Ireland (1988 to 1997, follow up 1.3-11.5 years).

Results: A total of 192 children were identified; 0.31/million/year. Most had congenital or inherited conditions, and there were more boys. Latterly, half were diagnosed antenatally. Ninety per cent were dialysed initially, most using home peritoneal cyclers, some by haemodialysis through central lines. Five per cent recovered sufficient function to come off dialysis. Most required tube feeding (often gastrostomy) and erythropoietin; some needed growth hormone. A total of 56% received a transplant (2% without prior dialysis) at (medians) 2.6 years and 12.3 kg. The 2 and 10 year survival of first kidneys was 78%. Growth improved following transplantation. Fourteen per cent died because treatment was not started or was withdrawn. Most had particularly complex renal conditions, or additional major non-renal diagnoses. Typically, decisions not to treat were made mutually between clinicians and families. When treatment was continued, 71% survived, and few had serious non-renal conditions. Most attended normal schools, and by 6 years of age, less than 10% still required dialysis. Infants starting treatment under and over 1 month of age fared equally well.

Conclusions: By school age, most infants treated for end stage renal failure will have a functioning transplant, reasonable growth, and will attend a normal class, regardless of the age at which they commence treatment. Treatment is seldom sustained in children who have serious additional medical conditions. It is reasonable to treat infants with uncomplicated renal failure.

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Early reports of treating very young children with end stage renal failure were discouraging.¹⁻⁴ Graft losses and mortality were high, and developmental outcomes sometimes poor.⁵ Despite substantial recent improvements in outcome for transplanted children, younger ones have continued to fare worse,⁶⁻⁹ though more optimistic views have been expressed recently.¹⁰ More controversially, increasing numbers of babies with end stage renal failure are now being treated. Paediatric nephrologists worldwide hold strikingly differing views about whether this is appropriate.¹¹ They are only two thirds as likely to treat a baby aged under 1 month as an older infant, and are twice as likely to accept a parent's decision to refuse treatment.

Few infants with end stage renal failure were treated in Britain or Ireland until the late 1980s, but all the regional centres have participated since then. The British Association for Paediatric Nephrology felt it was important to review their outcome nationally (some of these infants from one centre having been reported previously).¹²⁻¹⁵ We consider every child

under 2 that reached end stage renal failure during a 10 year period, whether they were treated or not.

PATIENT AND METHODS

Data were collected from all the regional paediatric nephrology units in Britain and Ireland on every child under the age of 2 who had reached end stage renal failure from January 1988 to December 1997 inclusive. The total population rose from 60.7 to 62.6 million during those 10 years (mean 61.7 million). Information was acquired during early 1999, giving a follow up period of 1.3-11.5 years. All cases were reviewed, including children that recovered sufficient function to come off dialysis later, and those who were not treated. All units could identify every affected infant, but few could identify women who chose to have a termination of pregnancy because an antenatal scan had predicted infantile renal failure.

The questionnaire sought the renal (and other) diagnoses, whether it had been predicted antenatally, the age at reaching end stage disease, the modality and difficulties of dialysis, and

Table 1 The annual numbers of children that reached end stage renal failure under the age of 2, the numbers treated and not treated, and the percentage diagnosed antenatally

	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	All
Total	18	19	16	17	21	20	21	18	15	27	192
Treated	18	17	14	16	19	17	21	17	13	25	177
Not treated	0	2	2	1	2	3	0	1	2	2	15
Antenatally diagnosed (%)	25	23	23	27	28	39	44	47	36	54	-

Table 2 The diagnoses of children that reached end stage renal failure before the age of 2 during the 10 years 1988–97 inclusive

Diagnosis	Treated	Not treated	Antenatal diagnosis (%)
Renal dysplasia	57	7	40
Posterior urethral valves	44	0	84
Finnish congenital nephrotic syndrome	26	2	8
Cortical necrosis	12	1	
Diffuse mesangial sclerosis and nephrotic syndrome (2 Drash)	8	1	
Recessively inherited polycystic kidney disease	6	2	25
Prune belly syndrome	4	0	50
Renal vein thrombosis	4	0	
Nephronophthisis	3	0	
Haemolytic uraemic syndrome	3	0	
Hyperoxaluria type 1	2	2	
Interstitial nephritis	2	0	
Wilms' tumour	2	1	
Cloaca, aortic thrombosis, glomerular fibrosis, glomerulonephritis	1 each	0	
Total	177	15	

whether erythropoietin, growth hormone, or nasogastric or gastrostomy feeding were given. The age and weight at transplantation, patient and graft survival, and the most recent graft function, weight, and height were recorded. For dialysed children, the current weight and height were noted. The educational status of survivors was reported for older children, and predicted for children attending nursery. The age and cause of death was recorded where appropriate. When treatment was not started or withdrawn, the reason and mechanism of the decision was sought.

