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EDUCATIONAL REVIEW

Lessons learned from the ESPN/ERA–EDTA Registry

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Abstract End-stage renal disease (ESRD) in children is a medically challenging condition. Due to its rarity and special features, methodologically sound collaborative studies are required. In 2007, a new European registry of pediatric renal replacement therapy (RRT), the ESPN/ERA–EDTA Registry, was launched. In recent years, the Registry has provided comprehensive data on incidence, prevalence, patient characteristics, RRT modalities, and mortality in pediatric ESRD, along with relevant insights into cardiovascular risk, anemia, nutrition and growth, transplantation outcomes, and rare diseases. In this review, we describe the study design and structure underlying the ESPN/ERA–EDTA Registry, summarize the major research findings from more than 20 publications, and discuss current limitations and the future challenges to overcome.

Keywords ESPN/ERA–EDTA registry · End-stage renal disease · Pediatric patients · Renal replacement therapy · Comorbidities · Outcome

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Introduction

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) in children are rare conditions, and therefore collaborative projects are needed. The European Society for Paediatric Nephrology (ESPN)/European Renal Association (ERA)–European Dialysis and Transplant Association (EDTA) Registry, i.e., the ESPN/ERA–EDTA Registry, was established in 2007, with the aim to collect and analyze data from all infants, children, and adolescents receiving renal replacement therapy (RRT) in Europe, including data from the ERA–EDTA Registry, as well as data from national pediatric registries and individual patient data from countries without national registries.

Historical perspective

The ERA–EDTA Registry was first launched in Amsterdam in 1964 [1]. The office moved to London in 1976 where it remained until the end of 1999. In 1971, a pediatric registry was added to the ERA–EDTA Registry, and the first annual reports on RRT in children aged <15 years were published in the early 1970s [2, 3]. This registry, which included data on patient level and center level, was successful for about 25 years. In 1993, a paper reported the 20-year experience of the pediatric RRT arm of the ERA–EDTA Registry, which included with >8,000 patients, summarizing a total of 49 publications [4]. However, the Registry experienced major problems in the 1990s and, after a last report published in 1996, ceased to provide pediatric data [5]. In 2000, the ERA-EDTA Registry made a completely new start and moved to the Academic Medical Center (AMC) in Amsterdam. Until 2007, data collection on children on RRT in Europe was limited to that of the ERA–EDTA Registry, but a new pediatric registry, the

ESPN/ERA–EDTA Registry, was launched in 2007 [6]. Since then, there has been a progressive increase in the number of countries providing data to the Registry, with 37 countries currently participating, covering a general population of more than 100 million children under the age of 15 years (Fig. 1).

Design and data collection

The ESPN/ERA–EDTA Registry is a population-based registry which collects individual data on RRT on an annual basis via European national registries. Data are collected by three methods. First, some countries have a specific pediatric RRT registry which provides data directly to the ESPN/ERA–EDTA Registry. Second, some countries have a national registry that participates in the ERA–EDTA Registry (providing a limited amount of variables) and covers both adults and children. These registries provide these data via this route. Third, for countries without a national registry, data on individual patients are collected directly via either Excel or Access sheets or an Internet-based data collection tool.

The database includes a so-called "essential dataset", namely, core data on demography, primary renal diagnosis (PRD), treatment modality, and outcomes that have to be provided to the Registry for all patients. Other data, such as anthropometric, clinical and medication-related parameters, and comorbidities are collected on a voluntary basis, and their completeness and provision differs per country. Finally, some additional data are now being collected for specific projects.

Funding and coordination

Appropriate funding and coordination are critical for an international registry such as the ESPN/ERA–EDTA Registry to meet the highest standards for data completeness, timeliness, and quality.

Funding of the ESPN/ERA–EDTA Registry is provided by the ERA–EDTA and the ESPN. The Registry has also obtained grants from the European Union via the Health Framework Programs. Furthermore, an unrestricted educational grant was initially provided by Amgen Inc. to assist the ESPN in the financial support of the Registry. The sites are not reimbursed for submission of the data.

The Registry staff comprises a study coordinator, a PhD student, and an advisor, whereas the scientific work is embedded as one of AMC's research lines. Students and visiting researchers from all over Europe also regularly contribute to data collection and analysis. Each national registry has its own quality data procedures, including audit. However, after retrieval of the data, consistency and quality checks are performed by the staff of the ESPN/ERA–EDTA Registry, and any inconsistencies are returned to the specific country of origin.

