European disparities in the incidence and outcomes of children with end-stage renal disease

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Infants Requiring Dialysis: Outcomes of Hemodialysis and Peritoneal Dialysis

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ABSTRACT

Background: The impact of different dialysis modalities on clinical outcomes has not been explored before in young infants with end-stage renal disease.

Methods: Study design: Cohort study. Setting & Participants: Data were extracted from the ESPN/ERA-EDTA Registry. This analysis included 1063 children aged ≤12 months who initiated renal replacement therapy (RRT) from 1991 to 2013. Factor: Type of dialysis modality. Outcomes & Measurements: Differences between infants treated with peritoneal dialysis (PD) or hemodialysis (HD) in patient survival, technique survival, and access to kidney transplantation were examined using Cox regression analysis while adjusting for age at dialysis initiation, gender, underlying renal disease, and country of residence.

Results: 917 infants initiated dialysis on PD and 146 on HD. Median age at dialysis start was 4.5 (IQR 0.7-7.9) months and median body weight 5.7 (IQR 3.7-7.5) kg. While the groups were homogeneous regarding age and gender, children treated with PD more often had CAKUT (48 vs. 27%), whereas those on HD suffered more frequently from metabolic disorders (12 vs. 4%). Risk factors for death were younger age at RRT initiation (HR: 0.94, 95% CI 0.90-0.97) and non-CAKUT etiology of ESRD (HR: 1.49, 95% CI 1.08-2.04). Mortality risk and likelihood of transplantation were equal in PD and HD patients, whereas HD patients had a higher risk of changing dialysis treatment (aHR: 1.64, 95% CI 1.17-2.31). Limitations: Inability to control for unmeasured confounders not included in the Registry database and missing data (i.e. comorbidities).

Conclusions: Despite a widespread preconception that HD should be reserved for cases where PD is not feasible, in Europe we found one in eight infants in need for chronic dialysis to be started on HD. Patient characteristics at dialysis initiation, prospective survival, and time to transplantation were very similar for infants commenced on HD or PD.

INTRODUCTION

The management of infants requiring chronic dialysis represents a significant challenge for pediatric nephrologists. Difficulties in feeding and maintaining fluid balance, growth failure, increased infection risks, and the presence of co-morbidities complicate the management of chronic renal failure in children <1 year of age [117]. Consequently, mortality rates in infants on dialysis are substantially higher than in older children [115].

In a multinational survey performed in the late 1990's, only 50% of pediatric nephrologists recommended initiation of RRT in infants with end-stage renal disease (ESRD) [201]. Since then, this attitude has been partially modified by reports demonstrating favorable results in growth, development, and renal transplantation in infants on dialysis given careful medical and nutritional management [143, 202–205]. The number of infants on RRT has increased over the past decades and according to the 2011 North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) Report, 13.2% of patients were less than 2 years old at dialysis initiation [68, 114].

Maintenance PD represents the preferred dialysis modality in infants [86, 120, 143, 202, 203]. Advantages over HD include potentially better preservation of residual kidney function [206], less dietary restrictions, avoidance of central vascular access placement, and the option to perform dialysis at home, though this requires a labor-intensive effort from the family [207]. The experience of treating infants with HD is limited [121, 208–211]. HD in infants is technically difficult and requires highly qualified nursing staff. However, in cases where PD is contraindicated for clinical reasons, fails, or is inappropriate due to psychosocial problems, HD remains the only alternative treatment until renal transplantation is feasible [145].

To our knowledge, no reports have compared the long-term outcomes of both dialysis modalities in infants. We therefore sought to compare the clinical characteristics and outcomes of PD and HD patients in a large cohort of children starting dialysis under 1 year of age.

METHODS

Study population

We analyzed data of 1081 infants who initiated RRT before 12 months of age between January 1, 1991 and December 31, 2013. The cohort included all patients collected within the framework of the European Society for Paediatric Nephrology/European Renal Association and European Dialysis and Transplant Association (ESPN/ERA-EDTA) Registry. Countries initiating infants on dialysis during the study period were: Austria, Belarus, Belgium, Bosnia-Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, the Netherlands, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, and the United Kingdom. Patient numbers per country are included in appendix 1.

