AJKD
Original Investigation

Infants Requiring Maintenance Dialysis: Outcomes of Hemodialysis and Peritoneal Dialysis

Enrico Vidal, MD, PhD,[1] Karlijn J. van Stralen, PhD,[2] Nicholas C. Chesnaye, MSc,[2] Marjolein Bonthuis, PhD,[2] Christer Holmberg, MD,[3] Aleksandra Zurowska, MD,[4] Antonella Trivelli, MD,[5] José Eduardo Esteves Da Silva, MD,[6] Maria Herthelius, MD,[7] Brigitte Adams, MD,[8] Anna Bjerre, MD, PhD,[9] Augustina Jankauskiene, MD, PhD,[10] Polina Miteva, MD,[11] Khadizha Emirova, MD,[12] Aysun K. Bayazit, MD,[13] Christoph J. Mache, MD,[14] Ana Sánchez-Moreno, MD,[15] Jérôme Harambat, MD, PhD,[16] Jaap W. Groothoff, MD, PhD,[17] Kitty J. Jager, MD, PhD,[2,18] Franz Schaefer, MD,[19,*] and Enrico Verrina, MD,[5,*] on behalf of the ESPN/ERA-EDTA Registry[†]

Background: The impact of different dialysis modalities on clinical outcomes has not been explored in young infants with chronic kidney failure.

Study Design: Cohort study.

Setting & Participants: Data were extracted from the ESPN/ERA-EDTA Registry. This analysis included 1,063 infants 12 months or younger who initiated dialysis therapy in 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 therapy initiation, sex, underlying kidney disease, and country of residence.

Results: 917 infants initiated dialysis therapy on PD, and 146, on HD. Median age at dialysis therapy initiation was 4.5 (IQR, 0.7-7.9) months, and median body weight was 5.7 (IQR, 3.7-7.5) kg. Although the groups were homogeneous regarding age and sex, infants treated with PD more often had congenital anomalies of the kidney and urinary tract (CAKUT; 48% vs 27%), whereas those on HD therapy more frequently had metabolic disorders (12% vs 4%). Risk factors for death were younger age at dialysis therapy initiation (HR per each 1-month later initiation, 0.95; 95% CI, 0.90-0.97) and non-CAKUT cause of chronic kidney failure (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 for changing dialysis treatment (adjusted HR, 1.64; 95% CI, 1.17-2.31).

Limitations: Inability to control for unmeasured confounders not included in the Registry database and missing data (ie, comorbid conditions). Low statistical power because of relatively small number of participants.

Conclusions: Despite a widespread preconception that HD should be reserved for cases in which PD is not feasible, in Europe, we found 1 in 8 infants in need of maintenance dialysis to be initiated on HD therapy. Patient characteristics at dialysis therapy initiation, prospective survival, and time to transplantation were very similar for infants initiated on PD or HD therapy.

Am J Kidney Dis. 69(5):617-625.

From the [1]Department of Women's and Children's Health, University-Hospital of Padova, Padova, Italy; [2]ESPN/ERA-EDTA Registry, Academic Medical Center, Amsterdam, the Netherlands; [3]Children's Hospital, Helsinki University Central Hospital, Helsinki, Finland; [4]Department of Nephrology and Hypertension for Children and Adolescents, Medical University of Gdańsk, Gdańsk, Poland; [5]Dialysis Unit, IRCCS Giannina Gaslini, Genoa, Italy; [6]Departamento da Criança e da Família, Hospital de Santa Maria, Lisboa, Portugal; [7]Karolinska Institutet–Karolinska University Hospital Huddinge, Stockholm, Sweden; [8]Queen Fabiola Children's University Hospital, Brussels, Belgium; [9]Department of Pediatrics, Oslo University Hospital-Rikshospitalet, Oslo, Norway; [10]Vilnius University, Center for Pediatrics, Vilnius, Lithuania; [11]University Hospital for Active Treatment of Pediatric Diseases, Sofia Medical University, Sofia, Bulgaria; [12]Moscow State University of Medicine and Dentistry, Moscow, Russia; [13]Department of Pediatric Nephrology, Çukurova University, Adana, Turkey; [14]Medical University Graz, Graz, Austria; [15]Hospital Infantil Universitario Virgen del Rocío, Sevilla, Spain; [16]Department of Pediatrics, Bordeaux University Hospital, Bordeaux, France; [17]Departmnent of Pediatric Nephrology, Emma Children's Hospital AMC, University of Amsterdam; [18]ERA-EDTA Registry, Academic Medical Center, Amsterdam, the Netherlands; and [19]Division of Pediatric Nephrology, University of Heidelberg, Center for Pediatrics and Adolescent Medicine, Heidelberg, Germany.

[*]F.S. and E.Ve. contributed equally to this work.

