Chapter 14: Report of the Paediatric Renal Registry

Summary

The demographics of the paediatric established renal failure (ERF) population have changed little over the past few years though there is a slow but steady growth in the total number of paediatric patients being cared for. There remains a disproportionately large prevalence and take-on rate of patients from the Asian subcontinent. The distribution of diseases causing ERF in childhood is similar to that given in previous reports. There are, however, significant differences in the distribution of these diseases across the ethnic groups with three autosomal recessive conditions accounting for 19.2% of all Asian patients presenting with ERF.

Primary focal segmental glomerulosclerosis is the single most common glomerular disease causing ERF in the paediatric population. This is a difficult condition to manage and carries an increased mortality compared to the ERF population as a whole. Cross-sectional analysis also shows that fewer patients with this condition have a functioning renal allograft.

An antenatal diagnosis of renal problems is often made. However, even with serious disorders that lead to ERF early in life, a routine 18–20 week anomaly scan is not guaranteed to detect the disorder. Overall, just 50% of patients with severe renal disorders leading to ERF in early life, who were born live and did not have major problems from pulmonary hypoplasia, were diagnosed antenatally.

Of patients presenting with chronic kidney disease progressing to ERF, 50% do so within two years of presentation, leaving little time for intervention with regard to growth and nutrition. For the remaining 50% there is a fall in height standard deviation score (SDS) from presentation to ERF, though this is limited to those presenting in the first 4 years of life. Nutrition was not apparently a problem with no significant change in weight SDS from presentation to ERF. Some of the height loss can be explained by patients with metabolic or syndromic diagnoses in the group of patients presenting in the first 4 years of life.

Five year survival of the paediatric ERF population is 92%. Death is more common in patients requiring dialysis within the first year of life, where the 5 year survival is just 66%.

Of the prevalent cohort of patients, 76% have a functioning allograft, with 15% on peritoneal dialysis and 9% on haemodialysis. Of those with functioning allografts, 81% are cadaveric. For patients on peritoneal dialysis just 13% are on CAPD. Significantly fewer patients from ethnic minority groups have a functioning renal allograft compared to White patients ($p < 0.0001$). For those on dialysis, significantly more patients from ethnic minority groups are on haemodialysis rather than peritoneal dialysis ($p = 0.0279$).

For patients with renal allografts, overall renal function as assessed by the calculation of predicted GFR from the serum creatinine is excellent. The mean predicted GFR for the cohort was 60 ml/min/1.73 sq.m. There was a slow fall in mean GFR with the longevity of the graft. The most accurate prediction of GFR from the serum creatinine was with the use of the Schwartz formula and a constant of 40 for all ages and genders. Cross-sectional analysis of the population, did not show any reduction in GFR for those patients who had abnormal bladders and were either on clean intermittent catheterisation (with or without bladder augmentation) or had a urinary diversion.

Allograft rejection episodes remain common within the first year of transplantation with between 25 and 50% of patients suffering rejection episodes. Thereafter, rejection remains a problem affecting between 10 and 15% of patients for each year of graft life.

The majority of late rejection episodes are biopsy proven, whereas a third of patients in the first year post-transplant, are still managed on the basis of a clinical diagnosis. Immunosuppressive regimes vary tremendously within the prevalent patient cohort. The majority of patients are managed with triple immunosuppression, consisting of a calcineurin inhibitor, steroids and either Azathioprine or Mycophenolate (76.7%). There has been a trend towards increasing usage of Tacrolimus with fewer patients now being started on Cyclosporin. Rejection episodes are increasingly being treated with Tacrolimus and Mycophenolate. Only a small number of patients received anti-lymphocyte or anti-thymocyte globulins.

Introduction

Whilst continuing to make progress in the installation of systems to allow continuous data acquisition from paediatric nephrology centres, the Paediatric Registry has maintained a system of annual data return to allow analysis of the population. Within this report, the demographics of the paediatric ERF population are explored, paying particular note to age and ethnic distribution. For the first time, the Registry has also been able to look at differences in the ethnic distribution of the diseases causing ERF.

Having achieved six years of continuous data collection, it is now possible to analyse mortality within the paediatric ERF population. Presentation of patients is re-explored for the first time since the 1999 report and the role of antenatal diagnosis is also examined.

Included in this report is a breakdown of the current treatment of patients with particular attention paid to the differences in management of ethnic minority groups. There is a special focus on primary focal segmental glomerulosclerosis being the single most common glomerular disease in childhood and there is a close examination of renal function, allograft rejection and immunosuppression in the current cohort of transplanted patients.

Paediatric ERF population

The demographics of the paediatric ERF population has changed little since the last report. Figure 14.1 shows the paediatric ERF population as it stood on the 1st April 2002. Within England, Wales and Northern Ireland virtually all patients under the age of 16 years are looked after within one of the 12 paediatric nephrology tertiary referral centres. Within Scotland, patient capture by the tertiary unit is less complete. However, for the purposes of this report, prevalence and take-on rate statistics were calculated using all the patients up to the age of 16 years. This allows for the inclusion of more patients than with the previous cut off point of 15 years and also allows the population to be broken down into four age bands each covering 4 years for comparison.

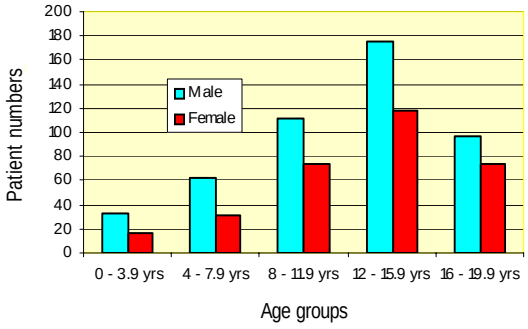

Figure 14.1. Age and sex distribution of the UK paediatric ERF population

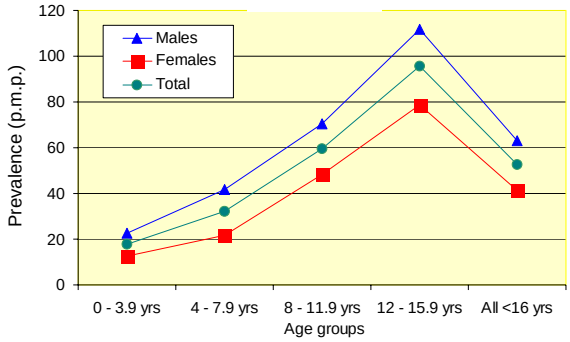

Figure 14.2. Prevalence of ERF in the UK under 16 year old population

The total number of patients being cared for in the 13 UK paediatric units in April 2002 was 804. Of these, 11 patients were actually above the age of 20 years and have therefore not been included in any further calculations of demographic statistics. 793 patients were below the age of 20 years, of whom 760 were below 18 years of age and 622 were below 16 years of age. This data is set out in Table 14.1. It is clear from this that although the majority of the workload of paediatric units is with patients under the age of 16 years, patients in late teenage and early adulthood constitute 21% of prevalent patient total and thus contribute significantly to unit activity. The age of transfer of patients from paediatric to adult units varies significantly. Decisions about patient transfer to adult units are generally made on an individual basis and will depend upon many factors, particularly, the presence or absence of co-morbid features, the patients' developmental and academic status and the duration of time the patient has been cared for within the paediatric setting. One final feature which influences transfer is the availability of dialysis spaces within adult units.

The prevalence of ERF in paediatric patients in the UK is shown in Table 14.2. Population statistics for this table have been taken from data available from the UK National Census conducted in 2001 and published at the www.statistics.gov.uk site. It can be seen that the total childhood population is estimated at 11.9 million and the prevalence of ERF overall stands at 52.4 per million of the childhood population. Looking at each age band individually, it can be seen that males outweigh females. The overall male to female ratio is 1.53:1. There is a steady increase in the prevalence of ERF all the way up to 16 years of age. This data is shown graphically in Figure 14.2.

The calculation of take-on rate is made difficult by the small numbers of new patients presenting, particularly when this is broken down further into different age-groups. For the purposes of this analysis, only the new patients taken on from April 1996 until April 2002 have been included. The take-on rates have then been calculated using average yearly figures over this 6 year period to eliminate problems of year to year variability.

Table 14.1. Age and sex distribution of the paediatric ERF population

Age Group	Males	Females	Total (%)
0–1.9 yrs	10	4	14 (1.7)
2–3.9 yrs	22	13	35 (4.4)
4–7.9 yrs	63	31	94 (11.7)
8–11.9 yrs	112	73	185 (23.0)
12–15.9 yrs	176	118	294 (36.6)
16–19.9 yrs	97	74	171 (21.3)
Total	480	313	793

Table 14.2. Prevalence of ERF in the UK under 16 year old population

	UK Population (millions)			ESRF Population			Prevalence (p.m.p)		
Age Group	**Males**	**Females**	**Total**	**Males**	**Females**	**Total**	**Males**	**Females**	**Total**
0–3.9 yrs	1.4100	1.3431	2.7531	32	17	49	22.70	12.66	17.80
4–7.9 yrs	1.5016	1.4277	2.9293	63	31	94	41.96	21.71	32.09
8–11.9 yrs	1.5915	1.5163	3.1078	112	73	185	70.37	48.14	59.53
12–15.9 yrs	1.5775	1.5013	3.0788	176	118	294	111.57	78.60	95.49
All <16 yrs	6.0806	5.7884	11.8690	383	239	622	62.99	41.29	52.41
UK Population	28.5812	30.2080	58.7892				13.40	7.91	10.58

Table 14.3 shows the take-on rate per million childhood population, divided according to age-group. The overall take-on rate is similar to that in other countries at about 7.7 per million of the childhood population. Take-on rate for patients presenting with ERF between the ages of 0–4 years and between the ages of 8–12 years is similar to this overall average. The take-on rate for patients between the ages of 12–16 years is higher at 11.3 per million childhood population, whilst there is a lower take-on rate of just 4.2 per million childhood population for patients between the ages of 4–8 years. This data is shown graphically in Figure 14.3 where the dip in the 4–8 year old group is quite apparent. This also shows the variability between the sexes with males being grossly over-represented in the 0–4 year old group.

The raw statistics for the patients being taken onto the ERF programme over the 6 year period from 1996–2002 are shown in Table 14.4. It can be seen that there is significant year to year variability in the total numbers presenting. It is also clear that there is an increasing number of patients between the ages of 16 and 20 years of age starting ERF management within paediatric units. Figure 14.4 shows the number of patients taken on over the past 6 years graphically. The variability from year to year seems to relate to a variable number of males accepted onto the programme, rather than any great variability in the number of females taken on. Although there is a lot of year to year oscillation, the slope of the trend line is clearly slowly rising.

Although older patients are being accepted onto the paediatric ERF programme, the relatively high take-on rate for patients between the ages of 12-15 years, together with the survival of patients taken on at a young age, is steadily increasing the total number of prevalent paediatric patients. Figure 14.5 shows the number of patients

Table 14.3. Take-on rate of patients under the age of 16 years with ERF in the UK.