We excluded patients who received a pre-emptive renal transplantation (n=10) and patients whose dialysis modality was not clearly specified (n=8). Patients entered the study on day 1 of dialysis and were then stratified by modality on day 30. For patients who died within the first month of treatment, the last treatment modality prior to death was considered for analysis.

Data collection

Age, gender, primary renal disease, initial treatment modality and any subsequent changes are obligatory information in the ESPN/ERA-EDTA Registry. Other parameters such as body weight, height, blood pressure, serum creatinine, albumin, hemoglobin, and parathyroid hormone (PTH) levels at baseline and during follow-up are provided on a voluntary basis, as well as the reasons for modality failure. Primary renal disease and causes of death were determined by the patients' nephrologists and classified according to the ERA-EDTA coding system [54]. No ethics committee approval or informed consent was required as the ESPN/ERA-EDTA Registry is based on observational and anonymized patient data collection.

Statistical analysis

The primary outcome studied was patient survival by dialysis modality. Secondary outcomes included comparison of clinical characteristics at dialysis onset, technique survival, and the likelihood of transplantation in infants receiving PD and HD. The primary analysis was performed on an "intention-to-treat" (ITT) basis where patients were assigned to the initial

dialysis modality (at day 30). As infants often tend to switch between modalities, we also performed a "per-protocol" (PP) analysis, assigning patients to the treatment they actually received. For both the ITT and PP analyses, patients were censored at transplantation, when renal function recovered, when lost to follow-up, reaching end of study period (December 31, 2013), or after 5 years of follow-up, whichever came first. Cumulative incidence competing risk curves were constructed for death (with transplantation as a competing risk), transplantation (with death as a competing risk), and modality switching (with both death and transplantation as competing risks) [57]. Cox regression was used to adjust for possible confounders, including age at start of dialysis, gender, and underlying renal disease. Due to the low number of patients in some smaller countries, and that some countries have either no HD or no PD patients, it was not possible to adjust for country as a fixed effect without making the model unstable. As an alternative to adjust for a potential country effect on clinical outcomes, a random country factor was added to the Cox model using the shared frailty model. This random effect allows patients within the same country to share a baseline hazard while allowing the hazard function to differ between countries, and therefore allows the model to account for the effects of unobserved heterogeneity between countries.

Demographic baseline and clinical characteristics were described with medians and interquartile ranges (IQR) or proportions, as appropriate. The Student's *t* was used to test for differences between treatment groups for normally distributed continuous variables, the Wilcoxon test for non-normally distributed continuous variables, and the χ^2 test for categorical variables. Estimated glomerular filtration rate (eGFR) was calculated by using the updated Schwartz formula [55]. Linear mixed models were used to compare mean levels of serum albumin, hemoglobin (Hb), blood pressure standard deviation scores (SDS), and PTH between the two treatment groups, whilst adjusting for multiple measurements within a patient, as well as for confounders. Height values were normalized to SDS for chronological age using recent national or European height-for-age charts [212]. As serum Hb changes during the first year of life, age specific SDS for Hb were calculated using KDIGO reference values. For the analyses of clinical and biochemical parameters, all measurements during the first year of dialysis were used except for the baseline measurements. Statistical tests were two-tailed and were considered significant when $p<0.05$. Data were analyzed using the SAS software (version 9.4, SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics

We identified a total of 1063 infants starting on dialysis. Of these, 919 started on PD and 144 on HD. At day 30, 14 PD patients had switched to HD and 12 HD patients had switched to PD. Fourteen patients died before day 30 (12 on PD and 2 on HD). Dialysis was initiated in 649 (61%) children at age 0-6 months and in 414 (39%) children at age 7-12 months. The baseline patient characteristics by initial dialysis modality are shown in table 1, whereas the estimated mean for the clinical and biochemical parameters during the first year of dialysis are reported in table 2. We found a higher proportion of hypoalbuminemic infants on PD, likely resulting from increased protein losses via the peritoneal membrane that at this age is often characterized by a hyperpermeable state. Conversely, infants on HD presented with significantly lower hemoglobin levels, possibly related to significant blood losses with the extracorporeal systems or more relevant fluid overload at the time of blood sampling, which is usually performed immediately before dialysis.