Current findings

The major findings of the ESPN/ERA–EDTA Registry are summarized in Table 1.

Incidence, prevalence, patient characteristics, and treatment modalities

Between 2009 and 2011, 1,697 children aged <15 years were started on RRT in 37 European countries, corresponding to an unadjusted incidence rate of 5.5 per million age-related population (pmarp) [7]. This rate was 6.5 pmarp in 2007 [8]. Among pediatric patients aged <20 years from 16 countries contributing to the ERA–EDTA Registry, the incidence has remained stable at 8–10 pmarp since 2001 [9]. The incidence of pediatric RRT in Europe has varied markedly between countries, with the lowest incidence in Eastern Europe (3.6 pmarp) followed by Southern (7.2 pmarp) and Western (7.8 pmarp) Europe, and the highest incidence in Northern Europe (8.1 pmarp) [10]. This difference between regions also explains the drop in incidence rate between 2007 and 2009–2011, as data from more Eastern European countries have been included in the recent period. These variations in incidence of RRT are mainly explained by differences in country macroeconomics which limit the provision of treatment, particularly in the youngest group of children with ESRD [10]. The most common cause of ESRD was congenital anomalies of the kidney and urinary tract (CAKUT), accounting for around 40 % of incident patients aged 0–14 years. Other major primary renal diseases included glomerulonephritis (15 %) and cystic kidney diseases (10 %). Almost half of children started RRT with peritoneal dialysis (PD) (47 %), followed by hemodialysis (HD) (33 %), and preemptive transplantation (20 %). The median estimated glomerular filtration rate (eGFR) at the start of RRT was 9 ml/min/1.73 m^2 [7]. By comparison, the incidence rate in children aged <15 years in the USA was twofold higher than that in Europe (11.6 pmarp in 2011), HD was the first treatment modality used in North American children, and RRT was started at a higher eGFR than in Europe [11, 12]. Among European children, eGFR at the start of RRT was mainly explained by age, gender, modality of RRT, and timing of nephrology referral in pre-RRT care [13]. The prevalence by the end of 2011 was 28 pmarp in children aged <15 years and 58 pmarp in children aged <20 years [7]. Similar to the incidence, considerable variations exist in