RESULTS

Incidence

A total of 192 children under the age of 2 reached end stage renal failure, or 0.31/million annually. There was little suggestion of an increasing incidence (table 1). Congenital and

inherited diagnoses predominated (table 2). The high ratio of boys to girls (2.6:1) was mainly caused by the frequency of sex specific conditions (posterior urethral valves, Drash and prune belly syndromes in boys, cloacas in girls), and the male preponderance of reflux associated dysplasia. Excluding these, the ratio was 1.3:1.

Initially, about a quarter were diagnosed antenatally, rising to about half latterly (table 1). Dilated urinary tracts were detected most easily (table 2); every boy with posterior urethral valves was identified in the last four years.

One unit caring for 3.1 million people reported that four women had opted for termination of pregnancy because their fetus had posterior urethral valves and severe oligohydramnios. No other data were available. Figure 1 summarises the outcomes for all the children, and each subgroup is considered separately below.

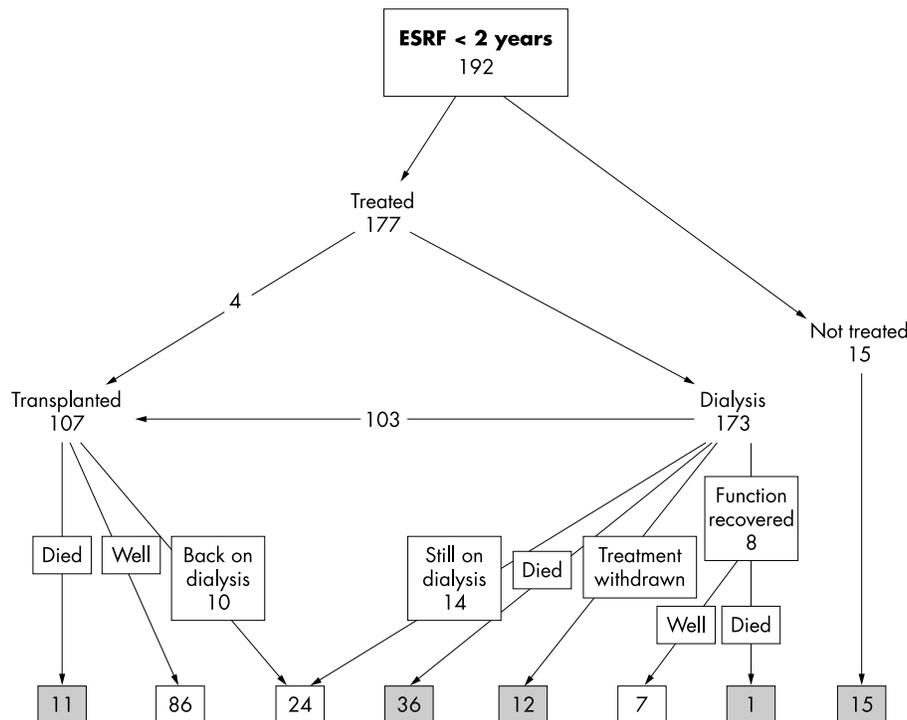


Figure 1 The outcome of 192 children who reached end stage renal failure under the age of 2 in the UK. In the bottom line the figures in plain boxes represent live children, and those in shaded boxes children that have died.

Table 3 Percentages of children on dialysis that received nasogastric or gastrostomy tube feeding, growth hormone, or erythropoietin during each year of the study

	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997
Nasogastric feeds	73	47	39	43	50	38	48	44	50	56
Gastrostomy feeds	7	27	39	21	39	44	38	50	42	36
Not tube fed	20	27	23	36	11	19	14	6	8	8
Growth hormone	27	13	15	7	5	19	14	19	25	*
Erythropoietin	47	50	46	71	89	88	91	75	82	84

Not all the tube feeding percentages add up to 100 because of rounding.

*The growth hormone numbers are not given for 1997 because the follow up period is too short.