In infants receiving PD, automated cycler regimens were applied in 71% of cases (out of the 605 patients for whom this information was available), whereas 29% of infants initially received manual intermittent or continuous ambulatory PD. Nearly all HD patients received in-center HD, except for one case treated with home-HD. For the 131 patients for whom this was known, 90% were treated with bicarbonate HD and 10% with hemodiafiltration. For 21 patients, we had information on the number of HD treatment sessions per week and the duration of each session. Ten out of 21 patients had 3 days of HD per week, while the remaining patients had 2 (1 case), 4 (2 cases), 5 (4 cases), 6 (2 cases), or 7 days (2 cases) per week. Total hours of HD per week were highly variable, ranging from 6 to 35, with a median of 12 hours. Information on the type of vascular access was available for 15 patients; a central line was used in 14 cases (median age at implantation of 8.4 months) and an arteriovenous graft was used in 1 case (placed at 7.5 months of age).

Table 1. Baseline patient characteristics by initial dialysis modality. P-values refer to comparison between PD and HD. [a] Adjusted for age at start.

	Available data	*All patients (n=1063)*	*PD (n=917)*	*HD (n=146)*	
	N (%)	*Median (IQR)*	*Median (IQR)*	*Median (IQR)*	*p*
Age (months)	1063 (100%)	4.5 (0.7-7.9)	4.3 (0.7-7.9)	5.1 (1.3-7.9)	0.4
Female gender (%)	1063 (100%)	33.2	32.4	38.4	0.2
Body weight (kg)	576 (54%)	5.7 (3.7-7.5)	5.5 (3.6-7.5)	6.3 (4.2-8.0)	0.06 [a]
Height (cm)	473 (44%)	60 (52-67)	60 (52-67)	62 (55-67)	0.2 [a]
Height SDS	473 (44%)	-1.1 (-2.4- -0.3)	-1.3 (-2.4-0.2)	-0.9 (-2.6-0.5)	0.2
BMI (kg/m^2)	491 (44%)	16.6 (15.3-18.8)	16.6 (15.3-18.9)	16.5 (15.4-18.7)	0.9
eGFR (ml/min/1.73 m^2)	313 (29%)	6.1 (4.4-8.4)	6.1 (4.4-8.0)	6.3 (4.2-8.8)	0.7
Primary diagnostic group (%)	1063 (100%)				<0.001
CAKUT		45.3	48.4	27.1	
Glomerulonephritis		4.7	4.7	4.7	
Cystic kidney disease		8.3	8.1	9.3	
Hereditary nephropathy		15.4	15.9	12.4	
Ischemic renal failure		4.7	4.2	7.8	
HUS		3.1	3.3	2.3	
Metabolic disorders		5.5	4.1	12.4	
Vasculitis		0.2	0	1.6	
Miscellaneous		9.4	8	17.8	
Unknown		3.5	3.3	4.7	

Table 2A. Unadjusted mean clinical and biochemical parameters during the first year of dialysis treatment. P-values refer to comparison between PD and HD. N = patients, n = measurements. BMI = Body Mass Index; PTH = serum parathyroid hormone.

	n	*N*	*Mean (95% CI)*
BMI (kg/m^2)	1920	705	16.1 (15.9-16.3)
Systolic BP SDS (mmHg)	1095	496	1.2 (1.0-1.4)
Diastolic BP SDS (mmHg)	983	434	1.7 (1.5-1.8)
Hemoglobin SDS	1068	498	-1.62 (-1.84 to -1.40)
Serum albumin (g/dL)	977	491	32.5 (31.8-33.2)
PTH (pg/mL)	892	422	496 (438-555)

Table 2B. Unadjusted mean clinical and biochemical parameters during the first year of dialysis treatment. P-values refer to comparison between PD and HD. N = patients, n = measurements. BMI = Body Mass Index; PTH = serum parathyroid hormone.