[†]A list of the members of the ESPN/ERA-EDTA Registry is provided in the Acknowledgements.

Received March 17, 2016. Accepted in revised form September 1, 2016. Originally published online December 9, 2016.

Address correspondence to Marjolein Bonthuis, PhD, ESPN/ERA-EDTA Registry, Department of Medical Informatics, Academic Medical Center, 1100 DE, Amsterdam, the Netherlands. E-mail: m.bonthuis@amc.uva.nl

0272-6386
http://dx.doi.org/10.1053/j.ajkd.2016.09.024

INDEX WORDS: Pediatric nephrology; infant; maintenance dialysis; peritoneal dialysis (PD); hemodialysis (HD); end-stage renal disease (ESRD); survival; outcome; renal replacement therapy (RRT); RRT modality; European Registery for Children on Renal Replacement Therapy; ESPN/ERA-EDTA Registry.

The management of infants requiring maintenance dialysis represents a significant challenge for pediatric nephrologists. Difficulties feeding and maintaining fluid balance, growth failure, increased infection risks, and the presence of comorbid conditions complicate the management of chronic kidney failure in children younger than 1 year.[1] Consequently, mortality rates in infants on dialysis therapy are substantially higher than those in older children.[2]

In a multinational survey performed in the late 1990s, only 50% of pediatric nephrologists recommended initiation of renal replacement therapy (RRT) in infants with end-stage renal disease.[3] Since then, this attitude has been somewhat altered by reports indicating favorable results in growth, development, and kidney transplantation in infants on dialysis therapy given careful medical and nutritional management.[4-8] The number of infants receiving RRT has increased during the past decades and according to the 2011 North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) Report, 13.2% of patients were younger than 2 years at dialysis therapy initiation.[9,10]

Maintenance peritoneal dialysis (PD) represents the preferred dialysis modality in infants.[4-6,11,12] Advantages over hemodialysis (HD) include potentially better preservation of residual kidney function,[13] fewer dietary restrictions, avoidance of central vascular access placement, and the option to perform dialysis at home, although this requires a labor-intensive effort from the family.[14] The experience of treating infants with HD is limited.[15-19] In infants, HD is technically difficult and requires highly qualified nursing staff. However, when PD is contraindicated for clinical reasons, fails, or is inappropriate because of psychosocial problems, HD is still the only alternative treatment until kidney transplantation is feasible.[20]

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

METHODS

Study Population

We analyzed data from 1,081 infants who initiated RRT at 12 months or younger in January 1, 1991, to December 31, 2013. The cohort included all patients collected within the framework of the European Society for Pediatric Nephrology (ESPN)/European Renal Association−European Dialysis and Transplant Association (ERA-EDTA) Registry. Countries initiating infants on dialysis therapy 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 Table S1 (provided as online supplementary material).

We excluded patients who received preemptive kidney transplantation (n = 10) and patients whose dialysis modality was not clearly specified (n = 8). Patients entered the study on day 1 of dialysis therapy 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, sex, primary kidney 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, and serum creatinine, albumin, hemoglobin, and parathyroid hormone levels at baseline and during follow-up are provided on a voluntary basis, as well as the reasons for modality failure. Primary kidney disease and causes of death were determined by the patients' nephrologists and classified according to the ERA-EDTA coding system.[21] All national registries providing data to the ESPN/ERA-EDTA Registry followed their national legislation with regard to ethics committee approval and patient informed consent.

Statistical Analysis

The primary outcome studied was patient survival by dialysis modality. Secondary outcomes included comparison of clinical characteristics at dialysis therapy onset, technique survival, and the likelihood of transplantation in infants receiving PD or HD. The primary analysis was performed on an intention-to-treat basis, and therefore patients were assigned based on their initial dialysis modality (at day 30). Because infants often tend to switch between modalities, we also performed a per-protocol analysis, for which patients were assigned based on the treatment they received. For both the intention-to-treat and per-protocol analyses, patients were censored at transplantation, when kidney function recovered, when lost to follow-up, at the end of the 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). Cox regression was used to adjust for possible confounders, including age at dialysis therapy initiation, sex, and underlying kidney 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 effects of unobserved heterogeneity between countries.

Demographic baseline and clinical characteristics were described with median and interquartile range or proportion, as appropriate. The t test was used to test for differences between treatment groups for normally distributed continuous variables; Wilcoxon test, for non-normally distributed continuous variables; and χ^2 test, for categorical variables. Estimated glomerular filtration rate was calculated using the updated Schwartz formula.[22] Linear mixed models were used to compare mean serum albumin and hemoglobin levels, blood pressure z scores, and parathyroid hormone levels between the 2 treatment groups while adjusting for multiple measurements within a patient, as well as for confounders. Height values were normalized to z scores for chronologic age using recent national or European height-for-age charts.[23] Because serum hemoglobin level changes during the first year of life, age-specific z scores for hemoglobin level were calculated using KDIGO (Kidney Disease: Improving Global Outcomes) reference values.[24] For analyses of clinical and biochemical parameters, all measurements during the first year of dialysis therapy were used except for baseline measurements. Statistical tests were 2 tailed and were considered significant for $P < 0.05$. Data were analyzed using SAS software (version 9.4; SAS Institute Inc).