	UK Population (millions)			New patients (average)			Take on Rate (p.m.p)		
Age Group	**Males**	**Females**	**Total**	**Males**	**Females**	**Total**	**Males**	**Females**	**Total**
0–3.9 yrs	1.4100	1.3431	2.7531	13.5	7.7	21.2	9.6	5.7	7.7
4–7.9 yrs	1.5016	1.4277	2.9293	7.3	5.0	12.3	4.9	3.5	4.2
8–11.9 yrs	1.5915	1.5163	3.1078	12.3	10.7	23.0	7.7	7.1	7.4
12–15.9 yrs	1.5775	1.5013	3.0788	18.8	16.0	34.8	11.9	10.7	11.3
All <16 yrs	6.0806	5.7884	11.8690	52.0	39.3	91.3	8.6	6.8	7.7
UK Population	28.5812	30.2080	58.7892				1.8	1.3	1.6

Table 14.4. New patients starting ERF treatment in paediatric units in the UK from 1996 to 2002

	New Patients Starting ESRF Treatment by Year (April to April)																				
	1996–1997			**1997–1998**			**1998–1999**			**1999–2000**			**2000–2001**			**2001–2002**			**Average**		
Age Group	**M**	**F**	**T**	**M**	**F**	**T**	**M**	**F**	**T**	**M**	**F**	**T**	**M**	**F**	**T**	**M**	**F**	**T**	**M**	**F**	**T**
0–3.9 yrs	7	4	11	25	5	30	15	9	24	9	7	16	12	13	25	13	8	21	13.5	7.7	21.2
4–7.9 yrs	4	3	7	8	7	15	10	8	18	9	0	9	7	6	13	6	6	12	7.3	5.0	12.3
8–11.9 yrs	15	10	25	6	8	14	14	9	23	11	10	21	8	16	24	20	11	31	12.3	10.7	23.0
12–15.9 yrs	17	18	35	23	13	36	23	18	41	14	24	38	13	10	23	23	13	36	18.8	16.0	34.8
16–19.9 yrs	3	0	3	2	3	5	5	1	5	4	6	10	9	8	17	10	3	13	5.5	3.5	9.0
All <16 yrs	43	35	78	62	33	95	62	44	106	43	41	84	40	45	85	62	38	100	52.0	39.3	91.3

under the age of 15 years being treated in paediatric units from 1986 until 2002. An upper age limit of 15 years has been used for this data to allow it to become comparable to statistics from previous reports. The upward trend is clearly apparent on this graph. Table 14.5 shows this data with a breakdown according to age-group. Here the data for patients between the ages of 15 and 20 years being looked after in paediatric units is included to give a true perspective of the workload. Again, it is clear that the numbers for patients up to the age of 5 years are remaining fairly constant, whereas the numbers of patients in later childhood being cared for in paediatric units, are increasing.

In the 2002 report, the increased prevalence and take-on rate of patients from the Asian sub-continent as compared with White patients and other ethnic minority groups were highlighted. Figure 14.6 shows the overall prevalence of ERF in children and the breakdown according to ethnicity. It can be seen that the prevalence of ERF in Asian patients is over twice that of White patients. The actual prevalence ratio of Asians to Whites is 2.3:1, whereas the prevalence ratio for Black patients compared to Whites is 0.74:1. Table 14.6 shows the absolute numbers of patients in each age-group, broken down according to ethnicity. This is shown graphically in Figure 14.7 where the percentage of patients belonging to each ethnic group is divided according to age-band.

It can be seen that there is no statistical difference in the age distribution of patients with ERF according to ethnicity.

The data for take-on rate, broken down according to age at starting ERF treatment, and ethnicity, is shown in Table 14.7. It can be seen that the take-on rate for patients from the Asian sub-continent is over 3 times that of White patients. Figure 14.8 shows the percentage of patients being taken on, broken down by age-group and ethnicity. Again, the age distribution of patients being taken on is no different between the ethnic minority groups and the White group. However, there is an increased take-on rate throughout childhood in the Asian population.

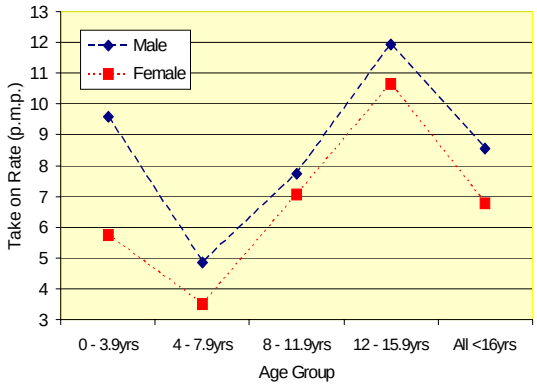

Figure 14.3. Take on rate of patients under the age of 16 years with ERF in the UK

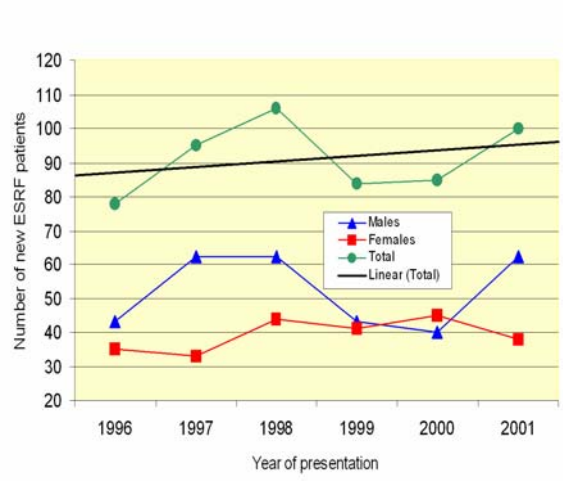

Figure 14.4. New patients starting ERF treatment each year

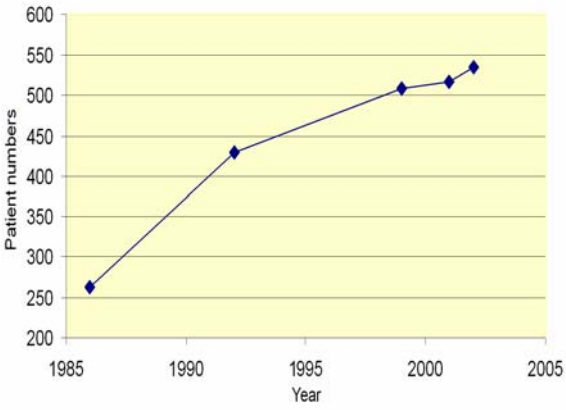

Figure 14.5. Trend in the number of patients with ERF below the age of 15 years

Table 14.5. All patients in paediatric renal units from '86 to '02

Age Group	Patient stock data for the years of; 1986	1992	1999	2001	2002
0 - 1.99 yrs		16	18	13	14
2 - 4.99 yrs		55	46	56	58
5 - 9.99 yrs		150	151	146	147
10 - 14.99 yrs		208	293	301	315
15 - 19.99 yrs			253	274	259
Total under 15 yrs	263	429	508	516	534
Total under 20 yrs			761	790	793

Table 14.6. Ethnic distribution of the paediatric ERF population.

Age Group	White	Asian	Black/Other	Total (%)
0 - 3.99 yrs	36	11	2	49 (6.2)
4 - 7.99 yrs	76	12	6	94 (11.7)
8 - 11.99 yrs	159	24	2	185 (23.0)
12 - 15.99 yrs	249	34	11	294 (36.6)
16 - 19.99 yrs	138	27	6	171 (21.3)
Total	658	108	27	793

Table 14.7. Take on rate of children with ERF in the UK, by ethnicity.

Ethnicity	UK Population (millions)	Patients starting ESRF treatment '96 - '02 0 - 3.99yrs	4 - 7.99yrs	8 - 11.99yrs	12 - 15.99yrs	Take on Rate (p.m.p)
White	10.62431	99	62	115	162	6.87
Asian	0.71849	24	11	20	37	21.34
Black	0.38558	3	0	3	6	5.19
Other	0.34094	1	1	0	4	2.93
Total	12.06032	127	74	138	209	7.57

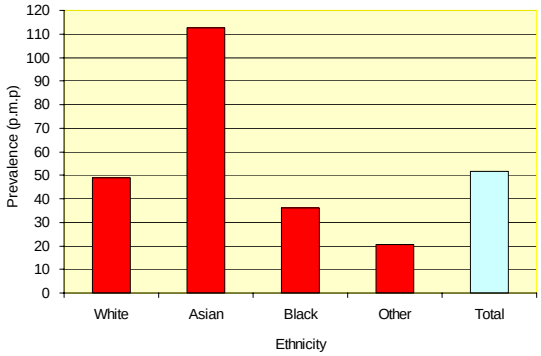

Figure 14.6. Prevalence of ERF in children in the UK, by ethnicity

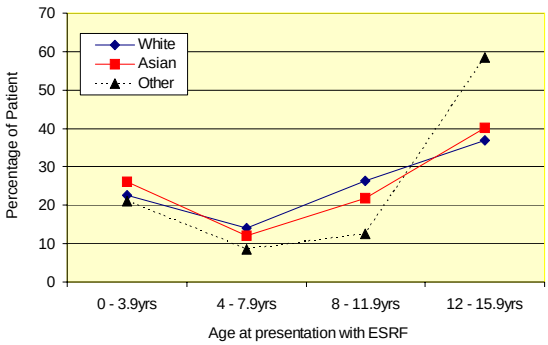

Figure 14.8. Percentage of patients starting ERF management divided by age and ethnicity

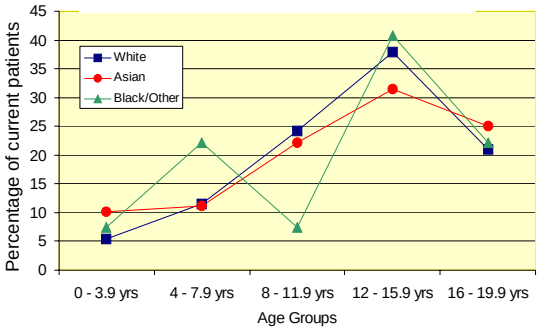

Figure 14.7. Proportion of patients presenting in each age band, by ethnicity

Causes of ERF in childhood

The underlying ERF diagnoses have been analysed with the cohort of 1186 patients registered on the Paediatric ERF Database for whom a primary cause of renal failure was given. Table 14.8 gives a breakdown of the diagnoses of these patients, divided into the 10 broad bands used for previous

reports. It is clear that the leading cause of ERF in childhood is renal dysplasia in one form or another; renal dysplasia itself and conditions associated with renal dysplasia, accounting for 25.8% of patients in ERF. Glomerulonephritides are the next most common cause, accounting for 20.7% of patients. This is a wide diagnostic group, covering a number of conditions, and the single most common glomerulopathy which is primary focal segmental glomerulosclerosis, accounts for just 8.2% of patients. Obstructive uropathy, accounts for 18.1% of patients and 75.7% of these patients had posterior urethral valves leading to obstructive uropathy.

Table 14.9 shows the broad diagnostic groups broken down according to age at commencement of ERF treatment. It can be seen that for some diagnoses such as renal dysplasia, the number of patients presenting steadily decrease with time through childhood. As one might expect, the opposite is the case for glomerular disease. This is shown graphically in Figure 14.9 for the four groups of renal dysplasia, obstructive uropathy, glomerular disease and reflux nephropathy. Whilst glomerular disease as a cause of renal failure increases with age and the number of patients presenting with obstructive uropathy slowly decreases with age, the graphs for renal dysplasia and reflux nephropathy can again be shown to be a mirror image of each other, renal dysplasia falling at the same rate as reflux nephropathy rises. As discussed in the 2002 report, it seems likely that this is a spectrum of the same condition (renal tract dysplasia with vesico-ureteric reflux) as the overall incidence of reflux nephropathy and renal dysplasia together is constant throughout childhood, accounting for a little over 30% of all paediatric ERF.

Figure 14.10 shows the same data for tubulo-interstitial disease, congenital nephrotic syndrome, metabolic disease and polycystic kidney disease. As expected, whilst there is a sharp fall-off in the number of patients with congenital nephrotic syndrome and polycystic kidney disease, presenting with ERF with age, there is a steady rise throughout the first 12 years of life in the numbers of patients starting ERF treatment with tubulo-interstitial and metabolic disease.