Children dialysed

Of 177 children given renal replacement, 173 were dialysed initially, and four were transplanted first. Some babies were born with end stage renal failure; 15% were dialysed within a fortnight, and over a third within four months.

Most dialysed children had complications of treatment; 81% had automatic cycling peritoneal dialysis initially, and 10% had chronic ambulatory peritoneal dialysis. Peritonitis was their commonest complication, and was the reason that 23% changed to haemodialysis. Virtually all of the children initially haemodialysed had access through central venous lines, many of which blocked or became infected; 33% were converted to peritoneal dialysis. The initial mode of dialysis was determined by centre preference rather than specific clinical indications.

Most dialysed children were also tube fed. This proportion increased with time, especially those with gastrostomies (table 3). Erythropoietin treatment also increased; over three quarters received it latterly (table 3). The variations in growth hormone use in the first few years were caused by children participating in a national therapeutic trial. Subsequently, about one fifth received growth hormone (table 3).

Many dialysed children were failing to thrive. In 64% their height, and in 36% their weight was below the 2nd centile: height standard deviation score (mean (SD)) -2.73 (1.80); weight standard deviation score -1.56 (1.52).

Eight children recovered sufficient renal function to come off dialysis. One died suddenly at 20 months. The others were well, aged 3.4–11.3 years, but had declining renal function; two have since been transplanted.

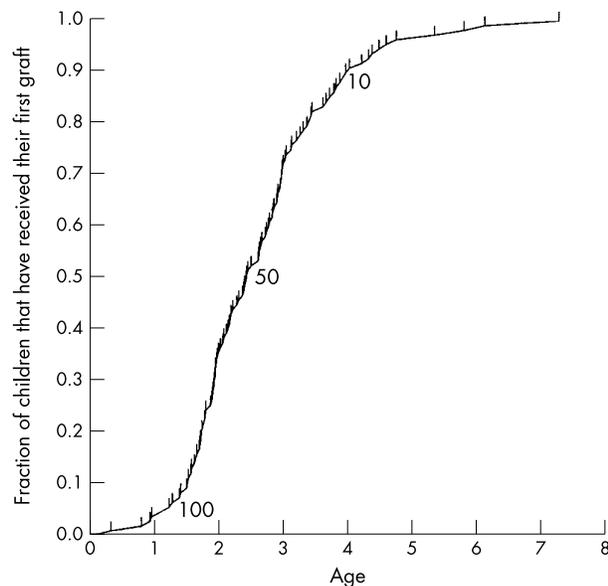


Figure 2 Kaplan-Meier plot of children who reached end stage renal failure before the age of 2, showing the age at which the transplanted children received their first graft. The numbers of cases available for analysis are indicated by the vertical bars and numbers.

Children transplanted

A total of 107 children were transplanted, 103 with prior dialysis. The median age at transplantation was 2.6 years (90% between 1.2 and 4.7), and the median weight was 12.3 kg (90% between 7.4 and 17.4). Only four were transplanted before their first birthday, and 87% were transplanted between 1 and 4 years (fig 2).

Twenty two kidneys were lost: eight from rejection, two from haemorrhage, and one each from sepsis, oxalosis, cyclosporin nephrotoxicity, and respiratory distress, possibly triggered by cyclosporin. Eight were lost from venous thrombosis, four in the first two years, and four during the last eight. First graft survival was 78% at 2 and 10 years, with about half the lost kidneys surviving for less than one month (fig 3). Thirteen children received a second kidney: seven are functioning, one had a successful third graft, two are back on dialysis, and three have died. Altogether, 11 transplanted children died (fig 3).

All eleven (10%) kidneys donated by a parent are functioning well. By contrast, 11 of 96 children died after a cadaveric graft (89% patient survival, $p = 0.29$, Fisher's exact test), and 24 lost the kidney (75% graft survival, $p = 0.05$).

The heights and weights of children with transplants were on higher centiles than those of dialysed children (fig 4). Their height was below the 2nd centile in 17% (height standard deviation score (mean (SD)) -1.14 (1.28)), and their weight was above the 98th centile in 8% (weight standard deviation score 0.01 (1.56)).