RESULTS

Patient Characteristics

We identified 1,063 infants initiating dialysis therapy. Of these, 919 started on PD, and 144, on HD therapy. At day 30, a total of 14 PD patients had switched to HD and 12 HD patients had switched to PD. Fourteen patients died before day 30 (PD, 12; HD, 2). Dialysis therapy was initiated in 649 (61%) infants at age 0 to 6 months and in 414 (39%) infants at age 7 to 12 months. Baseline patient characteristics by initial dialysis modality are shown in Table 1, whereas the estimated mean value for clinical and biochemical parameters during the first year of dialysis therapy are reported in Table 2. We found a higher proportion of hypoalbuminemic infants on PD therapy, 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 substantial blood losses with the extracorporeal systems, or, more likely, due to fluid overload at the time of blood sampling, which is usually performed immediately before a dialysis session.

In infants receiving PD, automated cycler regimens were applied in 71% of cases (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 of 21 patients had 3 days of HD per week, whereas 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 (median, 12 [range, 6-35] hours). Information

Table 1. Baseline Patient Characteristics by Initial Dialysis Modality

	Available Data	All (N = 1,063)	PD (n = 917)	HD (n = 146)	P[a]
Age, mo	1,063 (100)	4.5 [0.7 to 7.9]	4.3 [0.7 to 7.9]	5.1 [1.3 to 7.9]	0.4
Female sex	1,063 (100)	33.2	32.4	38.4	0.2
Body weight, kg	576 (54)	5.7 [3.7 to 7.5]	5.5 [3.6 to 7.5]	6.3 [4.2 to 8.0]	0.06[b]
Height, cm	473 (44)	60 [52 to 67]	60 [52 to 67]	62 [55 to 67]	0.2[b]
Height z score	473 (44)	−1.1 [−2.4 to −0.3]	−1.3 [−2.4 to 0.2]	−0.9 [−2.6 to 0.5]	0.2
BMI, kg/m^2	491 (44)	16.6 [15.3 to 18.8]	16.6 [15.3 to 18.9]	16.5 [15.4 to 18.7]	0.9
eGFR, mL/min/1.73 m^2	313 (29)	6.1 [4.4 to 8.4]	6.1 [4.4 to 8.0]	6.3 [4.2 to 8.8]	0.7
Primary diagnostic group	1,063 (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	0.0	1.6	
Miscellaneous		9.4	8.0	17.8	
Unknown		3.5	3.3	4.7	

Note: Values for categorical variables are given as count (proportion) or percentage; values for continuous variables, as median [interquartile range].

Abbreviations: BMI, body mass index; CAKUT, congenital anomalies of kidney and urinary tract; eGFR, estimated glomerular filtration rate; HD, hemodialysis; HUS, hemolytic uremic syndrome; PD, peritoneal dialysis.

[a]*P* values refer to comparison between PD and HD.

[b]Adjusted for age at initiation.

Table 2. Unadjusted Mean Clinical and Biochemical Parameters During First Year of Dialysis Treatment

	Overall			PD			HD			
	N[a]	N[b]	Mean (95% CI)	N[a]	N[b]	Mean (95% CI)	N[a]	N[b]	Mean (95% CI)	P[c]
BMI, kg/m^2 *z* scores	705	1,920	16.1 (15.9 to 16.3)	615	1,666	16.1 (15.9 to 16.3)	90	254	16.3 (15.7 to 16.9)	0.6
SBP	496	1,095	1.2 (1.0 to 1.4)	438	974	1.1 (1.0 to 1.3)	58	121	1.5 (1.0 to 2.0)	0.2
DBP	434	983	1.7 (1.5 to 1.8)	388	877	1.6 (1.5 to 1.8)	46	106	2.1 (1.7 to 2.5)	0.03
Hb	498	1,068	−1.62 (−1.84 to −1.40)	423	900	−1.40 (−1.64 to −1.15)	75	168	−2.73 (−3.28 to −2.17)	<0.001
Serum albumin, g/dL	491	977	32.5 (31.8 to 33.2)	434	878	32.1 (31.3 to 32.8)	57	99	36.4 (34.2 to 38.6)	<0.001
PTH, pg/mL	422	892	496 (438 to 555)	360	765	500 (433 to 568)	62	127	474 (321 to 628)	0.8

Abbreviations: BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure (in mm Hg); Hb, hemoglobin (in g/dL); HD, hemodialysis; PD, peritoneal dialysis; PTH, serum parathyroid hormone; SBP, systolic blood pressure (in mm Hg).
[a]Number of patients.
[b]Number of measurements.
[c]*P* values refer to comparison between PD and HD.

for type of vascular access was available for 15 patients; a central catheter was used in 14 cases (median age at implantation, 8.4 months) and an arteriovenous graft was used in 1 case (placed at age 7.5 months).