	PD			*HD*			*p*
	n	*N*	*Mean (95% CI)*	*n*	*N*	*Mean (95% CI)*	
BMI (kg/m^2)	1666	615	16.1 (15.9-16.3)	254	90	16.3 (15.7-16.9)	0.6
Systolic BP SDS (mmHg)	974	438	1.1 (1.0-1.3)	121	58	1.5 (1.0-2.0)	0.2
Diastolic BP SDS (mmHg)	877	388	1.6 (1.5-1.8)	106	46	2.1 (1.7-2.5)	0.03
Hemoglobin SDS	900	423	-1.40 (-1.64 to -1.15)	168	75	-2.73 (-3.28 to -2.17)	<0.001
Serum albumin (g/dL)	878	434	32.1 (31.3-32.8)	99	57	36.4 (34.2-38.6)	<0.001
PTH (pg/mL)	765	360	500 (433-568)	127	62	474 (321-628)	0.7

Patient survival and cause of death

The overall 5-year crude mortality rate in the entire cohort of infants receiving dialysis was 52.3 deaths per 1000 patients year (py). The overall cumulative incidence of death at 1, 2 and 5 years was 10.0% (95% CI 8.10%-11.7%), 13.1% (95% CI 11.0%-15.2%) and 16.1% (95% CI 13.8%-18.5%), respectively. Causes of death were infections (25.1%), cardiovascular disease (13.6%), withdrawing ESRD treatment (6.8%), respiratory failure due to fluid overload (3.1%), cerebrovascular accident (5.8%), malignancy (2.1%), miscellaneous (23.6%) and unknown/not available causes (19.9%). Among the 26 deaths for cardiovascular disease, the specific reported causes were sudden cardiac arrest (50%), myocardial infarction (4%), hypertensive cardiac failure (4%), and unknown causes of cardiac failure (42%). There were no significant differences in cause of death between children starting dialysis before and after the year 2000. Causes of death according to dialysis modality were also comparable.

Younger age at the start of RRT was a significant risk factor for death, with a 5% lower risk per month of later start (HR: 0.95, 95% CI 0.90-0.97; p<0.001). A significantly higher risk of death was found in patients with non-CAKUT diseases (HR: 1.49; 95% CI 1.08-2.04; p=0.03), while there was no significant mortality risk difference by gender (female vs. male, HR: 1.28; 95% CI 0.95-1.71) or between children starting dialysis before and after the year 2000 (post-2000 vs. pre-2000, HR: 0.93; 95% CI 0.67-1.29). Survival was also similar across countries (country frailties are presented in appendix 1).

Mortality risk comparison between HD and PD

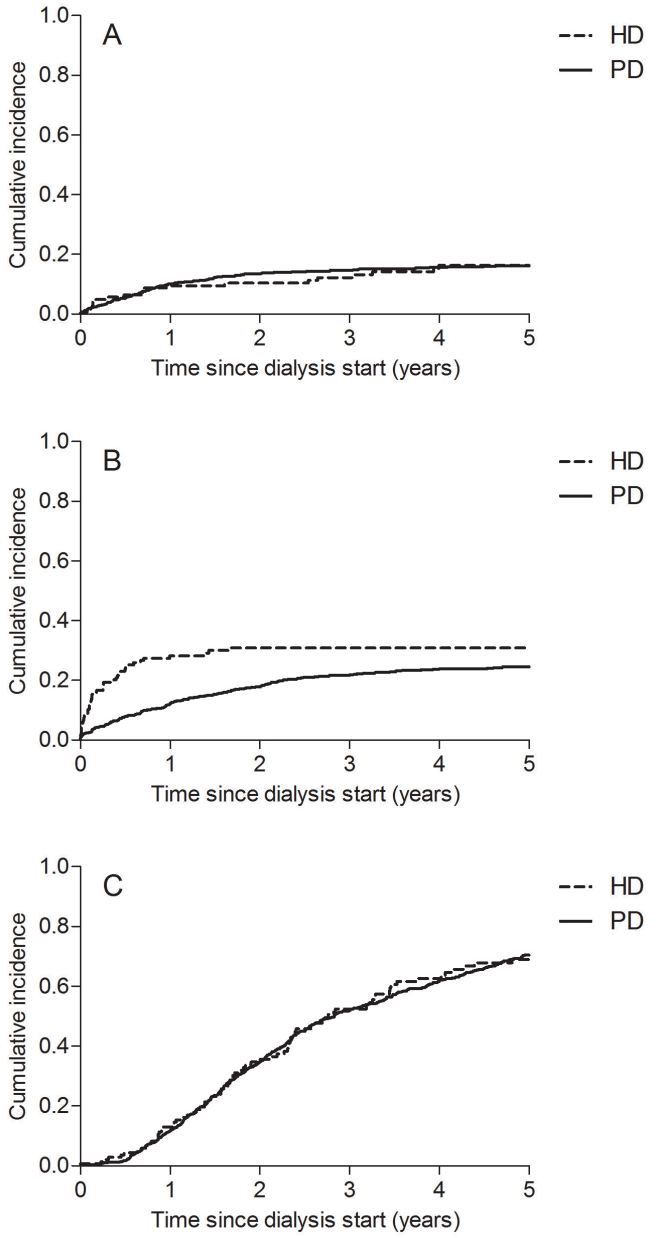
The crude 5-year mortality rate was 51.0 deaths per 1000 py for PD and 62.2 deaths per 1000 py for HD. The 5-year cumulative incidence of death is presented by dialysis modality in table 3 and figure 1A. In the ITT analysis, whilst censoring for transplantation, crude (HR: 1.08, 95% CI 0.69-1.68) and adjusted (aHR: 1.06, 95% CI 0.67-1.67) hazard ratios did not differ significantly between treatment groups. HD vs. PD hazard ratios did not differ significantly between children starting dialysis before and after the year 2000 (p-value for interaction term = 0.64). Among infants whose initial dialysis modality was PD, 135 of 143 deaths occurred while still on PD and 8 died while switched to HD. Among HD patients, 19 of 23 deaths occurred while still on HD and 4 were on PD. In the PP analysis, crude (HR: 0.76, 95% CI 0.47-1.22) and adjusted (aHR: 0.73, 95% CI 0.45-1.18) hazard ratios did not differ significantly between treatment groups.