Table 14.10 again shows the breakdown of patients according to diagnostic categories but this time the table has been subdivided according to the ethnic origin of the patient. Overall, 45.1% of White patients have either renal dysplasia or obstructive uropathy as a cause of renal failure. This figure is just 34.7% for the Asian population and this difference in the proportions of patients with dysplasia and obstructive uropathy compared to other diagnoses is significant ($p = 0.007$ – Fisher's exact test). The numbers of Black patients are small making statistical analysis difficult, but it is noticeable that whilst the proportion of patients with renal dysplasia is similar to the White population, obstructive uropathy is rare in Black patients.

The frequency of tubulo-interstitial and metabolic diseases is significantly increased in the Asian population compared to the White population ($p < 0.0001$ – Fisher's exact test). Within the tubulo-interstitial disorders group, this is secondary to a relatively large number of Asian patients with nephronophthisis as the cause of renal failure (17 of 167 Asian patients vs. 38 of 972 White patients, $p = 0.0014$ – Fisher's exact test). Within the metabolic disorders group, there is a relative excess of patients with cystinosis and primary hyperoxaluria type 1 (PH1) in the Asian population. In the White population there were 35 patients with cystinosis and 3 patients with PH1 out of a total of 972 patients. In the Asian population there were 11 patients with cystinosis and 4 patients with PH1 out of a total of 167 patients. Combining these two recessively inherited conditions, the difference between the White and Asian communities is significant ($p = 0.0083$ – Fisher's exact test).

Thus, from studying the whole cohort of patients registered on the Paediatric Registry, it is clear that one explanation for the increased prevalence and incidence of ERF

in the Asian community may be, at least in part, secondary to these three autosomal recessive conditions. Together they account for 19.2% of Asian patients with ERF. Consanguinity and a small genetic pool will play a major role in dictating the incidence of these conditions.

Within the Black population renal failure from glomerulonephritides, auto-immune disease and vasculitis was significantly more common than in the White population. Twelve of 29 Black patients with ERF had glomerular disease compared with just 195 of 972 White patients ($p = 0.0093$ – Fisher's exact test). It has been noted earlier that Blacks are relatively under represented in the ERF population. One explanation for this might will be the different patterns of disease seen in the Black population. With the paucity of obstructive uropathy causing renal failure and a tendency towards glomerular disease which present later in childhood, one could expect the total cohort of Black patients to be reduced. This data is shown graphically in Figure 14.11.

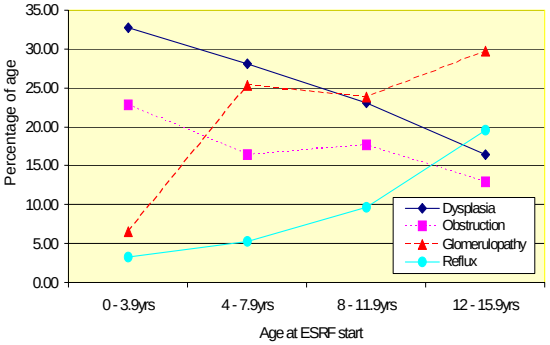

Figure 14.9. Percentage of incident patients with renal dysplasia, obstructive uropathy, glomerular disease and reflux nephropathy presenting by age

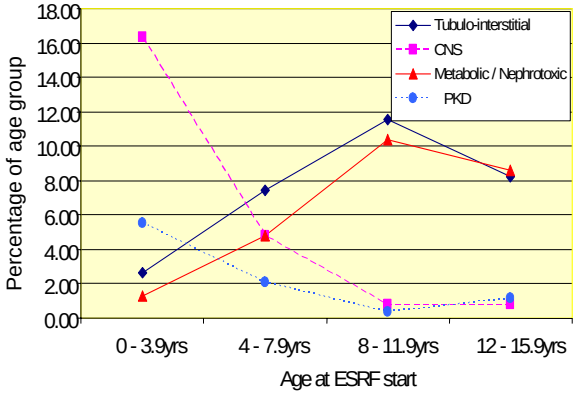

Figure 14.10. Percentage of incident patients with tubulo-interstitial disease, congenital nephrotic syndrome, metabolic/nephrotoxic disease and polycystic kidney by age

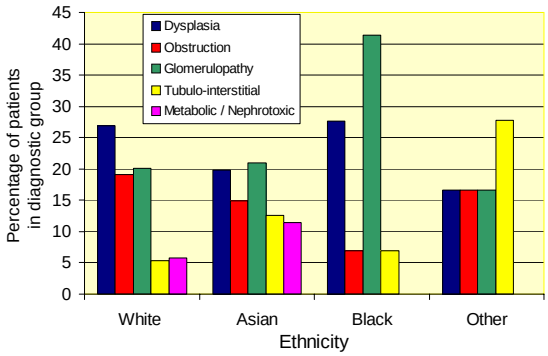

Figure 14.11. Frequency of diagnostic categories in different ethnic groups

Focus on primary focal segmental glomerulosclerosis

Primary focal segmental glomerulosclerosis accounts for 39.6% of paediatric patients in ERF from a glomerulopathy. Focal segmental glomerulosclerosis (FSGS) is a histological diagnosis and this term covers a spectrum of clinical disorders ranging from congenital nephrotic syndrome to childhood steroid resistant nephrosis. Typically congenitalnephrotic syndrome is either present from birth or becomes apparent over the first fewmonths of life. It would be considered unusual for true congenital nephrotic syndrome. Within the paediatric ERF regis-

Table 14.8. Grouped ERF diagnoses for 1186 patients registered on the Paediatric Registry.

Diagnostic Group	Males	Females	Total	% of Total
Renal Dysplasia and related conditions				
Renal dysplasia	161	73	234	19.73
Prune belly syndrome	22	0	22	1.85
Renal hypoplasia	8	13	21	1.77
Multicystic dysplastic kidneys	9	6	15	1.26
Branchio-oto-renal syndrome	5	2	7	0.59
Lawrence Moon Biedl syndrome	2	2	4	0.53
Megacystis megaureter	3	0	3	0.25
Total with Primary Renal Dysplasia	210	96	306	25.80
Obstructive Uropathy				
Posterior urethral valves	163	0	163	13.74
Neuropathic bladder	9	10	19	1.60
Congenital bladder outlet obstruction (not PUV)	10	5	15	1.26
Congenital obstructive uropathy (not BOO)	11	4	15	1.26
Acquired obstructive uropathy	3	0	3	0.25
Total with Obstructive Uropathy	196	19	215	18.13
Glomerulonephritis, Vasculitis and Glomerulopathy				
Primary focal segmental glomerulo-sclerosis	45	52	97	8.18
D+ Haemolytic uraemic syndrome	14	20	34	2.87
Henoch Schoenlein nephritis	10	11	21	1.77
Alport's syndrome	13	4	17	1.43
Glomerulonephritis (unspecified)	4	6	10	0.84
Mesangio-capillary glomerulonephritis Type 1	6	2	8	0.67
Mesangio-capillary glomerulonephritis Type 2	2	6	8	0.67
D neg Haemolytic uraemic syndrome	3	5	8	0.67
Crescentic glomerulonephritis	5	6	11	0.93
IgA nephropathy	3	4	7	0.59
Proliferative glomerulonephritis	3	4	7	0.59
Systemic Lupus Erythematosis	1	4	5	0.42
Anti-GBM disease	0	4	4	0.34
Vasculitis (unspecified)	0	3	3	0.25
Microscopic polyarteritis nodosa	1	1	2	0.17
Wegner's granulomatosis	1	1	2	0.17
Membanous nephropathy	0	1	1	0.08
Total with Glomerular Disease	111	134	245	20.66
Reflux Nephropathy and CRF of Uncertain Aetiology				
Reflux nephropathy	42	47	89	7.50
Chronic renal failure - uncertain aetiology	9	11	20	1.69
Total with Reflux Nephropathy and CRF of Uncertain Aetiology	51	58	109	9.19
Primary Tubular and Interstitial Disorders				
Nephronophthisis	31	29	60	5.06
Primary interstitial nephritis	8	5	13	1.10
Renal tubular acidosis	3	0	3	0.25
Tubular disorders (other)	1	1	2	0.17
Barrter's syndrome	2	0	2	0.17
Total with Primary Tubular and Interstitial Disorders	45	35	80	6.75

Table 14.8 (continued)

Diagnostic Group	Males	Females	Total	% of Total
Metabolic Diseases and Drug Nephrotoxicity				
Cystinosis	24	22	46	3.88
Cyclosporin Nephrotoxicity	8	3	11	0.93
Primary hyperoxaluria type 1	4	3	7	0.59
Other cytotoxic drug nephrotoxicity	1	3	4	0.34
Mitochondrial Cytopathy	1	1	2	0.17
Metabolic Diseases (other)	2	0	2	0.17
Nephrocalcinosis	0	1	1	0.08
Cis-Platinum nephrotoxicity	1	0	1	0.08
Drug nephrotoxicity (unspecified)	0	1	1	0.08
Total with Metabolic Diseases and Drug Nephrotoxicity	41	34	75	6.32
Congenital Nephrotic Syndrome				
Congenital nephrotic syndrome (unspecified)	7	23	30	2.53
Congenital nephrotic syndrome (Finnish)	13	14	27	2.28
Congenital nephrotic syndrome (DMS)	6	1	7	0.59
Congenital nephrotic syndrome (FSGS)	2	2	4	0.34
Total with Congenital Nephrotic Syndrome	28	40	68	5.73
Renal Vascular Disorders				
Cortical necrosis	10	10	20	1.69
Renal vein thrombosis	9	4	13	1.10
Renal artery stenosis	2	1	3	0.25
Renal artery thrombosis	1	1	2	0.17
Renal trauma	1	1	2	0.17
Total with Renal Vascular Disorders	23	17	40	3.37
Polycystic Kidney Disease				
Autosomal recessive PKD	11	12	23	1.94
Polycystic kidney disease (other)	4	3	7	0.59
Tuberous Sclerosis PKD	0	1	1	0.08
Total with Polycystic Kidney Disease	15	16	31	2.61
Malignant and Related Diseases				
Wilms' tumour	8	6	14	1.18
Wilms' nephropathy	1	1	2	0.17
Mesoblastic nephroma	1	0	1	0.08
Total with Malignant and Related Diseases	10	7	17	1.43

Table 14.9. ERF diagnostic groups for 1011 patients registered on the paediatric registry by age at start of ERF

	ESRF diagnoses for patient with ESRF start aged:							
	0–3.9yrs		4–7.9yrs		8–11.9yrs		12–15.9yrs	
Diagnostic Group	**No**	**% of total**	**No**	**% of total**	**No**	**% of total**	**No**	**% of totals**
Dysplasia	100	32.68	53	28.04	60	23.08	42	16.41
Obstruction	70	22.88	31	16.40	46	17.69	33	12.89
Glomerulopathy	20	6.54	48	25.40	62	23.85	76	29.69
Reflux	10	3.27	10	5.29	25	9.62	50	19.53
Tubulo-interstitial	8	2.61	14	7.41	30	11.54	21	8.20
CNS	50	16.34	9	4.76	2	0.77	2	0.78
Reno-vascular	19	6.21	8	4.23	6	2.31	5	1.95
Metabolic / Nephrotoxic	4	1.31	9	4.76	27	10.38	22	8.59
PKD	17	5.56	4	2.12	1	0.38	3	1.17
Malignant	8	2.61	3	1.59	1	0.38	2	0.78

Table 14.10. ERF diagnostic groups, divided according to ethnicity

ESRF diagnoses split by ethnic group:	White patients		Asian patients		Black patients		Other patients	
Diagnostic Group	No	% of Total	No	% of Total	No	% of Total	No	% of Total
Renal Dysplasia	262	26.95	33	19.76	8	27.59	3	16.67
Obstructive Uropathy	185	19.03	25	14.97	2	6.90	3	16.67
Glomerular Disease	195	20.06	35	20.96	12	41.38	3	16.67
Reflux Nephropathy and CRF of Uncertain Aetiology	94	9.67	11	6.59	2	6.90	2	11.11
Primary Tubular and Interstitial Disorders	52	5.35	21	12.57	2	6.90	5	27.78
Congenital Nephrotic Syndrome	53	5.45	14	8.38	1	3.45	0	0.00
Renal Vascular Disorders	36	3.70	3	1.80	1	3.45	0	0.00
Metabolic Diseases and Drug Nephrotoxicity	56	5.76	19	11.38	0	0.00	0	0.00
Polycystic Kidney Disease	24	2.47	5	2.99	1	3.45	1	5.56
Malignant and Related Diseases	15	1.54	1	0.60	0	0.00	1	5.56

try 102 patients have been registered with FSGS as a cause of ERF. There were only 5 patients documented as having “congenital nephrotic syndrome with FSGS” and interestingly some of these presented beyond the age of 1 year. Similarly, some patients registered as just having primary FSGS as a cause of ERF, presented before the age of one year. For the purposes of this analysis, therefore, both of these groups have been amalgamated.