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/1,000 patient-years. The overall cumulative incidence of death at 1, 2, and 5 years was 10.0% (95% confidence interval [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 RRT (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 from cardiovascular disease, 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 causes of death between infants initiating dialysis therapy before and after 2000. Causes of death according to dialysis modality were also comparable.

Younger age at dialysis therapy initiation was a significant risk factor for death, with a 5% lower risk per month of later initiation (hazard ratio [HR], 0.95; 95% CI, 0.90-0.97; $P < 0.001$). A significantly higher risk for death was found in patients with non−congenital anomalies of kidney and urinary tract (CAKUT) diseases (HR, 1.49; 95% CI, 1.08-2.04; $P = 0.03$), whereas there was no significant mortality risk difference by sex (female vs male: HR, 1.28; 95% CI, 0.95-1.71) or between infants initiating dialysis therapy before and after 2000 (2000 or later vs pre-2000: HR, 0.93; 95% CI, 0.67-1.29). Survival was also similar across countries (country hazard ratios are presented in Table S1).

Mortality Risk Comparison Between HD and PD

Crude 5-year mortality rates were 51.0 deaths/1,000 patient-years for PD and 62.2 deaths/1,000 patient-years for HD. The 5-year cumulative incidence of death is presented by dialysis modality in Table 3 and Fig 1A. In the intention-to-treat analysis, while censoring for transplantation, crude (HR, 1.08;

Table 3. Five-Year Cumulative Incidence of Death, Modality Switch, and Transplantation and Corresponding aHRs

Outcome	Overall	HD	PD	aHR for HD vs PD (95% CI)
Death[a]	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[b]	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[c]	70.2% (67.1%-73.4%)	69.0% (60.2%-77.9%)	70.5% (67.1%-73.8%)	0.95 (0.70-1.29)

Note: Unless otherwise indicated, values are given as 5-year cumulative incidence (95% confidence interval).
Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HD, hemodialysis; PD, peritoneal dialysis.
[a]Death with transplantation as competing risk.
[b]Dialysis modality switch with both death and transplantation as competing risks.
[c]Transplantation with death as competing risk.