Two transplanted children had major non-renal medical problems from birth, one with transposition of the great

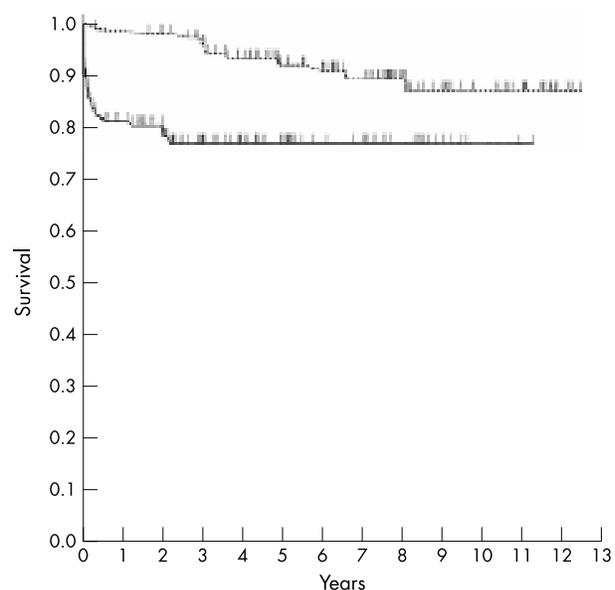


Figure 3 Patient and kidney survival curves after the first graft into 107 children who reached end stage renal failure before the age of 2. The numbers of cases available for analysis are indicated by the vertical bars.

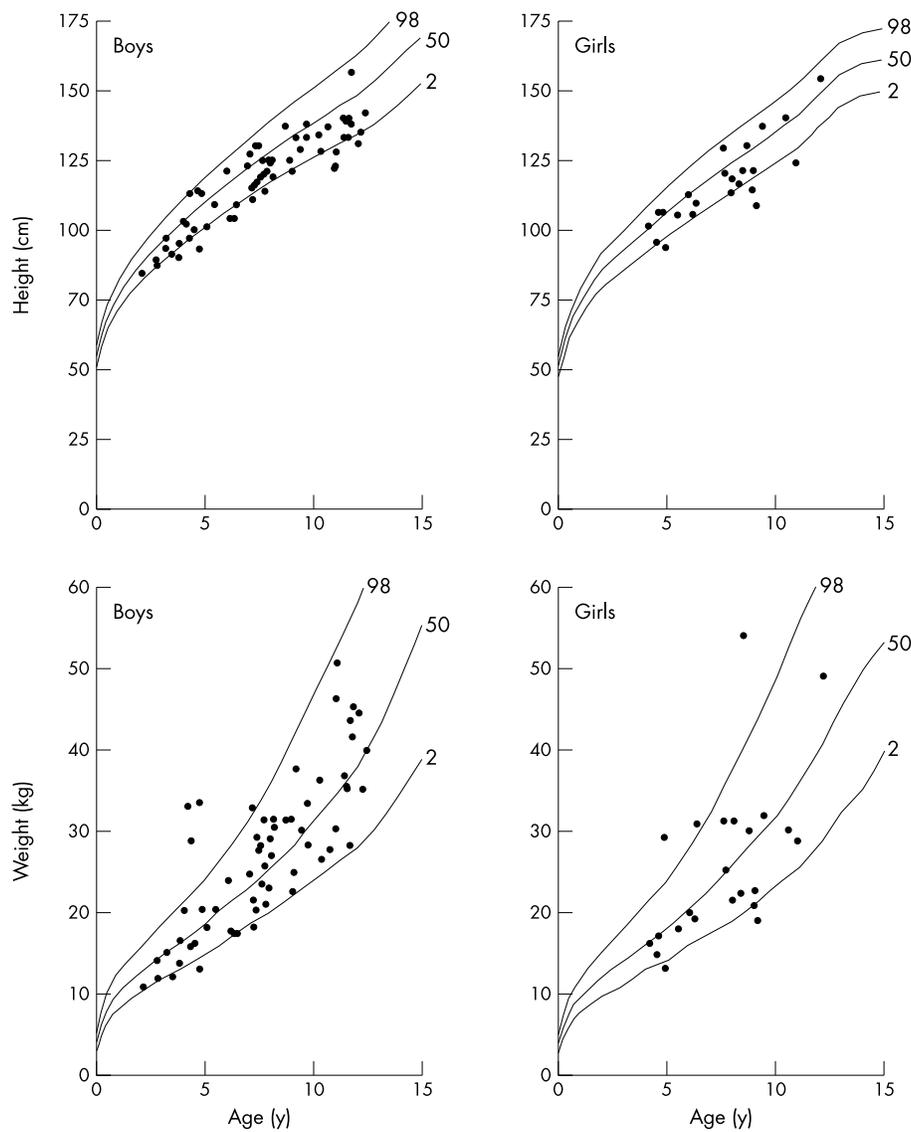


Figure 4 The most recent height and weight values for 63 boys and 23 girls who currently have a functioning transplant, compared to the normal 2nd, 50th, and 98th centiles.