Experience and skills in treating infants on HD may vary across European countries. To explore the potential impact on survival of a country's experience in treating infants on HD, we first looked at the interaction effect between country and dialysis modality on mortality and found that this was statistically insignificant (type 3 test, p=0.19). In addition, we added the ratio HD/PD patients (HD vs PD, HR: 1.00, 95% CI 0.62-1.62) and the proportion of HD patients per country (HD vs PD, HR: 0.96, 95% CI 0.59-1.57) as a proxy for HD country experience to the Cox model, which had little effect on the hazard ratio. Survival remained similar after excluding those countries that had no infants treated with HD (aHR: 1.07, 95% CI 0.64-1.70).

Table 3. The cumulative incidence of death (with transplantation as a competing risk), modality switching (with both death and transplantation as competing risks), and transplantation (with death as a competing risk), and corresponding adjusted hazard ratios for HD vs. PD patients.

Outcome	*Overall* *5-year cumulative incidence % (95% CI)*	*HD* *5-year cumulative incidence % (95% CI)*	*PD* *5-year cumulative incidence % (95% CI)*	*HD vs. PD adjusted hazard ratio (95% CI)*
Death	16.1 (13.8-18.5)	16.3 (9.60-23.1)	16.1 (13.6-18.7)	1.06 (0.67-1.67)
Dialysis switch	25.5 (22.7-28.3)	30.9 (23.1-38.7)	24.6 (27.5-21.6)	1.54 (1.07-2.20)
Transplantation	70.2 (67.1-73.4)	69.0 (60.2-77.9)	70.5 (67.1-73.8)	0.95 (0.70-1.29)

Figure 1. Cumulative incidence curves for A) death (with transplantation as a competing risk), B) modality switching (with both death and transplantation as competing risks), and C) transplantation (with death as a competing risk).



Technique survival

The overall cumulative incidence for dialysis modality switching at 1, 2, and 5 years was 14.5% (95% CI 12.4%-16.7%), 19.7% (95% CI 17.3%-22.2%), and 25.5% (95% CI22.7%-28.3%), respectively. The 5-year cumulative incidence for dialysis modality switching is presented by dialysis modality in table 3 and figure 1B. Patients on HD had a 1.64-fold higher risk of changing dialysis treatment (95% CI 1.17-2.31; p=0.004), as compared to patients on PD. This effect remained even after adjustment for confounders (aHR: 1.54, 95% CI 1.07-2.20; p=0.02) and was stronger during the first year of dialysis (aHR: 2.79, 95% CI 1.81-3.99). We registered 198 modality failures among PD and 44 among HD infants. Reasons for modality failure are reported in detail for patients where this information was available in appendix 2: peritonitis (63%) was the main cause of failure in PD patients followed by exit site or tunnel infection (13%), and patient/family choice (56%) was the main cause in HD patients followed by vascular access failure (20%).