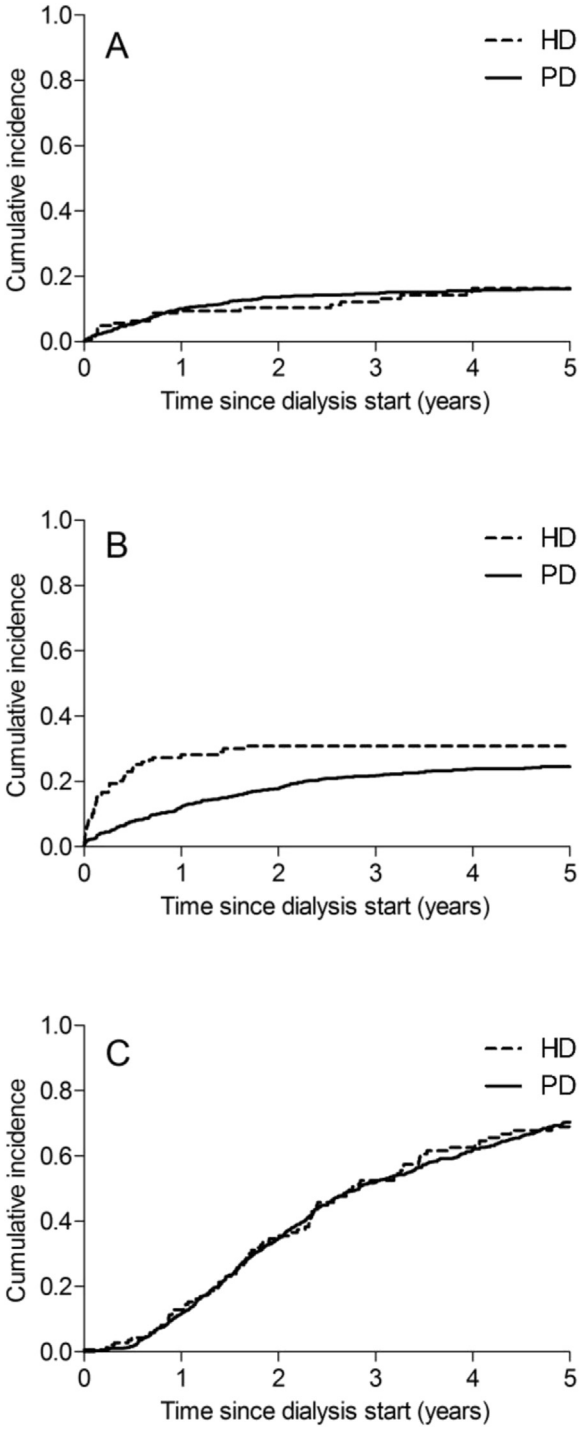

Figure 1. Cumulative incidence curves for (A) death (with transplantation as a competing risk), (B) modality switching (with both death and transplantation as competing risks), and (C) transplantation (with death as a competing risk). Abbreviations: HD, hemodialysis; PD, peritoneal dialysis.

95% CI, 0.69-1.68) and adjusted (aHR, 1.06; 95% CI, 0.67-1.67) HRs did not differ significantly between treatment groups. HRs for HD versus PD did not differ significantly between infants initiating dialysis therapy before and from 2000 onwards (P for interaction = 0.6). Among infants whose initial dialysis modality was PD, 135 of 143 deaths occurred while still on PD therapy and 8 infants died while switched to HD therapy. Among HD patients, 19 of 23 deaths occurred while still on HD therapy and 4 were while switched to PD therapy. In the per-protocol analysis, crude (HR, 0.76; 95% CI, 0.47-1.22) and adjusted (aHR, 0.73; 95% CI, 0.45-1.18) HRs did not differ significantly between treatment groups.

Experience and skills in treating infants on HD therapy may vary across European countries. To explore the potential impact on survival of a country's experience in treating infants on HD therapy, we first looked at the interaction effect between country and dialysis modality on mortality and found that this was not statistically significant (type 3 test: $P = 0.2$). In addition, we added the ratio of HD to PD patients and the proportion of HD patients per country as proxies for HD country experience to the Cox model, which had little effect on risk for mortality with HD versus PD (HRs of 1.00 [95% CI, 0.62-1.62] and 0.96 [95% CI, 0.59-1.57], respectively). Survival remained similar after excluding countries that had no infants treated with HD (aHR, 1.07; 95% CI, 0.64-1.70).

Technique Survival

Overall cumulative incidences of dialysis modality switching at 1, 2, and 5 years were 14.5% (95% CI, 12.4%-16.7%), 19.7% (95% CI, 17.3%-22.2%), and 25.5% (95% CI, 22.7%-28.3%), respectively. The 5-year cumulative incidence for dialysis modality switching is presented by dialysis modality in Table 3 and Fig 1B. Patients on HD therapy had a 1.64-fold higher risk for changing dialysis treatment (95% CI, 1.17-2.31; $P = 0.004$) as compared with patients on PD therapy. 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 therapy (aHR, 2.79; 95% CI, 1.81-3.99). We registered 198 modality failures among PD and 44 among HD infants. In Table S2, reasons for modality failure are reported in detail for patients for whom this information was available: 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 for changing the type of dialysis (HR per 1 month older, 0.96 [95% CI, 0.93-0.99]; $P = 0.03$). This was not the case among PD patients (HR per 1 month older, 0.98 [95% CI, 0.95-1.02]; $P = 0.4$), but was strongly present among HD patients (HR per 1 month older, 0.82 [95% CI, 0.75-0.91]; $P < 0.001$). Among patients initiating on PD therapy and compared with those

with CAKUT diseases, 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 kidney disease. There were differences in the likelihood of switching dialysis modalities between countries (Table S1). Compared with other European counties, the United Kingdom had a significant increased risk for modality switching (HR, 1.90; 95% CI, 1.31-2.77).

Time to Transplantation

Within 5 years after dialysis therapy initiation, 70.2% (95% CI, 67.1%-73.4%) of all patients had received a kidney transplant. Information about the donor source was available for 524 of 608 transplants, showing that 63% of patients had received deceased donor donation, and 37%, living related donor donation. The 5-year cumulative incidence of transplantation is presented by dialysis modality in Table 3 and Fig 1C. The probability of receiving a transplant did not differ significantly between the 2 treatment groups (HR, 1.03; 95% CI, 0.78-1.37), even after adjustment for age, sex, and primary kidney disease (aHR, 0.95; 95% CI, 0.70-1.29).

Factors affecting the chance of transplantation included age at dialysis therapy initiation and primary kidney disease. Older patients were more likely to receive a transplant (HR per 1 month older, 1.05 [95% CI, 1.02-1.07]; $P < 0.001$), as were patients with glomerulonephritis and hereditary nephropathies (compared to CAKUT, adjusted for age: aHRs of 1.65 [95% CI, 1.09-2.48; $P = 0.02$] and 1.54 [95% CI, 1.15-2.06; $P = 0.004$], respectively) 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 transplantation rates (Table S1).