Table 14.11 shows the ethnic distribution of the patients with FSGS. It is clear that this is a condition affecting all ethnic groups. There is a slight but not statistically significant increase in the incidence in the Black population. Similarly, this condition is evenly distributed between males and females. Of the total of 102 patients with this diagnosis, data on presentation and some details of their clinical course were available in 85 patients. Figure 14.12 shows the age at presentation to a paediatric nephrologist for these patients. The figure is divided into 4 year age bands but for clarity the 0–3.99 year band is further subdivided into two. It is clear that this condition presents with decreasing frequency with time. Almost half (39) of the 85 patients presented in the first 4 years of life though only 5 of these presented within the first year. Roughly a quarter of patients presented between the ages of 4 to 8 years and the final quarter presented between the ages of 8 and 16 years.

FSGS is a condition (or rather group of conditions) for which there is no proven treatment. Despite the use of cytotoxic agents, steroids, immunosuppressants and, in some cases, plasma exchange, approximately 50% progress to renal failure. Figure 14.13 shows the time from presentation to ERF for this cohort. There is a decline in the number of patients maintaining renal function with time. 50% of those who are going to progress to ERF will have done so within 2 years of presentation and 80% by 5 years

Table 14.11. Ethnic distribution of patients with FSGS

Ethnicity	Patients	Cohort	% of cohort
White	83	972	8.5
Asian	14	167	8.4
Black	4	29	13.8
Other	1	18	5.6
Total	102	1186	8.6

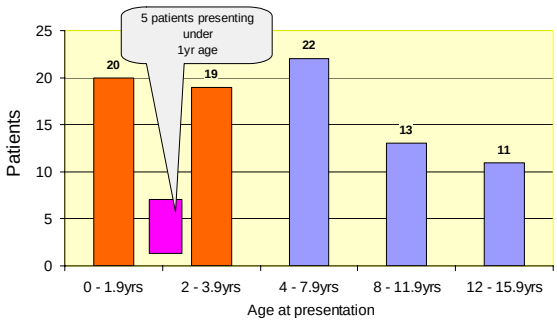

Figure 14.12. Age at presentation to nephrology services of patients with FSGS

after presentation. Age of onset of disease has no bearing on the time taken to progress to ERF. Figure 14.14 shows the median time to ERF from presentation broken down according to age of presentation. It must be stressed that this data relates only to those who progressed to ERF. As the Registry only currently collects data on ERF patients we have no data on the total patient number with FSGS and those not progressing to ERF. It is clear that the trend is for a decreased time from presentation to ERF with increasing age of disease onset. However, the variability in each group is exceedingly wide (Table 14.12) and this trend is not statistically significant.

Management of primary FSGS once ERF ensues is the same as for any other patient with ERF. However, there are frequently problems before the onset of renal failure secondary to complications of the nephrotic state. In addition, the risk of disease recurrence in a renal allograft is recognised to be in the order of 20–40%. As it has only been possible to study the current cohort cross-sectionally, outcome data is limited. At the time of the analysis, 31 of the cohort of 102 patients had been transferred to adult nephrology units and follow up data were not available. Nine patients (8.8%) had died. As will be shown later, this is greater than one would expect for paediatric patients with ERF as a whole – demonstrating the difficulties in caring for patients with this condition. Forty patients had functioning renal allografts. Six of these had received living related donations and 34 had cadaveric grafts. Twenty two patients were on dialysis, 15 on peritoneal dialysis and 7 on haemodialysis. Thus just 64.5% of patients being treated in the paediatric centres had a functioning allograft. This compares with an overall figure for paediatric patients of 76.3% of patients having a functioning allograft on cross-sectional analysis. The difference between the proportion of patients with FSGS with an allograft and those with other conditions who have an allograft is significant (p = 0.0297 – Fisher's exact test).

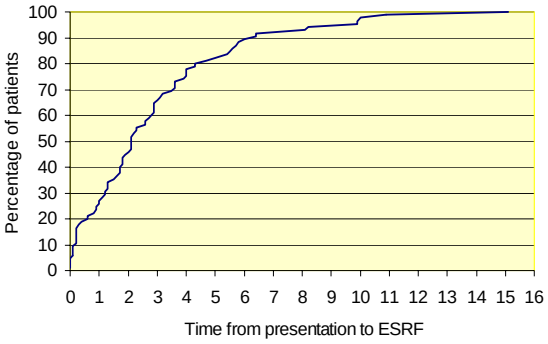

Figure 14.13. Time from presentation to ERF for patients with FSGS

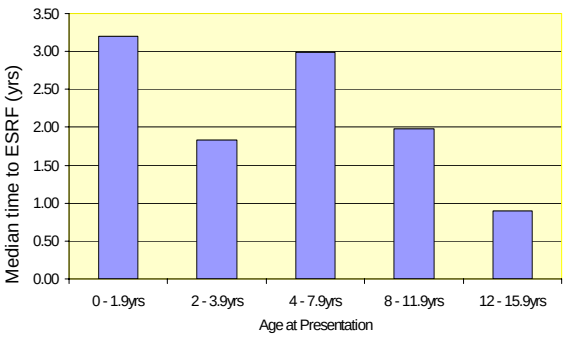

Figure 14.14. Median time from presentation to ERF in patients with FSGS by age

Table 14.12. Time from presentation to ERF for patients with FSGS.

Presentation		Time to ESRF			
Age group	**Patients**	**Mean (yrs)**	**Median (yrs)**	**Min (yrs)**	**Max (yrs)**
0–1.9yrs	20	4.57	3.20	0.00	15.10
2–3.9yrs	19	2.41	1.83	0.00	9.97
4–7.9yrs	22	3.36	2.99	0.02	9.86
8–11.9yrs	13	1.84	1.98	0.19	4.98
12–15.9yrs	11	1.27	0.90	0.05	1.27

Antenatal diagnosis

One major difference between ERF in children and adults is the possibility of detecting the conditions that lead to ERF antenatally. This can then lead to two forms of intervention. In cases where a severe abnormality is detected, a termination of the pregnancy can be offered. Alternatively, in cases of obstructive uropathy, antenatal intervention can be attempted, though evidence that this has a significant effect on outcome is sparse. The ability to make an antenatal diagnosis has increased with time as has the number of potential mothers having an anomaly scan at 18–20 weeks of gestation. Study of the whole paediatric ERF population tends to be biased towards those who present with ERF early in life as they have a greater duration of care within the paediatric unit. For the purposes of this analysis, the cohort includes the 602 new patients presenting with ERF from April 1996 until April 2002.

Amongst the 602 patients presenting over this six year period with ERF, 59 (9.8%) had an antenatal diagnosis of renal disease made. Clearly the possibility of making an antenatal diagnosis depends upon the disease in question being a developmental rather than an acquired problem. In addition, it would have to be detectable on antenatal ultrasonography. This would entail there being either significant dilatation of the renal tract or an abnormal appearance to the kidneys – usually either increased size and echogenicity or the presence of large visible cysts.

Table 14.13 shows the conditions in which an antenatal diagnosis was made together with the total number of patients in the cohort with these conditions. One patient was noted to have had an antenatal diagnosis but an ERF diagnosis was not given, leading to their exclusion from this data set.

As expected, the limitations of antenatal ultrasound mean that only five conditions were diagnosable on antenatal scans. Of these, only 26.3% of patients were diagnosed antenatally. As antenatal ultra-sonography is dealing with the detection of varying degrees of either dilatation of the renal tract and/or renal echogenicity, one might expect that there would be a higher diagnosis rate in patients who were more severely affected and were destined to progress to ERF earlier. Equally, one might expect that a greater proportion of those entering ERF within the first few years of life would be detected antenatally than those who enter ERF in later childhood.

Figure 14.15 shows the proportion of patients with each of the antenatally diag-

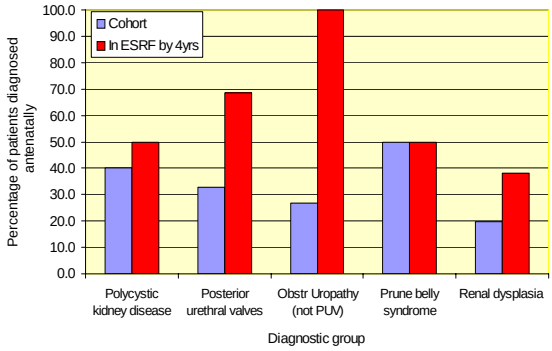

Figure 14.15. The proportion of patients in whom an antenatal diagnosis was made, by diagnostic group and age at entry into ERF

Table 14.13. Conditions for which antenatal diagnoses were made

Antenatal Dx	Patients in Cohort	Diagnosed	Cohort	In ESRF by 4 yrs	Diagnosed	In ESRF by 4 yrs
Polycystic kidney disease	15	6	40.0	10	5	50.0
Posterior urethral valves	58	19	32.8	19	13	68.4
Obstr Uropathy (not PUV)	15	4	26.7	2	2	100.0
Prune belly syndrome	8	4	50.0	2	1	50.0
Renal dysplasia	126	25	19.84	42	16	38.1
Total	222	58	26.13	75	37	49.33

nosable conditions who were diagnosed antenatally. The figure is divided into two sections. For each condition the first bar shows the overall proportion with that condition who were detected antenatally, whereas, the second bar shows the proportion of those who entered ERF within the first four years of life who were detected antenatally.

Renal dysplasia was the most common condition in this group that could be detected antenatally. However, only 20% of cases were diagnosed antenatally. Even when considering the patients who were in ERF within the first four years of life, only 38% had been antenatally detected. These results clearly highlight the limitations of antenatal ultrasound scanning. Renal dysplasia is a condition where there might be clear cut signs of abnormality at ultrasonography, with renal tract dilatation and cyst formation or echogenicity of the kidneys. Equally, the kidneys may appear small or relatively normal on ultrasound. Oligohydramnios is often the first sign that leads to concern in patients with a major renal anomaly. However, patients with renal dysplasia often have salt losing polyuric renal failure. This leads to normal amniotic fluid volumes.

Posterior urethral valves is the next most common condition diagnosable antenatally. Although one might expect the renal tract dilatation accompanying this condition to make it easily diagnosable, it is noteworthy that only 32.8% of cases presenting were diagnosed antenatally and even for those with early onset renal failure, only 68.4% were antenatally detected. This clearly highlights the limitations of 18 to 20 week anomaly scans. Although many patients with severe obstructive uropathy from posterior urethral valves will be detected at this stage through a combination of renal tract dilatation and oligohydramnios, it is perfectly possible to have normal appearances at this stage or just mild renal tract dilatation, only to develop the evidence of severe obstructive uropathy later in pregnancy. These cases would only be detectable if a further routine antenatal scan at about 28 weeks gestation were added to the current routine anomaly scan which is performed at 18–20 weeks gestation.