Overall, older patients had a lower risk of changing the type of dialysis (HR: 0.96 per month, 95% CI 0.93-0.99; p=0.03). This was not the case among PD patients (HR: 0.98 per month, 95% CI 0.95-1.02; p=0.4), but was strongly present among HD patients (HR: 0.82 per month, 95% CI 0.75-0.91; p<0.001). Among patients starting on PD and compared to CAKUT, those with metabolic disorders were more likely to change to HD (aHR: 6.29, 95% CI 3.32-11.94; p<0.001), as were patients with hereditary nephropathies (aHR: 1.75, 95% CI 1.04-2.95; p=0.04). The likelihood of changing from HD to PD was not affected by the underlying renal disease. There were differences in the likelihood of switching dialysis modalities between countries (appendix 1). Compared to other European counties, the UK had a significant increased risk of modality switching (HR: 1.90, 95% CI 1.31-2.77).

Time to transplantation

Within 5 years after start of dialysis, 70.2% (95% CI 67.1%-73.4%) of all patients had received a kidney transplant. Information about the donor source was available in 524 out of 608 transplants, showing that 63% of patients had received a deceased donor and 37% a living-related donor. The 5-year cumulative incidence of transplantation is presented by dialysis modality in table 3 and figure 1C. The probability of receiving a transplant did not differ

significantly between the two treatment groups (HR: 1.03, 95% CI 0.78-1.37), even after adjustment for age, gender, and primary renal disease (aHR: 0.95, 95% CI 0.70-1.29).

Factors affecting the chance of transplantation included age at dialysis initiation and primary renal disease. Older patients were more likely to receive a transplant (HR: 1.05 per month increase in age, 95% CI 1.02-1.07; p<0.0001), as were patients with glomerulonephritis (compared to CAKUT, adjusted for age, aHR: 1.65, 95% CI 1.09-2.48; p=0.02), hereditary nephropathies (compared to CAKUT, adjusted for age, aHR: 1.54, 95% CI 1.15-2.06; p=0.004) and metabolic disorders (compared to CAKUT, HR: 2.23, 95% CI 1.43-3.47; p<0.001). The chance of receiving a transplant also differed significantly between countries, with notably Scandinavian countries showing higher transplant rates (appendix 1).

DISCUSSION

In this study, we report on the largest cohort of infants receiving maintenance dialysis ever examined. Overall survival in infants was 84% at 5 years after commencing dialysis, with similar mortality rates and transplant access in PD and HD patients, but a higher risk of early technique failure among those treated with HD.

Mortality rates in children receiving chronic dialysis are at least 30 times higher than in the general pediatric population, with even higher relative risks in very young children [8]. Five published reports have described the short and long-term survival of infants receiving maintenance dialysis [115, 117, 145, 204, 213] which ranged from 62% to 87% at 1 year and from 50% to 79% at 5 years. Our study places the average European infant on dialysis in the upper range of the reported survival. Recent pediatric RRT studies describe a trend of improving patient survival. Among 628 infants on chronic PD in the NAPRTCS database, the 3-year survival on dialysis improved from 75.8% to 84.6% between the periods 1992-1999 and 2000-2012 [110], and survival in infants who initiated chronic dialysis before 1 year of age approached that of older children in the more recent cohort. Based on previous studies, a mortality "risk profile" seems evident; apart from age at dialysis initiation, survival is influenced by small-for-gestational-age birth [117], primary renal disease [115, 142], the presence of co-morbidities [142, 145, 203], and residual urinary output [206]. Our study provides

corroborative evidence that early age at initiation of RRT and non-CAKUT etiology of ESRD are predictors of death on dialysis.