arteries (since surgically corrected) and one with VATER syndrome who will require surgical stomas to provide continence. Two developed problems later, one with sensory-neural deafness, and one with a mild hemiparesis. One transplanted child was repeatedly salt poisoned by his mother, but sustained no long term physical harm.

Children who died

Deaths fell into three groups. Some babies were not offered renal replacement, some were treated and had this withdrawn, and some died despite treatment (fig 5).

Children not treated

Fifteen infants (8%) were not treated, and died. There was no trend with time (table 1). In 14, the parents and clinical team agreed on the no-treatment option. One family wanted their baby dialysed, but the clinicians felt this was not feasible because he also had a large diaphragmatic hernia; he died very quickly.

Several non-treated babies had diagnoses with potentially complicated management problems, two with Finnish nephrotic syndrome, and two with hyperoxaluria-1 which typically requires kidney and liver transplantation. Four had

serious additional diagnoses: microcephaly and blindness, Down's syndrome with a congenital heart defect, Alagille's syndrome, and extensive necrotising enterocolitis. Two children had complications linked to the renal diagnosis: severe pulmonary hypoplasia, and a preterm infant with Drash syndrome and a Wilms's tumour. Seven babies died within a month, seven more by six months, and one at 18 months (fig 5, curve a).

Treatment withdrawal

Twelve children (7% of those treated) subsequently had dialysis withdrawn. These, too, were usually mutual decisions by parents and clinical teams. Several children had additional medical problems, either recognised at birth (Down's syndrome), or later, including cystic fibrosis, cerebral infarction following hypovolaemia, major seizures, global delay and microcephaly, with and without blindness, and a combination of hypertrophic cardiomyopathy, cerebellar hypoplasia, and autism. Some children had treatment withdrawn because the renal failure management alone had produced an unacceptably poor quality of life. Most of these children died under 1 year of age, and all died before 3 years (fig 5, curve b).

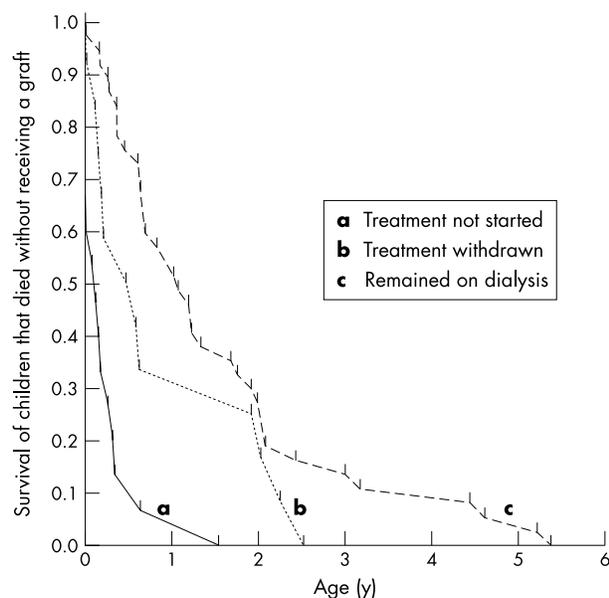


Figure 5 Survival curves for children who reached end stage renal failure before the age of 2, and died (a) because treatment was not started, (b) because treatment was withdrawn, or (c) despite remaining on dialysis.

Table 4 Numbers and percentages of the 192 children reaching end stage renal failure under 2 years of age, according to their survival and current treatment

Patient status	Number	%
<i>Alive</i>		
Recovered function	7	4
Functioning transplant	86	45
On dialysis	24	13
Total	117	61
<i>Dead</i>		
Never treated	15	8
Recovered function, but died later	1	1
Dialysis treatment withdrawn	12	6
Died while on dialysis	36	19
Transplanted, then died	11	6
Total	75	39

Not all the percentages add up to 100% because of rounding.