The picture for polycystic kidney disease is similar. One might expect polycystic kidney disease to be easily detectable antenatally through the combination of enlarged echogenic kidneys and oligohydramnios. In fact only 50% of cases entering ERF in the first 4 years of life were diagnosed antenatally. As with obstructive uropathy, it needs to be stressed that this is due to the nature of the disease and the timing of routine anomaly scans rather than the ability of those performing these scans to detect problems. Though a proportion are detected early, an 18 week scan can appear completely normal whilst a 24–28 week scan can then show enlarged echogenic kidneys and oligohydramnios. This pregnancy may then continue with the development of massive renal enlargement, anhydramnios and the birth of an infant who dies of pulmonary hypoplasia.

It thus appears from the data analysed that antenatal scanning is an inaccurate tool, diagnosing an average of just 50% of severe renal disorders that lead to early ERF. However, the data here only include patients who have been born and have survived long enough to become included in a regional ERF programme. There are no data on the number of patients detected where a termination of pregnancy has taken place, nor are there any data on the patients who have either been born and suffered early neonatal death, usually through pulmonary hypoplasia, or have not developed renal failure. If these patients were to be included, the proportion of infants with significant renal anomalies being diagnosed by antenatal screening would improve significantly. Collaboration with regional foetal management registries and neonatal units will be necessary in order to compile these statistics.

Presentation of patients to nephrology services

The timing of presentation to nephrology services is of particular importance in paediatric renal disease if clinicians are going to have enough time to prepare patients for ERF management and, more importantly, optimise care, to delay the onset of ERF where feasible and ensure that growth and nutrition are appropriate.

When last reviewed for the 1999 report, it was only possible to analyse a cross-sectional view of the population. These data would inevitably give a somewhat biased result as it did not represent the true spectrum of the ages of patients presenting with ERF. Whilst those who presented within the first few years of childhood would have been included in this data, even if their entry into ERF had been 12 years earlier, those who entered renal failure late in childhood would have been transferred to adult services and omitted from the analysis. To look at the presentation details of an accurate representation of the paediatric ERF population, the complete cohort of 602 patients presenting in ERF over the past 6 years from 1996 was analysed.

Presentation data were available for 570 members of this cohort (94.7%). Figure 14.16 shows the percentage of patients entering the ERF programme each year after presentation. With just over 40% of patients entering ERF within the first year of their presentation to nephrology services, and a further 9% entering ERF within the second year after presentation, only 50% of patients spend a significant time under nephrology care before starting the ERF programme. The timing of entry into ERF for this 50% is spread out over a decade. As might be expected, age of commencement of ERF influences this picture. Those starting ERF at a younger age have declined into ERF faster and 64% of those presenting in ERF within the first 4 years of life have entered ERF within the first year of their presentation to nephrology services. For the other age groups the pattern is similar. There is an initial peak with between 25 and 40% going into ERF within the first year of presentation. Six to 16% will then enter ERF over the second year and the rest are then spread out with time.

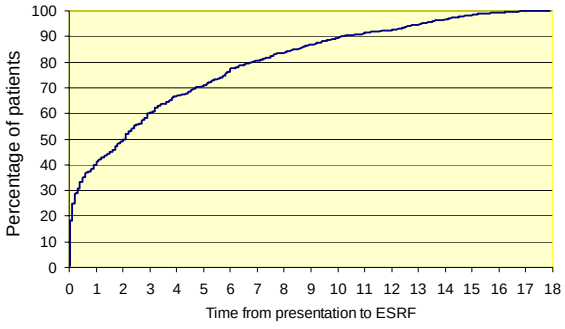

Figure 14.16. Percentage of patients who have entered ERF for each year after presentation

Clearly, patients who start ERF treatment within two years of presentation have diseases that are rapidly progressive at the time of presentation, or have progressed markedly by the time they have presented. Whichever, there is little leeway in these patients to optimise growth and nutritional status before entering the ERF programme. The remaining 50%, however, do spend a significant time with nephrology services and it would be hoped that, with the help of supplementary or gastrostomy feeds, growth hormone, control of renal osteodystrophy and erythropoietin, patient care would be improved.

Of the 288 patients who took in excess of two years from presentation to enter ERF, data on height were available for 277 (96%) and data on weight were available for 223 (77%). Figure 14.17 shows a box and whisker plot of height SDS at presentation and at the commencement of ERF treatment. The central line in the box represents the media and the outer lines the 25th and 75th percentiles, whilst the whiskers denote the range.

Overall, there is clearly a fall in height SDS from presentation to the start of ERF treatment. The data is normally distributed and the difference between the two groups is significant ($p < 0.0001$ – paired t test). Breaking the group down according to age of presentation, it is clear that most of the

patients with poor growth presented in the first year of life. Figure 14.18 shows a similar box and whisker plot for patients heights of patients presenting in the first four years of life (both at presentation and at ERF) and the heights of patients presenting above the age of four years (both at presentation and at ERF). While there is a fall in height SDS between presentation and ERF, for those presenting in the first 4 years of life ($p < 0.0001$ – paired t test), there was no significant difference between the height SDS at presentation and ERF for those presenting over the age of 4 years ($p = 0.847$ – paired t test).

One factor that could well explain the poor growth in those presenting in the first four years of life is nutrition. Much effort has been made to optimise the nutrition of children in ERF, whose appetites are exceedingly poor, using supplementary and gastrostomy feeds. Figure 14.19 shows a box and whisker plot of weight SDS for the whole group at presentation and ERF. It is clear that although the median weight at both points is slightly below average, there is no significant fall in weight SDS between presentation and ERF.

Breaking this group down into those who present in the first four years of life and those who present later (Figure 14.20) it can be seen that there is in fact a mean weight gain, with a narrowing of the spectrum of weight SDS, for those presenting early whilst those who present later show a small fall in weight SDS. These data would suggest that, overall, the nutritional policy being implemented is successful and that other factors are instrumental in the poor height gain for those presenting in the first four years of life. In some, this could be related to syndromic or metabolic diagnoses that are associated with inherent poor growth. Another factor that needs to be investigated is the timing and extent of the use of growth hormone in this specific population.

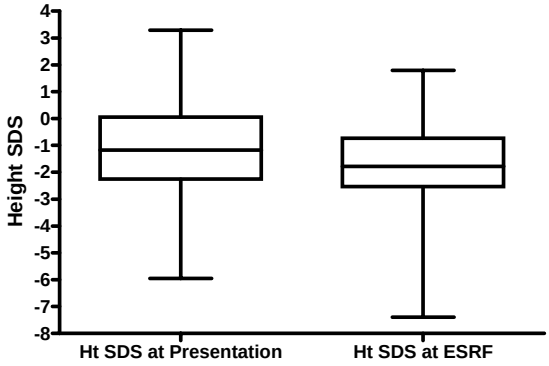

Figure 14.17. Height SDS at presentation and at entry into ERF

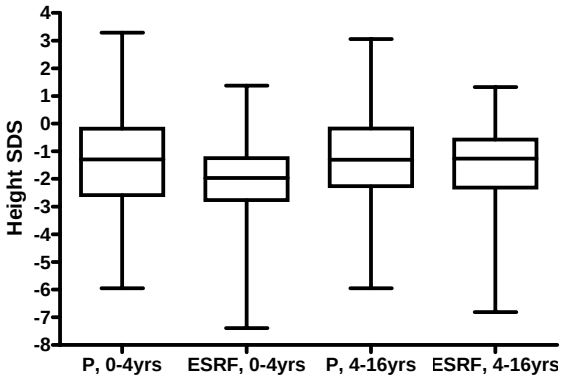

Figure 14.18. Height SDS at presentation and entry into ERF, by age of presentation

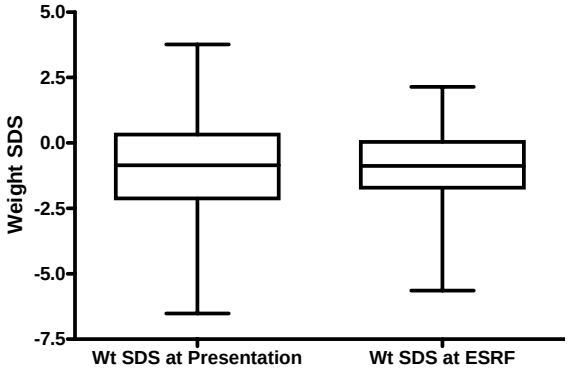

Figure 14.19. Weight SDS at presentation and entry into ERF

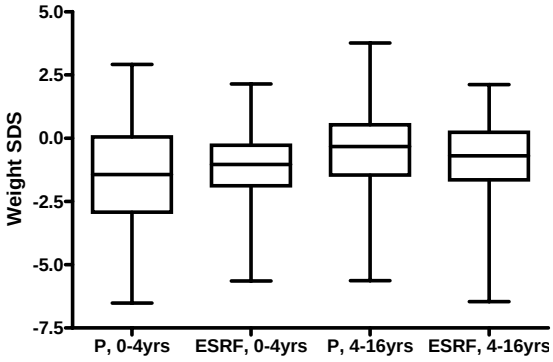

Figure 14.20. Weight SDS at presentation and entry into ERF, by age of presentation

Death in the paediatric ERF population

The study of mortality is clearly important when considering the paediatric ERF population. Unfortunately, although a large number of patients have been entered into the Registry, this cohort will not include all the patients dying as the entry of patients at the inception of the Registry only included then "current" patients. To analyse subsequent mortality as a proportion of the number of patients entered, would thus give a falsely low figure. To analyse mortality, the incident cohort of patients commencing ERF treatment from April 1996 was used.

As patients commencing treatment in 2001–2002 will often have only entered ERF shortly before the data collection time of April 2002 (and therefore will have a very short follow-up period), they have been excluded. A cohort of 489 patients who started ERF treatment between the 1st April 1996 and the 31st March 2001 remained. These patients all have a minimum follow up of 1 year with a range of 1 to 6 years.

Of the 489 patients, 29 had died giving an overall mortality of 5.9%. Death in the paediatric ERF patients fell into three broad categories.

1. Patients who died through either the inability to obtain or to maintain dialysis access.
2. Patients who died from severe secondary complications – usually infection.
3. Patients who died from problems associated with co-morbid conditions – usually syndromic diagnoses, other congenital abnormalities or major handicaps.

Figure 14.21 shows a life table analysis for these patients. It can be seen that the 5 year survival for patients presenting with ERF in childhood is 92%. There is a marked discrepancy between the mortalities for patients presenting at different ages. The mortality for those presenting within the first 4 years of life, was almost 19%. The mortality for those presenting later in childhood was fairly constant at between 2 and 4%.

Table 14.14 gives the number of patients who died within each age-group. Of the 20 patients who died having started ERF treatment within the first 4 years of life, 13 (65%) were actually in ERF within the first year of life. Within the cohort, there were 47 patients starting ERF treatment within the first year of life, giving an overall mortality for this selected population of 27.7%.