DISCUSSION

In this study, we report on what is to our knowledge the largest cohort of infants receiving maintenance dialysis ever examined. Overall survival in infants was 84% at 5 years after dialysis therapy initiation, with similar mortality rates and transplantation access in PD and HD patients, but higher risk for early technique failure among those treated with HD.

For children receiving maintenance dialysis, mortality rates are at least 30 times higher than those in the general pediatric population; relative risks are even greater in very young children.[25] Five published reports have described the short- and long-term survival of infants receiving maintenance dialysis,[1,2,7,20,26] which ranged from 62% to 87% at 1 year and from 50% to 79% at 5 years, respectively. Our study places the average European infant receiving dialysis in the upper range of reported survival. Recent pediatric dialysis studies describe a trend of improving patient survival. Among 628 infants receiving maintenance PD in the NAPRTCS database, 3-year survival on dialysis therapy improved from 75.8% to 84.6% between 1992 to 1999 and 2000 to 2012,[27] and survival in infants who initiated maintenance dialysis therapy 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 therapy initiation, survival is influenced by small-for-gestational-age birth,[1] primary kidney disease,[2,28] the presence of comorbid conditions,[6,20,28] and residual urinary output.[28] Our study provides corroborative evidence that early age at dialysis therapy initiation and non-CAKUT cause of chronic kidney failure are predictors of death while being treated with 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 infants with chronic kidney failure were initiated on HD therapy. This proportion is higher than that reported in the 2011 NAPRTCS report,[10] in which 70 of 927 (8.2%) children aged 0 to 1 year initiated dialysis therapy with HD. Analyzing survival in more than 1,600 children and adolescents with chronic kidney failure in Australia and New Zealand, McDonald and Craig[25] found no differences in mortality risk between HD and PD patients. However, only 26 of 1,634 children included in this study were younger than 12 months. In a large US cohort of children initiating dialysis therapy in 1990 to 2010, Mitsnefes et al[29] reported a protective role of PD as compared to HD in children younger than 5 years at RRT initiation, but the proportion of infants was again negligible. In the current study, we found no difference in mortality risk between infants selected to initiate dialysis therapy on PD or HD, respectively. Extracorporeal RRT is generally considered a reserve technology in infants, to be used when PD fails.[12] Current recommendations suggest HD as the initial modality in infants with metabolic disorders and those with clinical contraindications for PD. Our findings suggest that HD is an equally safe alternative when PD fails, is contraindicated, or in settings in which PD is unavailable or unfeasible.

Our results show that the overall probability for shifting dialysis modality was higher in infants initially treated with HD as compared to PD. We did not find previous studies comparing technique survival in small children on maintenance dialysis therapy because in most single-center case series, younger children were almost exclusively treated with PD. In our study, HD therapy was most often withdrawn because of parental decision and poor central catheter function. In infants, HD is most often performed in-center and with a median time of 12 hours per week. This schedule relieves families from the 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. Maintenance of a safe and efficient vascular access is also crucial in small children requiring RRT. Poor central catheter 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[16] found an infection rate leading to catheter revision of 35%, a value that is higher than rates reported in other series including older children.[30] In our study, 20% of patients (when this information was available) had HD access failure, whereas 2 recent single-center studies reported extremely low catheter infection rates, as well as prolonged catheter survival times in infants receiving maintenance HD.[18,19] Although PD allows preservation of vascular access for future use, when prescribing maintenance 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 dialysis 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 the outcome of infants receiving this mode of therapy.

Because small body size often precludes preemptive transplantation, infants usually spend a longer period on dialysis than older children. In our case, more than half the patients had received a kidney transplant after 3 years of dialysis therapy, and 70%, after 5 years. Importantly, the choice of pretransplantation 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.[31]

We are aware of the limitations of this Registry study covering a long period during which the management of infants with chronic kidney failure may have changed (although era had little effect on the outcomes studied). First, our ability to control for confounders (ie, comorbid conditions, urine output, and the 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, other outcome measures (eg, quality of life, growth and development, nutritional status, and cardiovascular function) may be deemed equally important when discussing the long-term picture of infants receiving dialysis. Last, the statistical power for comparing outcomes between dialysis modalities might be inadequate because of a relatively small number of participants.

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 therapy. The study provides evidence that may help physicians in the decision-making process when facing the management of chronic kidney failure in infants. According to our results, patient survival and access to kidney transplantation appeared similar for infants initiating dialysis therapy on PD or HD, suggesting that HD may represent a safe and effective alternative dialysis modality in infants with chronic kidney failure. 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.