Deaths despite treatment

Forty seven children (27% of those treated) died on dialysis ($n = 36$) or following transplantation ($n = 11$). In four cases, death was a result of non-renal diagnoses specifically associated with infantile renal disease: two had pulmonary hypoplasia, and two developed liver failure with recessively inherited polycystic kidney disease. Most deaths had similar causes to those seen in older patients receiving renal replacement.

Table 5 Current treatment modalities of patients alive at the time of the study, according to age

Treatment modality	Age groups of patients (y)											
	0-2		2-4		4-6		6-8		8-10		Over 10	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Dialysis	5	(100)	10	(53)	4	(17)	2	(8)	1	(5)	2	(9)
Recovered function	0	(0)	1	(5)	2	(9)	1	(4)	1	(5)	2	(9)
Transplanted	0	(0)	8	(42)	17	(74)	23	(88)	19	(90)	19	(83)

Not all the percentages add up to 100% because of rounding.

Most dialysis deaths were infective, including septicaemia following Tenckhoff or central venous line infections. Fluid imbalance caused one case each of cerebral and pulmonary oedema. Hyperkalaemia killed four children, probably caused a cardiac arrest in another, and may have contributed to four cases labelled as sudden infant death syndrome. One boy with inferior vena cava and renal vein thrombosis at birth had a pulmonary embolus at 3 months. Another boy died from septic shock and haemorrhage after a fundoplication. Figure 5, curve c, shows the ages at death of dialysed children.

Among transplanted children, four deaths occurred within one week, from haemorrhage, heart failure, septicaemia, and hyperkalaemia following hyperacute rejection. Later deaths were from gastrointestinal bleeds ($n = 2$), immunosuppression linked infections (one each, cytomegalovirus and *Pneumocystis carinii*), transplant artery haemorrhage following angioplasty ($n = 1$), recurrence of oxalosis (in one child given only a kidney), and one unexplained sudden death. Figure 3 shows their survival curve.

Overview of the survivors

Table 4 summarises the present status of all the children. The 117 survivors are 61% of the total cases, 66% of those treated, and 71% of those where it was continued. The currently dialysed children are younger than those with transplants (mean 3.6 v 7.6 years); it is likely that several of these will be transplanted eventually. Cross sectional data on the survivors (table 5) show that most preschool children, but very few schoolchildren are dialysed.

Of the 105 surviving children old enough to assess, 91 attended a normal school, or were expected to, but 16 of these required a classroom helper's support. Fourteen children attended special schools, 11 for their developmental and emotional needs, and three for physical reasons.

Effect of age at starting treatment

Table 6 compares the outcomes of children treated in the first month of life with those treated up to a year, or during their second year. A significantly larger proportion of children treated early went on to recover function. The higher mortality among children dialysed before 1 month did not reach statistical significance. Fewer children that started treatment early have a transplant compared to those dialysed from their second year of life ($p < 0.001$), probably because the data were collected when they were younger (though they are also slightly younger and lighter when transplanted). The age of starting treatment made no difference to graft survival, or post-transplant height or weight standard deviation scores, or to those requiring special education.

DISCUSSION

We show that each year in Britain and Ireland, one child aged under 2 years will reach end stage renal failure per three million people. It is perhaps surprising that the incidence was so stable. We had expected it to gradually rise because several British paediatric nephrologists had expressed reservations about treating babies at a national conference within a year of

Table 6 Outcomes compared according to the age that the children commenced renal replacement

Patient status	Age at reaching end stage renal failure		
	<1 month (n=31)	1–12 months (n=76)	1–2 years (n=70)
Of those treated:			
Recovered function (%)	16	3*	1**
Died (%)	45	37	26
Transplanted (%)	36	55	77***
Of those transplanted:			
Age at transplant (years)	2.1	2.4	2.8†
Weight at transplant (kg)	11.0	11.8	12.8†
Duration of transplant (years)	3.8	3.4	4.1
Current graft survival (%)	91	76	80
Height standard deviation score	-1.67	-1.55	-1.33
Weight standard deviation score	-0.83	-0.26	-0.04
Of surviving children at time of study:			
% attending a special school	20	27	14

The symbols indicate that there are statistically significant differences between the children commencing renal replacement within that age group and the children treated under 1 month of age. * χ^2 , $p < 0.05$; ** χ^2 , $p < 0.02$; *** χ^2 , $p < 0.001$.
†Mann-Whitney U, $p = 0.05$; ‡Mann-Whitney U, $p < 0.01$.

the period studied. We believe that the figures are reliable; the paediatric nephrology centres are confident of their complete recall, and it is unlikely that infants will have been diagnosed in district hospitals and not referred, especially latterly. It is a pity that there was so little data on termination of pregnancy because anecdotal experience suggests that it may have a major impact, halving the number of babies born with severe renal impairment as a result of posterior urethral valves in one centre. The improvement in antenatal diagnosis makes this option available to more women. A prospective study would be valuable.