Figure 14.22 shows a life table analysis for those entering ERF within the first year of life. It demonstrates that the one year survival for this group of patients is 78% whilst the 5 year survival is just 66%. Table 14.15 details the diagnoses of the patients starting ERF treatment within the first year of life and also gives the number with each

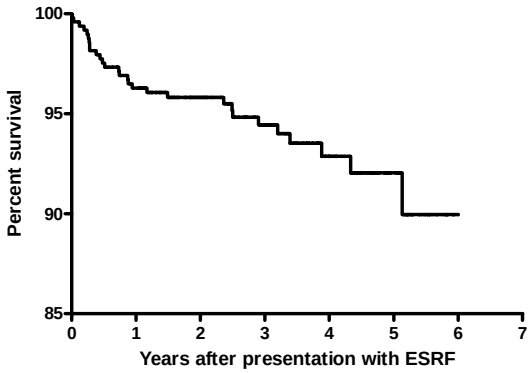

Figure 14.21. Survival analysis for patients starting ERF treatment from 1st April 1996 to 31st March 2001

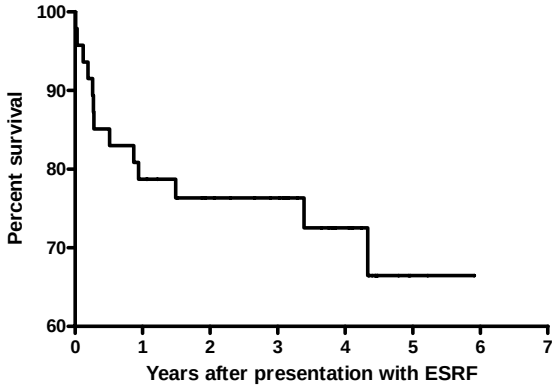

Figure 14.22. Survival analysis for patients below the age of 1 year starting ERF treatment from 1st April 1996 to 31st March 2001

Table 14.14. Number of patients with ERF who have died, by age at the start of ERF

ESRF start age	Patients	Deceased	% deceased
0–3.9yrs	106	20	18.9
4–7.9yrs	62	2	3.2
8–11.9yrs	107	2	3.7
12–15.9yrs	173	4	2.9
16–19.9yrs	41	1	2.4
Total	489	29	5.9

diagnosis who died. It is clear that there is a marked discrepancy in the mortality rates between diagnoses.

Of the 9 patients with obstructive uropathy, 8 had posterior urethral valves and one had a different form of bladder outlet obstruction. The mortality within this group was the highest at 55.6%. The 6 patients with renovascular disease, consisted of 3 with renal venous thromboses and 3 who developed bilateral cortical necrosis. Patients with renovascular disease and those with polycystic kidney disease both also had a high mortality rate at 50% and 40% respectively. The outcome for patients with renal dysplasia was better with only a 15% mortality, whilst there were no deaths amongst the small cohort with congenital nephrotic syndrome (Figure 14.23). Of the three patients with “other” diagnoses, one patient suffered from atypical haemolytic uraemic syndrome, whilst two did not have a cause for their ERF given. Clearly, if both of these patients were to have any of the three main diagnoses associated with a high mortality, the overall mortality figures for these diagnoses would be significantly changed because of the small cohort being examined.

Table 14.16 shows a break-down of the total patient cohort according to ethnicity. It is clear that the overall mortality within the ethnic minority groups appears to be higher

Table 14.15. Number of patients starting RRT in the 1st year of life and the number dying, by cause of ERF

ESRF diagnosis	Patients	Deceased	% deceased
Obstructive uropathy	9	5	55.6
Renovascular disease	6	3	50.0
Polycystic kidney disease	5	2	40.0
Renal dysplasia	20	3	15.0
Congenital nephrotic syndrome	4	0	0.0
Other	3	0	0.0
Total	47	13	27.7

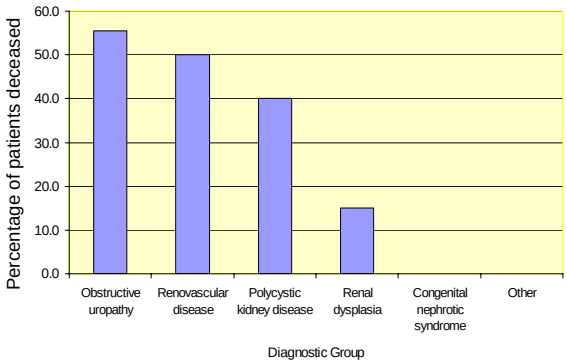

Figure 14.23. Percentage of patients starting dialysis in the first year of life who died, by cause of ERF

Table 14.16. Deaths in patients with ERF, divided according to ethnicity

Ethnicity	Patients	Deceased	% deceased
White	400	22	5.5
Asian	72	8	11.1
Black	12	1	8.3
Other	5	1	20

than for White patients and in particular the mortality for patients from the Asian subcontinent was twice that of White patients. This was not secondary to an excess of ethnic minority group patients starting ERF treatment within the first 4 years of life. Due to the overall small number of patients who died, these differences failed to reach statistical significance but will need to be reconsidered in the future.

Current ERF modalities

Of the 804 patients with ERF being treated within the 13 tertiary paediatric nephrology centres on 1st April 2002, data on current treatment modality was available for 756 (94%). Table 14.17 shows the break-down of patients according to treatment modality compensated by an increase in the number of living related donations (Figure 14.25).

As before, just over 75% of patients have a functioning transplant. Of the remaining quarter of the population, two thirds are managed on peritoneal dialysis and one third on haemodialysis. Figure 14.24 shows this distribution graphically and also details the proportion of peritoneal dialysis patients who are on CAPD as opposed to cycling peritoneal dialysis and the proportion of transplant patients who have received a living related rather than cadaveric allograft.

It can be seen that CAPD is becoming increasingly unpopular within paediatric practice with only 13% of patients on peritoneal dialysis using this form of treatment. The proportion of patients overall with allografts from living donors is still low at 18.6%, though the trend has been for there to be fewer cadaveric transplants performed year by year and this has been compensated by an increase in the number of living related donations (Figure 14.25).

There were notable differences in the treatment modalities used between different ethnic groups. This data is shown in Table 14.18. Whilst almost 80% of White patients had a functioning renal allograft, only 62% of Asian patients had a functioning allograft and this figure reduced further to just under 50% for the small number within other ethnic groups.

Comparing the proportion of patients with a functioning allograft in the White population with that from all other ethnic groups combined, the difference was highly significant ($p < 0.0001$ – Fisher's exact test). For those who do have a functioning allograft, the proportion with grafts from living related donations is greater within the White patients than in other ethnic groups, though this difference fails to reach statistical significance (Table 14.19).

Whilst more patients from ethnic minority groups are on dialysis compared to the

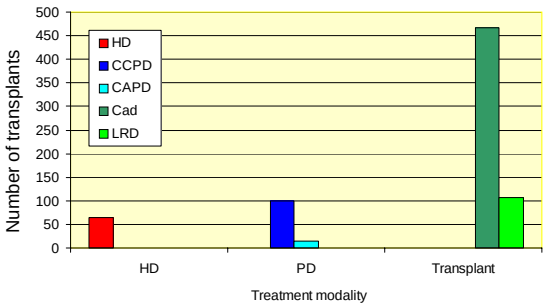

Figure 14.24. Current modality of ERF treatment for the paediatric population in April '02

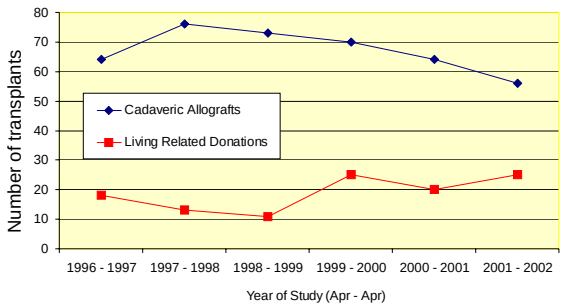

Figure 14.25. Paediatric transplant activity 1996–2002

Table 14.17. Current modality of ERF treatment for the paediatric population in April '02

Treatment modality	Total	(%)	CCPD	(%)	CAPD	(%)	Cadaveric	(%)	Living Related	(%)
Haemodialysis	64	8.5								
Peritoneal dialysis	114	15.2	99	86.8	15	13.2				
Transplant	574	76.3					467	81.4	107	18.6

White population, it is also interesting to note the differences in the modality of dialysis treatment employed between ethnic groups. Just 30.6% of White patients undergoing dialysis are being treated with haemodialysis, whereas, 48% of patients from ethnic minority groups are being treated with haemodialysis. The difference between the proportions of dialysis patients on haemodialysis is significant (p = 0.0279 – Fisher's exact test).

This data is of tremendous importance when planning paediatric ERF services across the UK. Factors determining the lower proportion of patients with a functioning allograft amongst ethnic minority groups probably relate to the differences between their HLA pool and that of the pool of cadaveric donors. The large number of patients from ethnic minority groups who are blood group B also makes cadaveric transplantation more difficult. Data on waiting times is not available at present to make this analysis complete. Increased use of living related transplantation in the ERF population from ethnic minority groups would clearly be an advantage.

It is not clear from the data available exactly why patients from ethnic minority groups are more likely to be on haemodialysis than peritoneal dialysis. Factors determining this would include practical medical considerations such as the length of time a patient has been on dialysis and previous graft loss or problems with peritoneal dialysis. Other factors that could influence the decision include problems with communication and accommodation. As was shown in the 2001 report, the distribution of ethnic minority group patients is uneven across the 13 paediatric tertiary referral centres with some having none and others having a very large proportion. Until the exact reasons for the increased use of haemodialysis in those from ethnic minority groups have been established and addressed, it is clear that some paediatric units are going to require increased resources with regard to the provision of haemodialysis places, nursing staff and vascular access.

Table 14.19. Type of allograft in transplanted patients, divided according to ethnicity.

	Type of Allograft			
Ethnicity	**Cadaveric**	**(%)**	**LRD**	**(%)**
White	403	80.9	95	19.1
Asian	53	84.1	10	15.9
Black	8	88.9	1	11.1
Other	3	75.0	1	25.0

Patients with functioning renal allografts

As patients with functioning renal allografts formed 76% of the current paediatric ERF population, analysis of this group is clearly important with regard to assessing the effectiveness of paediatric ERF management. Previously, only crude cross-sectional analyses have been performed. Even now with a limited number of years' follow-up (functional data collection only began in 1999) and the ever-changing population due to new transplants being performed and older patients being transferred or losing their grafts, meaningful, longitudinal analysis is difficult.

Clearly, one of the main faults with cross-sectional analysis is that it fails to take

Table 14.18. Current treatment modality for paediatric patients, divided according to ethnicity.

	Treatment Modality							
Ethnicity	**HD**	**(%)**	**PD**	**(%)**	**Transplant**	**(%)**	**Other**	**(%)**
White	38	6.1	86	13.8	498	79.7	3	0.5
Asian	20	19.6	19	18.6	63	61.8	0	0.0
Black	5	25.0	6	30.0	9	45.0	0	0.0
Other	1	12.5	3	37.5	4	50.0	0	0.0
Total	64	8.1	114	15.1	574	76.0	3	0.4

account of the longevity of a graft and the differences that occur between grafts which have recently been performed compared with those that have been in place for many years. To try and overcome this problem, data have been collected based upon the age of each graft. As the Paediatric Registry is currently only collecting data at a single point each year, the data collection has now been structured to ensure that for patients with functioning allografts the point of data collection coincides with the transplant anniversary. For those patients whose grafts have been recently implanted, data are collected at 3 months (0.25 years) post-transplant. Thereafter, data are collected on or around the anniversary of the transplant yearly. This way, even using cross-sectional analysis, it is now possible to group allografts according to time since engraftment, in order to allow meaningful comparisons to be made.

Transplant function

Of 574 patients with functioning renal allografts and data logged for April 2002, 14 had no details of graft age and were therefore omitted from the analysis. Figure 14.26 shows the number of allografts with data collected for each transplant anniversary. As would be expected, the majority of transplants are relatively recent with 121 being at or under their first anniversary at the point of data collection and 101 being at their second anniversary. There is, thereafter, the expected steady decline in the number of grafts at later anniversaries. There were, however, 46 grafts which had reached their 10th anniversary or above. It must be stressed that the falling numbers of patients with grafts that have been in place for some years is not a reflection on graft survival. Transfer of patients to adult units is the main reason for this.