ACKNOWLEDGEMENTS

This article was written on behalf of the ESPN/ERA-EDTA Registry and the ERA-EDTA Registry, which is an official body of the ERA-EDTA.

The authors thank E.N. Levtchenko, D. Haffner, Z. Massy, and C. Stefanidis for being members of the ESPN/ERA-EDTA Registry Committee; and D. Shtiza, R. Kramar, R. Oberbauer, S. Baiko, A. Sukalo, K. van Hoeck, F. Collart, J.M. des Grottes, D. Pokrajac, D. Roussinov, D. Batinić, M. Lemac, J. Slavicek, T. Seeman, K. Vondrak, J.G. Heaf, U. Toots, P. Finne, C. Grönhagen-Riska, C. Couchoud, M. Lasalle, E. Sahpazova, N. Abazi, N. Ristoka Bojkovska, G. von Gersdorff, C. Scholz, B. Tönshoff, K. Krupka, B. Höcker, L. Pape, N. Afentakis, A. Kapogiannis, N. Printza, G. Reusz, C.S. Berecki, A. Szabó, T. Szabó, Z.S. Györke, E. Kis, R. Palsson, V. Edvardsson, B. Gianoglio, S. Maringhini, C. Pecoraro, S. Picca, S. Testa, S. Rudaitis, V. Said-Conti, S. Gatcan, O. Berbeca, N. Zaikova, S. Pavićević, T. Leivestad, I. Zagozdzon, C. Mota, M. Almeida, C. Afonso, G. Mircescu, L. Garneata, E.A. Molchanova, N.A. Tomilina, B.T. Bikbov, M. Kostic, A. Peco-Antic, B. Spasojevic-Dimitrijeva, G. Milosevski-Lomic, D. Paripovic, S. Puric, D. Kruscic, L. Podracka, G. Kolvek, J. Buturovic-Ponikvar, G. Novljan, N. Battelino, A. Alonso Melgar and the Spanish Pediatric Registry, S. Schön, K.G. Prütz, L. Backmän, M. Stendahl, M. Evans, B. Rippe, C.E. Kuenhi, E. Maurer, G.F. Laube, S. Tschumi, P. Parvex, A. Hoitsma, A. Hemke, and all centers participating in the RichQ

study, R. Topaloglu, D. Ivanov, R. Pruthi, F. Braddon, S. Mannings, A. Cassula, and M.D. Sinha for contributing data to the ESPN/ERA-EDTA Registry.

Aspects of this work were presented in abstract form at the 51st ERA-EDTA Congress, May 31 to June 3, 2014, Amsterdam, the Netherlands.

The authors thank the patients, their parents, and the staff of all the dialysis and transplantation units that have contributed data via their national registries and contact persons.

Support: None.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Contributions: Research idea and study design: EVi, KJvS, NCC, KJJ, FS, EVe; data acquisition: KJvS, NCC, MB, CH, AZ, AT, JEEDS, MH, BA, AB, AJ, PM, KE, AKB, CJM, AS-M, JH, JWG; data analysis/interpretation: EVi, KJvS, NCC, MB, JH, JWG, KJJ, FS, EVe; statistical analysis: EVi, KJvS, NCC; supervision or mentorship: KJJ, FS, EVe. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. EVi takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Peer Review: Evaluated by 3 external peer reviewers, a Statistical Editor, a Co-Editor, and Editor-in-Chief Levey.

SUPPLEMENTARY MATERIAL

Table S1: PD and HD patient distribution by country and HRs for patient survival, dialysis modality switching, and transplantation likelihood.

Table S2: Reasons for dialysis failure, by dialysis modality, in patients for whom data are available.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2016.09.024) is available at www.ajkd.org

REFERENCES

1. Mekahli D, Shaw V, Ledermann SE, et al. Long-term outcome of infants with severe chronic kidney disease. *Clin J Am Soc Nephrol*. 2010;5(1):10-17.

2. Alexander RT, Foster BJ, Tonelli MA, et al. Survival and transplantation outcomes of children less than 2 years of age with end-stage renal disease. *Pediatr Nephrol*. 2012;27(10):1975-1983.

3. Geary DF. Attitudes of paediatric nephrologists to management of end-stage renal disease in infants. *J Pediatr*. 1998;133:154-156.

4. Ledermann SE, Scanes ME, Fernando ON, et al. Long-term outcome of peritoneal dialysis in infants. *J Pediatr*. 2000;136:24-29.

5. Laakkonen H, Holtta T, Lonnqvist T, et al. Peritoneal dialysis in children under two years of age. *Nephrol Dial Transplant*. 2008;23:1747-1753.

6. Vidal E, Edefonti A, Murer L, et al. Peritoneal dialysis in infants: the experience of the Italian Registry of Paediatric Chronic Dialysis. *Nephrol Dial Transplant*. 2012;27(1):388-395.