Many more infants were offered renal replacement than might be expected, given the views expressed by paediatric nephrologists worldwide in 1998.¹¹ In almost every case the decision on whether to treat was made mutually by parents and the clinical team. Generally, dialysis was started unless the infants had an additional serious medical diagnosis. Several had treatment withdrawn after extra clinical problems emerged, and there were few children with multiple medical problems among the long term survivors. The fact that peritoneal dialysis was the modality of choice was similar to other reports,^{9, 16} and not a surprise, given the fact that haemodialysis necessitates technically demanding hospital based treatment. Further, adequate clearances are seldom produced in small children,¹⁷ probably because of the widespread use of double lumen vascular access lines which limit the blood flow that can be achieved.¹⁸

Managing end stage renal failure in young children involves much more than just dialysis. As well as dietary modifications, fluid restrictions, and oral medications, other treatments are increasingly used, including overnight gastrostomy feeding, and subcutaneously administered erythropoietin and growth hormone. Though these undoubtedly improve general health and nutrition, they can make life arduous for the children and their families alike. Despite that, few families opted to withdraw treatment unless there were other adverse factors. The higher than expected incidence of sudden infant deaths among dialysed children was probably caused by acute biochemical disturbances, such as hyperkalaemia. These, and the fluid imbalances implicated as a cause of some of the morbidity and mortality, probably reflect the near impossibility for families of constantly having to maintain strict regimens for their small children.

Survival in these children is lower than in those who reach end stage later. However, some cases should be excluded from

our calculations, namely those whose deaths result from a careful decision not to start or to withdraw treatment, or from a specific infantile renal failure syndrome. Survival among the remainder compares closely with that in older children. The fall in graft thrombosis rates during the decade was probably mainly related to vascular anastomoses being created more proximally. Our first graft survival rates compare well to those for North American children who were transplanted when significantly older, but during a similar time period. Our two and 10 year kidney survival rates of 78% were almost identical to the five year North American figure for live donors,¹⁹ and much higher than their cadaveric graft figure of 64%.²⁰ One centre has reported almost 100% two year graft survival in children weighing less than 15 kg at transplantation.²¹

The fact that most of our survivors already have a functioning transplant before they start school minimises the social impact of their illness compared to those children still needing dialysis and associated therapies. Also, our children show significant catch up growth. This is encouraging but not surprising; most children's growth deteriorates still further after transplantation, except for the youngest.^{9, 19, 20} It has been argued that dialysing rather than transplanting under the age of 2 gives a lower mortality, but that transplanting soon after that maximises the growth potential.⁹ This is the strategy that has been followed in Britain and Ireland, with some success. Our assessment of their social and educational functioning is crude but encouraging, with most children coping well at normal schools. Ultimately, a detailed psychological assessment of every child and a review of their educational achievements would be very valuable.

Many paediatric nephrologists believe that only older infants with end stage renal failure should be treated, and not those under a year, and certainly not those under one month.¹¹ Our data provide no evidence to support their view. Though the mortality is higher in babies treated from under 1 month of age, most that recover function are also from this group. These babies are ones who are believed to be in end stage irrecoverable renal failure, but who subsequently improve sufficiently to come off dialysis. It is clearly difficult, but extremely important, to make a confident diagnosis of end stage in the very young; eight of our cases only needed temporary dialysis, but would have died if they had not been treated. Babies that are ultimately transplanted have the same graft function and survival, and better growth than those from the older groups. It is, therefore, illogical to plan a renal

replacement policy based on the patient's age at entry. Many physicians have a fear of doing harm by enabling the survival of children whose only reward is to suffer, either by undergoing physical discomfort and pain, or by being severely handicapped by a poor quality of life. The clinical policy pursued in Britain and Ireland has been to treat children of any age unless they have overwhelmingly serious additional diagnoses, or seem to their parents and the clinical team to be suffering excessively. The quality of life of the survivors appears to justify this approach.

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