Assessment of renal function has been mainly through analysis of the serum creatinine recorded at the time of the graft anniversary. To correct for size, a predicted GFR

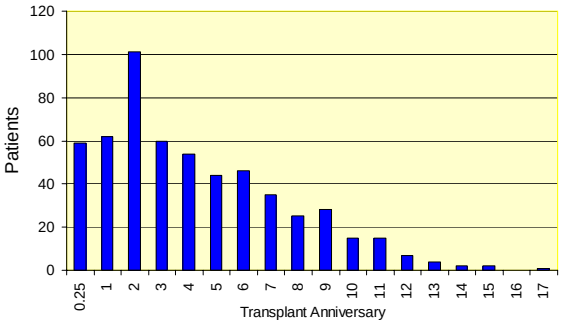

Figure 14.26. Current longevity of transplants on cross-sectional analysis of the paediatric population

(pGFR), can be calculated using the variable constant according to age and sex as described by Haycock and Schwartz. The formula used is:

$$\text{pGFR} = \frac{\text{Height (cm)} \times K}{\text{Creatinine } (\mu\text{mol/L})}$$

where K is a constant which varies with age and sex. Excluding the neonate, a constant of 40 is used in the first 2 years of life, 49 between 2 years and 13 years of age, 60 for males over the age of 13 years, and 49 for females over 13 years. These formulae have only been validated in normal populations. For ease of use and also to avoid abrupt transitions in pGFR, many nephrologists use a single factor of 40 for all patients irrespective of age and sex.

It is well-recognised that the accuracy of prediction of the GFR from the serum creatinine on the patients' height is variable. Particularly in transplant patients where tubular toxicity from calcineurin inhibitors can be significant, tubular secretion of creatinine can contribute to renal creatinine clearance leading to a falsely high pGFR. The aim of the Registry has been to collect data on formal GFR assessment annually. Not all units routinely perform formal GFR assessments and so for 2002, only 100 formal GFR results were available. These results have been used to examine the accuracy of prediction of GFR from the creatinine using the formulae available.

Figure 14.27 shows the age and sex distribution of the 100 patients with a formal GFR,

a height and creatinine measurement to allow calculation of a pGFR. Figure 14.28 shows the age and sex distribution of all 525 patients for whom a pGFR could be calculated.

It can be seen that there is no major difference between the distributions, though there are no children under the age of 4 years in the cohort with a formal GFR. In neither group were there any patients below the age of two years. Within the 100 with a formal GFR measurement, there were 13 who were male and over the age of 13 years. Thus using the standard formula, there would be 87 patients for whom the pGFR calculation constant would be 49 and 13 for whom it would be 60. No patients would have a calculation constant of 40, which in the standard formula is reserved for those under 2 years of age, but which many UK nephrologists use for all patients irrespective of age.

Figure 14.29 shows the mean and standard deviation of the formal GFR in this patient group compared with the pGFR using a constant of 40 for all patients, a constant of 49 for all those above 2 years of age (all patients in this group) and the true formula with a constant of 60 for males over 13 years of age and a constant of 49 for others. It can be seen that in all scenarios the pGFR is significantly greater than the formal GFR ($p < 0.0001$, paired t tests).

The agreement between the formal GFR and the pGFR was closest when a constant of 40 was used for all patients. Figures 14.30 and 14.31 show the formal GFR on the 'x' axis plotted against the pGFR on the 'y' axis using different constants as described above. For each graph a regression line is drawn with the line forced through the origin. These confirm that the best agreement between GFR and pGFR is when a constant of 40 is used at all ages.

There are several reasons why this may be the case. The formulae have been derived to account for varying muscle mass at different ages. The relationship between height and muscle mass is not likely to be the same in patients who have had ERF compared to the normal population. Puberty is often delayed in ERF patients leading to a delay in the accompanying increase in muscle mass – particularly in boys. Patients with transplants are likely to have increased tubular creatinine losses leading to a lower plasma creatinine level for any particular GFR. On the basis of this, all subsequent calculations of pGFR have been made using a constant of 40 at all ages.

As discussed earlier, height and creati-

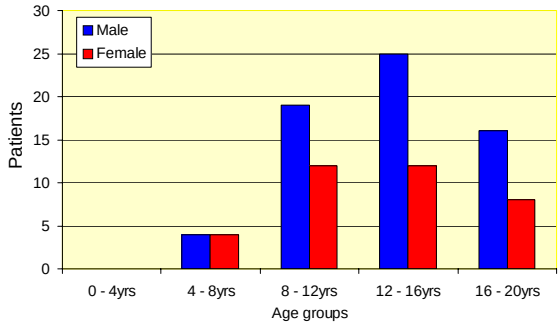

Figure 14.27. Age and sex distribution of 100 transplanted patients with a formal GFR estimation

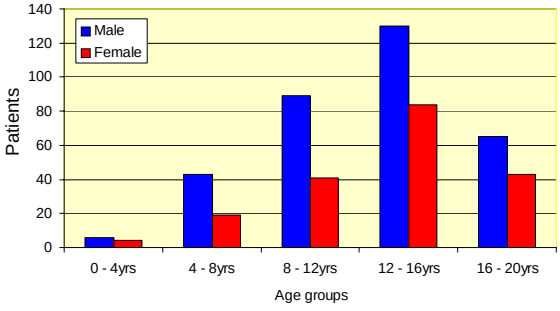

Figure 14.28. Age and sex distribution of 524 transplanted patients with a pGFR estimation

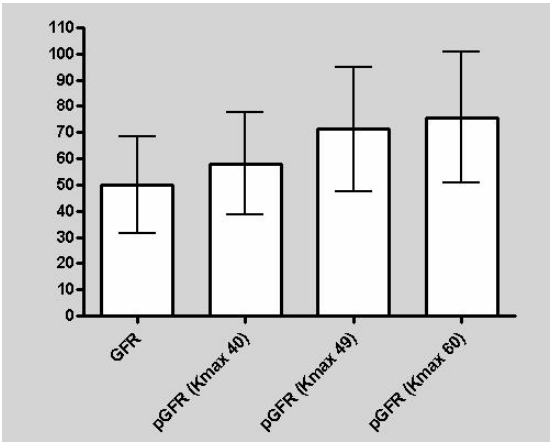

Figure 14.29. Formal GFR compared with pGFR using different constants.

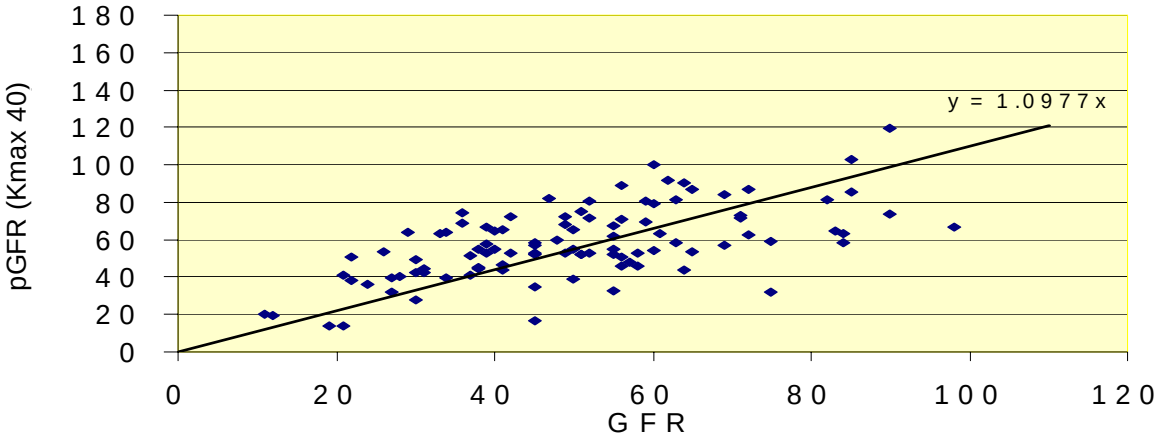

Figure 14.30. Formal GFR compared with pGFR using a constant of 40 for all patients

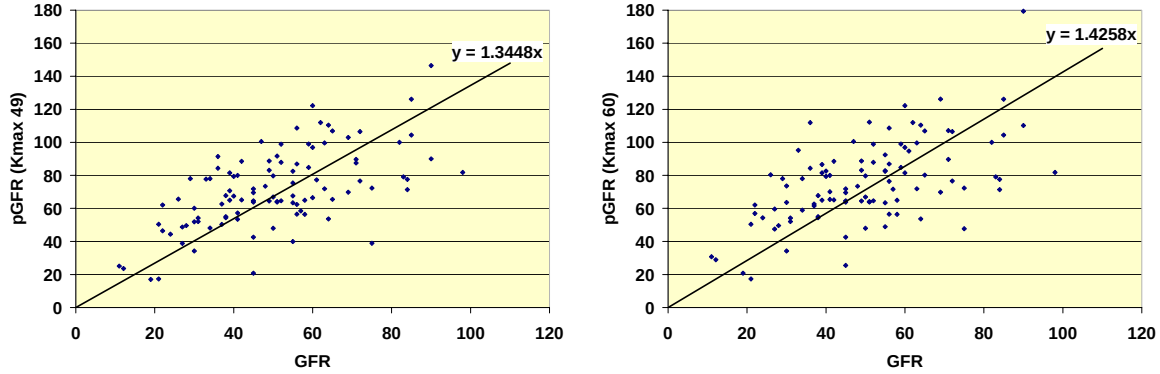

Figure 14.31. Formal GFR compared with pGFR using a constant of 49 for all patients (left) and 60 for males over 13 years age, 49 for other patients (right)

nine were recorded in 525 patients (91.4%), allowing the calculation of pGFR. Figure 14.32 shows the mean pGFR for the population divided according to transplant anniversary. The error bars denote the standard deviation of the mean. Overall, the mean GFR at each age was excellent and ranges from 67 to 90 ml/min/1.73 sq.m.

There is a slow trend towards declining GFR with age of allograft as demonstrated in Figure 14.33. The correlation between allograft age and pGFR is significant (p = 0.0175). These data are skewed by the absence of patients who have lost grafts and also those who have transferred to adult units. Inclusion of the patients who have lost grafts with time would significantly increase the slope of the line. In time, when more longitudinal data is collected, a more accurate picture of the changes in allograft function and the generation of life table analyses will become possible.

One feature which is specific to paediatric transplantation is the large proportion of patients with urological problems and abnormal bladders as a cause of their renal failure. This leads to a relatively large proportion of patients who are either on clean intermittent catheterisation (CIC), an augmented bladder which requires CIC, or who have a urinary diversion. In all these circumstances the risk of infection is increased and the chances of then having worse renal function increased.

In the cohort of 574 patients, 477 had details of urinary drainage (83.1%). Of these, 410 had normal bladders and 390 of these had heights and creatinines available for the calculation of a pGFR. There were 25 patients on CIC alone, of whom, 23 had a pGFR available and 23 patients with bladder augmentations on CIC of whom 20 had a pGFR available. Nineteen patients were documented as having a urinary diversion of

whom 18 had a pGFR available.

Figure 14.34 shows the mean and standard deviation for the pGFR in each of these groups. There was no significant difference in pGFR with mode of urinary drainage. It must, however, be noted that due to the small numbers available, these data are not corrected for graft age. Longitudinal data on renal function will be required to see if the rate of decline in pGFR with time is different in those with abnormal urinary drainage.