To date, the lack of sufficiently large infant cohorts has precluded the analysis of the impact of dialysis modality on survival in infants. The high rate of infants starting RRT in Europe and the establishment of a pan-European population based pediatric RRT registry allowed us to analyze short- and long-term mortality in this age group by dialysis modality. In our cohort, 13.5% of ESRD infants were started on HD. This proportion is higher than that reported in the 2011 NAPRTCS report [114], where 70 (8.2%) out of 927 children aged 0-1 year initiated dialysis on HD. Analyzing survival in more than 1600 children and adolescents with ESRD in Australia and New Zealand, McDonald et al. found no differences in mortality risk between HD and PD patients [8]. However, only 26 out of 1634 children included in this study were younger than 12 months. In a large US cohort of children initiating dialysis between 1990 and 2010 [34], Mitsnefes et al. reported a protective role of PD as compared with HD in children younger than 5 years at RRT start, but the proportion of infants was again negligible. In the current study, we found no difference in mortality risk between infants selected to start dialysis on PD or HD, respectively. Extracorporeal RRT is generally considered a reserve technology in infants, to be used when PD fails [120]. Current recommendations suggest HD as the initial modality in infants with metabolic disorders and in those with clinical contraindications for PD. Our findings suggest that HD is an equally safe alternative when PD fails, it is contraindicated or in those settings in which PD is unavailable or unfeasible.

Our results show that the overall probability for shifting the dialysis modality was higher in infants treated with HD as compared with PD. We did not find previous studies comparing technique survival in small children on chronic dialysis, since in most single-center case-series younger children were almost exclusively treated with PD. In our study, HD was most often withdrawn because of parental decision and poor central line function. HD in infants is most often performed in-center and with a median time of 12 hours per week. This schedule relieves families from burden of home therapy, but still requires a great effort; small patients have to be brought regularly to the pediatric dialysis unit, creating potential problems in the parents' work environment. The maintenance of a safe and efficient vascular access is also crucial in small children requiring RRT. Poor central line function due to catheter malposition

or thrombosis, and line infections are the most common limiting factors in achieving successful HD. When HD was used in infants for a continuous period of 3 months or longer, Shroff et al. found an infection rate leading to line revision of 35% [209], a value that is higher than the rates reported in other series including older children [214]. In our study, 20% of patients (where this information was available) had HD access failure, whereas two recent single-center studies reported remarkably low catheter infection rates and prolonged catheter survival times in infants receiving chronic HD [121, 211]. While PD enables preservation of vascular access for future use, when prescribing chronic HD in small children, both the immediate impact and potential long-term sequelae of a central vascular access positioned early in patients who will have a long period of RRT ahead of them should be considered. Experienced personnel devoted to the care and handling of HD catheters may represent a crucial factor for both catheter survival and outcome of infants receiving this mode of therapy.

Since small body size often precludes pre-emptive transplantation, infants usually spend a longer period on dialysis than older children. In our case, more than half of patients had received a kidney transplant after 3 years of dialysis, and 70% after 5 years. Importantly, the choice of pre-transplant dialysis modality did not influence access to transplantation. This concept has never been analyzed in children, although it is known in the adult dialysis population [215].

We are aware of the limitations of this registry study covering a long period of time during which the management of infants with ESRD may have changed (although era had little effect on the outcomes studied). Firstly, our ability to control for confounders (i.e. co-morbidities, urine output, patient's socioeconomic status and ethnicity) was limited by large amounts of missing data. In addition, we cannot exclude the possibility of residual confounding due to unmeasured variables or potential confounding by indication. In evaluating the association between exposure and outcomes, we used hard measures; however, there may be other outcome measures, such as quality of life, growth and development, nutritional status, and cardiovascular function that may be deemed equally important when discussing the long-term picture of infants receiving dialysis.

Despite these limitations, most of which are inherent to observational research, to our knowledge this is the largest study performed to date to compare clinical outcomes in infants on PD and HD. The study provides evidence that may help physicians in the decision-making process when facing the management of ESRD in infants. According to our results, patient survival and access to kidney transplantation appeared similar for infants initiating dialysis on HD and PD, suggesting that HD may represent a safe and effective alternative dialysis modality in infants with ESRD accepted for RRT. The choice of dialysis modality in this age group should take into account specific benefits and drawbacks of either technique, thus individualizing the choice that best fits the needs of the patient and family.

Appendix 2.

Cause	*HD* *N (%)*	*PD* *N (%)*
Abdominal complications (except for peritonitis in PD)	0 (0)	2 (4.3)
Cardiovascular instability	1 (4)	0 (0)
Dialysis access failure	5 (20)	1 (2.2)
Inadequate dialysis	1 (4)	1 (2.2)
Patient/family choice	14 (56)	3 (6.5)
Peritoneal catheter infection	0 (0)	6 (13)
Peritoneal membrane failure	0 (0)	1 (2.2)
Peritonitis	0 (0)	29 (63)
Other	4 (16)	3 (6.5)
Total	25 (100)	46 (100)

Appendix 1.