7. Wedekin M, Ehrich JHH, Offner G, et al. Renal replacement therapy in infants with chronic renal failure in the first year of life. *Clin J Am Soc Nephrol*. 2010;5:18-23.

8. Teh JC, Frieling ML, Sienna JL, et al. Attitudes of caregivers to management of end-stage renal disease in infants. *Perit Dial Int*. 2011;31(4):459-465.

9. van der Heijden BJ, van Dijk PC, Verrier-Jones K, et al. Renal replacement therapy in children: data from 12 registries in Europe. *Pediatr Nephrol*. 2004;19(2):213-221.

10. North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) Annual Report, 2011. https://web.emmes.com/study/ped/annlrept/annualrept2011.pdf. Accessed February 5, 2016.

11. Ronnholm KAR, Holmberg C. Peritoneal dialysis in infants. *Pediatr Nephrol*. 2006;21:751-756.

12. Zurowska AM, Fischbach M, Watson AR, et al. European Paediatric Dialysis Working Group. Clinical practice recommendations for the care of infants with stage 5 chronic kidney disease (CKD5). *Pediatr Nephrol*. 2013;28(9):1739-1748.

13. Feber J, Schärer K, Schaefer F, et al. Residual renal function in children on haemodialysis and peritoneal dialysis therapy. *Pediatr Nephrol*. 1994;8(5):579-583.

14. Kiliś-Pstrusińska K, Wasilewska A, Medyńska A, et al. Psychosocial aspects of children and families of children treated with automated peritoneal dialysis. *Pediatr Nephrol*. 2013;28(11):2157-2167.

15. Donckerwolcke RA, Bunchman TE. Hemodialysis in infants and small children. *Pediatr Nephrol*. 1994;8:103-106.

16. Shroff R, Wight E, Ledermann S, et al. Chronic hemodialysis in infants and children under 2 years of age. *Pediatr Nephrol*. 2003;18:378-383.

17. Feinstein S, Rinat C, Becker-Cohen R, et al. The outcome of chronic dialysis in infants and toddlers – advantages and drawbacks of haemodialysis. *Nephrol Dial Transplant*. 2008;23:1336-1345.

18. Quinlan C, Bates M, Sheils A, et al. Chronic hemodialysis in children weighing less than 10 kg. *Pediatr Nephrol*. 2013;28:803-809.

19. Pollack S, Eisenstein I, Tarabeih M, Shasha-Lavski H, Magen D, Zelikovic I. Long-term hemodialysis therapy in neonates and infants with end-stage renal disease: a 16-year experience and outcome. *Pediatr Nephrol*. 2016;31(2):305-313.

20. Hijazi R, Abitbol CL, Chandar J, et al. Twenty-five years of infant dialysis: a single center experience. *J Pediatr*. 2009;155(1):111-117.

21. ERA-EDTA Registry. *ERA-EDTA Registry Annual Report 2013*. Amsterdam, the Netherlands: Department of Medical Informatics, Academic Medical Center. 2015.

22. Schwartz GJ, Muñoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol*. 2009;20(3):629-637.

23. Bonthuis M, van Stralen KJ, Verrina E, et al. Use of national and international growth charts for studying height in European children: development of up-to-date European height-for-age charts. *PLoS One*. 2012;7(8):e42506.

24. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int Suppl*. 2012;2:279-335.

25. McDonald SP, Craig JC; Australian and New Zealand Paediatric Nephrology Association. Long-term survival of children with end-stage renal disease. *N Engl J Med*. 2004;350(26):2654-2662.

26. Ehrich JH, Rizzoni G, Brunner FP, et al. Renal replacement therapy for end-stage renal failure before 2 years of age. *Nephrol Dial Transplant*. 1992;7(12):1171-1177.

27. Carey WA, Martz KL, Warady BA. Outcome of patients initiating chronic peritoneal dialysis during the first year of life. *Pediatrics*. 2015;136(3):e615-e622.

28. Wood EG, Hand M, Briscoe DM, et al. Risk factors for mortality in infants and young children on dialysis. *Am J Kidney Dis*. 2001;37(3):573-579.

29. Mitsnefes MM, Laskin BL, Dahhou M, et al. Mortality risk among children initially treated with dialysis for end-stage kidney disease, 1990-2010. *JAMA*. 2013;309(18):1921-1929.

30. Goldstein SL, Macierowski CT, Jabs K. Hemodialysis catheter survival and complications in children and adolescents. *Pediatr Nephrol*. 1997;11(1):74-77.

31. Chalem Y, Ryckelynck JP, Tuppin P, et al. Access to, and outcome of, renal transplantation according to treatment modality of end-stage renal disease in France. *Kidney Int*. 2005;67(6):2448-2453.