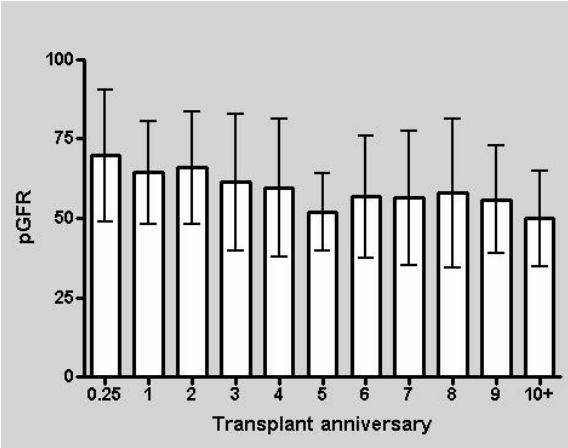

Figure 14.32. Predicted GFR (mean + SD) in renal allografts of varying age

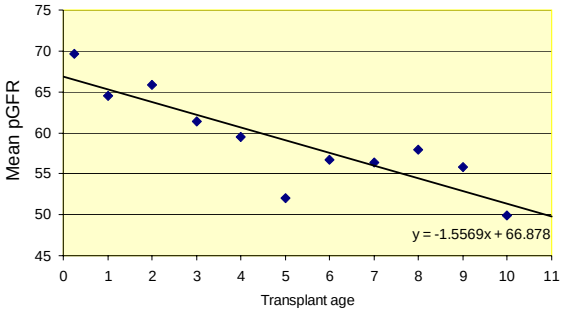

Figure 14.33. Change in mean predicted GFR with age of transplant.

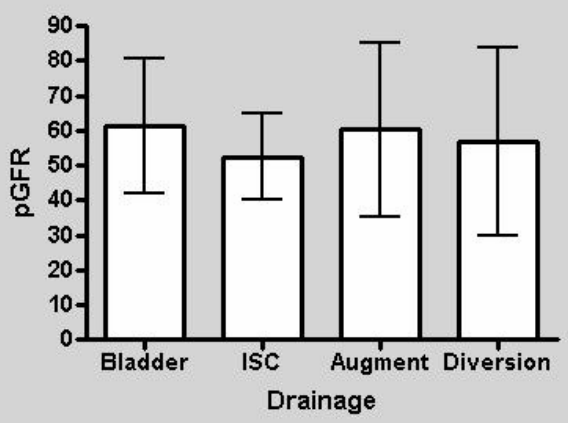

Figure 14.34. Analysis of pGFR in prevalent patients with functioning allografts by mode of drainage

Transplant rejection and immunosuppression

Rejection, acute or chronic, remains a major cause of allograft dysfunction and loss. Over the past 5 years there have been a number of trials of differing forms of immunosuppression with the aim of limiting rejection. The Paediatric Registry records for each transplant anniversary both the number of rejection episodes that have occurred since the last anniversary record and the number of these rejection episodes that were biopsy proven. Interpretation of these figures is somewhat hampered by differing interpretations of what constitutes a single rejection episode. For this reason, this analysis simply looked at the number of patients who had rejection episodes and the proportion of these patients whose rejection episodes were at one time or another biopsy proven.

Figure 14.35 shows the percentage of patients at each anniversary review having rejection episodes since the previous anniversary. It is clear that within the first year many patients are suffering rejection episodes, though under two thirds of these patients have had biopsy proven rejection and the remainder have been treated on a clinical basis.

In patients who have had their grafts longer, the number having rejection episodes is much reduced and the proportion of these rejection episodes which are biopsy proven are greater. By two years after transplantation, roughly 10% of patients have biopsy proven episodes of rejection each year; whereas within the first two years, between 25 and 30% are having these episodes.

The immunosuppressive regimes used in this cohort of patients were very variable. Data on immunosuppression were available for 544 patients (97%). The vast majority

were receiving immunosuppression with a calcineurin inhibitor. Only 19 patients (3.5%) were not on either Cyclosporin or Tacrolimus; with these patients being treated with a combination of either Mycophenolate and Prednisolone or Azathioprine and Prednisolone.

For those receiving a calcineurin inhibitor, 317 (58.3%) were taking Cyclosporin whilst 208 (38.2%) were taking Tacrolimus. In both groups, the vast majority were on triple therapy with either additional Azathioprine and Prednisolone or additional Mycophenolate and Prednisolone. 12.5% of the patients on Tacrolimus were on dual therapy with Tacrolimus and either Prednisolone, Azathioprine or Mycophenolate, whilst 24.5% of those on Cyclosporin were on dual therapy with these agents. Three patients were on Cyclosporin monotherapy. This data is shown graphically in Figure 14.36.

Figure 14.37 shows the percentage of patients receiving either Tacrolimus or Cyclosporin at varying times from transplantation. The mirror image trend lines clearly show the steady trend towards the usage of Tacrolimus rather than Cyclosporin, with 70% of the most recently transplanted patients receiving Tacrolimus. When analysed by intention to treat, these data show that many units still start immunosuppression with Cyclosporin-based treatment. Of the 114 patients with a transplant at or under one year of age, 55 (48.2%) started on Cyclosporin-based therapy but 10 patients were converted to Tacrolimus following episodes of rejection leading to the

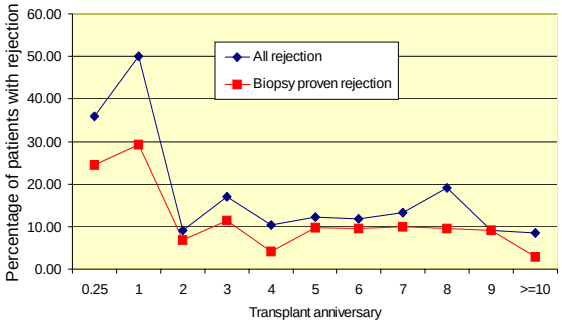

Figure 14.35. Percentage of patients with rejection episodes according to graft age

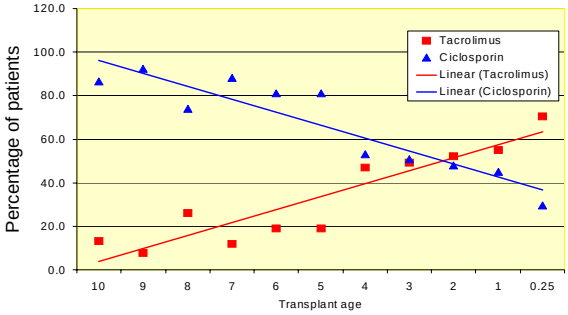

Figure 14.37. Percentage of patients receiving either Tacrolimus or Cyclosporin, according to age of graft

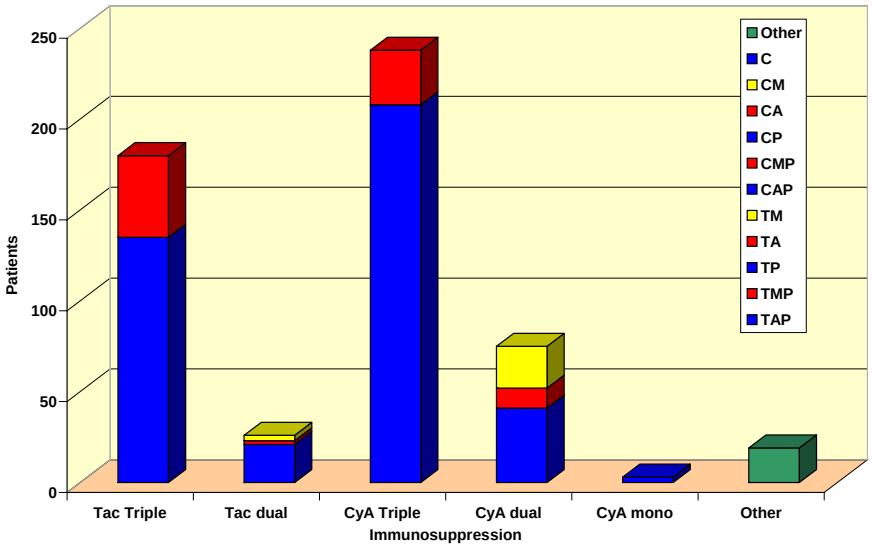

Figure 14.36. Immunosuppressive regimes in patients with renal allografts (C = cyclosporin, T = tacrolimus, A = azathioprine, M = mycophenolate and P = prednisolone)

marked increase in the proportion receiving Tacrolimus.

Most rejection episodes were treated with pulsed Methylprednisolone followed in a proportion by either a change from Cyclosporin to Tacrolimus or from Azathioprine to Mycophenolate. Just 5 of the 114 patients receiving an allograft in the past year, received anti-thymocyte globulin (4.4%).

Conclusion

The demographics of the paediatric ERF population are not changing greatly, though the steadily rising numbers of prevalent patients will have resource implications. There are marked differences in the current management of patients from the ethnic minority groups with fewer patients having functioning renal allografts and more patients being treated with haemodialysis. Not only does this have resource implications overall, but the high proportion of ethnic minority group patients in certain localities will require special attention to the provision of paediatric ERF services in these areas.

The timing of patient presentation to nephrology services is variable and although 50% are in ERF within two years of presentation, this is not unreasonable, bearing in mind the nature of the diseases causing their renal failure. For the remaining population, it is noteworthy that poor growth is principally a problem of those presenting within the first 4 years of life and that nutrition appears to be being well-managed with no fall in weight SDS. The cause for poor growth in those presenting early in life needs to be explored further to ascertain whether intervention might be effective. The earliest presentation is with antenatal diagnosis but it is unclear from the data presented that only a proportion of those with severe renal anomalies causing ERF are diagnosed early. It needs to be recognised that this is an inevitable result of reliance on an 18–20 week anomaly scan. If increased antenatal detection of serious renal anomalies is desired, additional third trimester scanning will be required.

In paediatric ERF patients, death was relatively rare with an overall 92% 5 year survival rate. Death was more frequent, in those commencing dialysis in the first year of life where the 5 year survival rate is just 66%. In addition, the specific high mortality rate of patients with congenital obstructive uropathy and polycystic kidney disease who enter ERF in the first year of life needs to be taken into account when counselling parents for whom an antenatal diagnosis has been made.

Over 75% of the prevalent paediatric ERF population have a functioning transplant. For those on dialysis, twice as many patients are on peritoneal dialysis than haemodialysis. The use of CAPD is rare with 87% of peritoneal dialysis patients receiving home machine cycling dialysis. Significantly, fewer patients from ethnic minority groups had a transplant compared to the White population and hence more were on dialysis. For those on dialysis, patients from ethnic minority groups were more likely to receive haemodialysis than peritoneal dialysis.

Renal function in transplanted patients is good, though GFR declines with graft longevity. It needs to be recognised that predicted GFR from the serum creatinine overestimates true GFR, though the latter remains very acceptable in those patients where it has been measured. For the calculation of a predicted GFR from the serum creatinine the Schwartz formula can be used with a constant of 40 for all age-groups and both sexes.

The diagnosis and treatment of acute allograft rejection seems to be variable between centres with only two thirds of patients having rejection episodes confirmed by biopsy in the first year after transplantation. Immunosuppressive regimes are equally varied, though the general trend is clearly towards the usage of Tacrolimus-based triple immunosuppression. With just ten centres undertaking paediatric renal transplantation in the UK, the use of a single

protocol for immunosuppression and the diagnosis of allograft rejection would be a sensible step forward. Uniformity of approach would also make the incorporation of clinical trials of immunosuppressive regimes easier.

This report was compiled by Dr MA Lewis and Mrs J Shaw.

It was reviewed, revised and approved by the Paediatric Renal Registry subcommittee comprising:

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Dr Chris Reid
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