	HD *(n)*	*PD* *(n)*	*Total* *(n)*	*Patient survival* *HR (95% C.I.)*	*Modality switching* *HR (95% C.I.)*	*Transplantation* *HR (95% C.I.)*
Austria	7	26	33	1.07 (0.66-1.73)	1.11 (0.55-2.25)	2.15 (1.18-3.92)
Bosnia and Herzegovina	6	1	7	1.07 (0.61-1.87)	0.85 (0.33-2.19)	0.55 (0.11-2.85)
Belgium	10	23	33	0.88 (0.54-1.44)	0.70 (0.35-1.40)	0.77 (0.40-1.47)
Bulgaria	1	0	1	1.00 (0.55-1.80)	0.97 (0.32-2.95)	0.99 (0.13-7.81)
Belarus	1	3	4	1.02 (0.58-1.81)	1.63 (0.57-4.63)	0.89 (0.27-2.88)
Switzerland	2	26	28	0.82 (0.50-1.37)	1.40 (0.72-2.72)	0.91 (0.48-1.72)
Czech Republic	2	6	8	1.22 (0.71-2.12)	0.91 (0.35-2.36)	0.30 (0.07-1.22)
Germany	2	14	16	1.00 (0.58-1.72)	0.65 (0.25-1.68)	3.41 (1.45-8.05)
Denmark	3	13	16	0.98 (0.57-1.68)	0.85 (0.36-1.99)	1.98 (0.96-4.08)
Spain	23	62	85	1.15 (0.75-1.78)	0.87 (0.49-1.55)	2.59 (1.55-4.32)
Finland	1	93	94	0.66 (0.41-1.06)	1.48 (0.85-2.57)	4.63 (2.74-7.84)
France	12	61	73	0.92 (0.59-1.45)	1.40 (0.84-2.35)	1.87 (1.11-3.16)
Greece	0	19	19	0.95 (0.56-1.58)	1.01 (0.47-2.17)	0.19 (0.07-0.53)
Croatia	1	6	7	1.09 (0.62-1.92)	2.66 (1.00-7.09)	0.44 (0.13-1.54)
Hungary	0	5	5	0.92 (0.52-1.63)	1.20 (0.47-3.08)	0.67 (0.21-2.07)
Italy	6	121	127	0.77 (0.49-1.21)	1.26 (0.69-2.29)	1.15 (0.63-2.11)
Lithuania	0	4	4	0.93 (0.53-1.65)	0.72 (0.27-1.94)	0.32 (0.08-1.37)
The Netherlands	7	48	55	1.04 (0.67-1.63)	1.50 (0.90-2.50)	0.96 (0.55-1.68)
Norway	3	12	15	1.01 (0.58-1.74)	0.92 (0.39-2.20)	5.25 (2.50-11.03)
Poland	0	34	34	1.20 (0.75-1.93)	0.59 (0.27-1.30)	0.97 (0.51-1.86)
Portugal	0	13	13	1.00 (0.58-1.72)	0.83 (0.36-1.94)	0.51 (0.21-1.23)
Romania	3	5	8	1.20 (0.68-2.10)	0.80 (0.29-2.23)	1.02 (0.24-4.34)
Serbia	1	1	2	0.98 (0.55-1.76)	0.79 (0.28-2.19)	1.58 (0.43-5.79)
Russia	3	49	52	1.21 (0.77-1.91)	0.59 (0.29-1.19)	0.69 (0.36-1.34)
Sweden	0	51	51	1.36 (0.86-2.17)	1.16 (0.59-2.28)	5.87 (3.40-10.15)
Slovenia	2	1	3	0.96 (0.54-1.72)	1.26 (0.43-3.71)	0.58 (0.11-3.06)
Slovakia	0	2	2	0.97 (0.54-1.73)	0.90 (0.31-2.62)	0.75 (0.12-4.67)
Turkey	0	25	25	0.96 (0.58-1.58)	0.41 (0.17-0.95)	0.16 (0.05-0.59)
United Kingdom	50	193	243	0.96 (0.69-1.33)	1.90 (1.31-2.77)	1.27 (0.79-2.05)