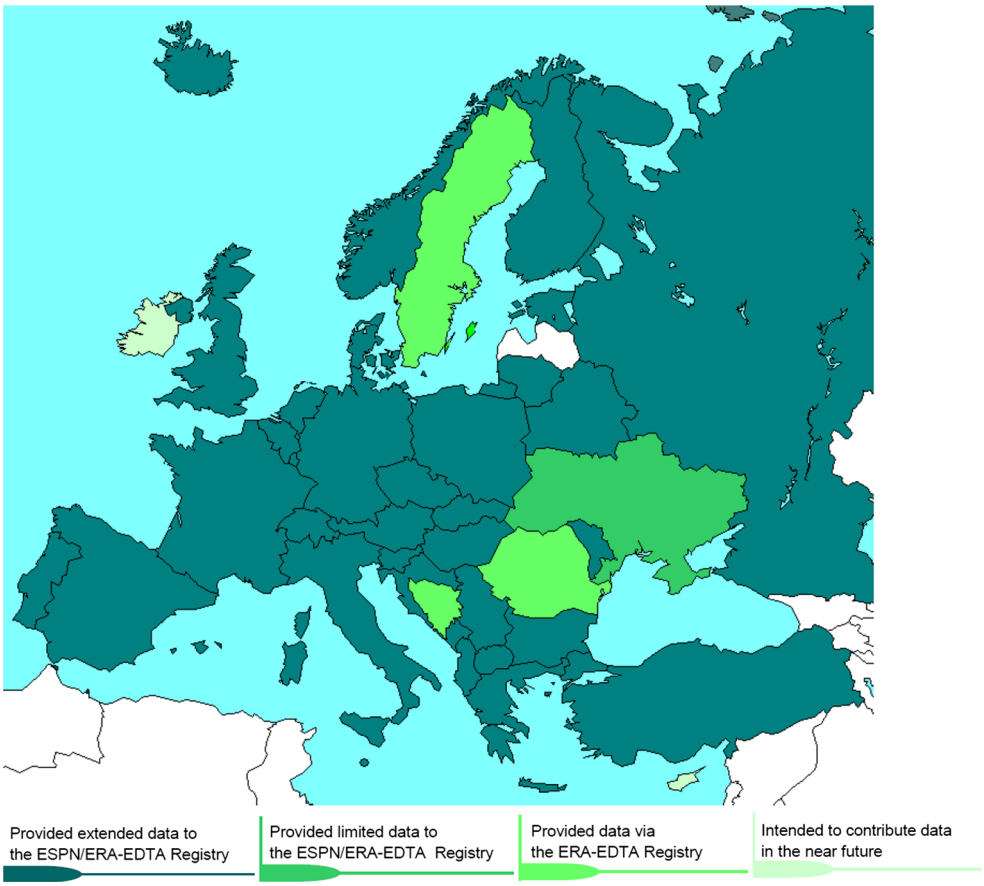

Fig. 1 Countries participating in the European Society for Paediatric Nephrology/European Renal Association–European Dialysis and Transplant Association (*ESPN/ERA–EDTA*) Registry at the end of 2014

the prevalence of RRT within Europe, with a prevalence ranging from <10 pmarp in several countries to >80 pmarp in Finland [7]. Although the reasons for differences in pediatric RRT demographics in Europe remain largely unknown, economic disparities between countries do affect these figures, as recently shown in PD prevalence and kidney transplantation rate and prevalence [14–16].

Cardiovascular disease

Hypertension is a well-known complication of CKD and an important risk factor for cardiovascular disease, one of the leading causes of death in ESRD children and young adults. A report from the ESPN/ERA–EDTA Registry assessed the prevalence of and risk factors for hypertension among >3,000 children on RRT from 15 countries [17]. Hypertension, defined as either systolic or diastolic blood pressures (BP) of≥95th percentile or the use of antihypertensive medication, was observed in 70 % of HD, 68 % of PD, and 66 % of transplant recipients without significant change between 1999 and 2009. Uncontrolled hypertension irrespective of the use of antihypertensive medication was found in 45 % of HD, 35 % of PD, and 21 % of transplanted patients. Similarly, poor control of hypertension has been reported in U.S. children on RRT [18]. The ESPN/ERA–EDTA Registry study also confirmed that younger age (<3 years), a relatively short time on RRT, and being on HD as compared to kidney transplantation or PD were independent risk factors for uncontrolled hypertension [17]. In addition, the highest BP in children on HD was found among those with the lowest body mass index (BMI). Conversely, BP was significantly positively associated with BMI in transplanted children. Longitudinal analyses suggested that hypertensive HD patients or transplant recipients tend to decrease their BP over time, while a persistent hypertensive status was seen among those on PD. This study highlighted the magnitude of the problem of hypertension in children with ESRD and recommended that greater efforts should be made to control BP effectively in this population.

Dyslipidemia, another well-known cardiovascular risk factor, was found among 85 % of PD, 76 % of HD, and 56 % of transplanted patients included in an ESPN/ERA–EDTA Registry study on almost 1,000 patients from 19 different European countries [19]. Although less prevalent than hypertriglyceridemia (74 % PD, 61 % HD, and 23 % after transplantation), elevated non-high-density lipid (HDL)-cholesterol levels, which seem to be most important for cardiovascular disease, were found in one third of patients. The youngest patients on PD showed the highest triglyceride and non-HDL-cholesterol levels, probably caused by the glucose load from the dialysis fluid and supplemental feeding.

Table 1 Major findings of the European Society for Paediatric Nephrology/European Renal Association–European Dialysis and Transplant Association Registry

Major findings of the ESPN/ERA–EDTA Registry
Incidence/patient characteristics
•Stabilized incidence of RRT of 5.5 per million age-related children aged <15 years between 2009 and 2011
•Higher pediatric RRT incidence in Northern Europe, associated with a more favorable macroeconomic situation
•CAKUT: most common primary renal disease (40 %) in age group 0–14 years
•PD: first RRT modality in 47 % of patients
Mortality
•23 deaths per 1,000 patient-years; mortality rate ratio: 50; 4-year survival on RRT: 94 %
•Starting dialysis vs. pre-emptive kidney Tx associated with sixfold increase in mortality
•Fourfold higher mortality in patients aged 0–4 years compared to adolescent patients.
•Survival in patients with neonatal onset of RRT: 81 and 76 % at 2 and 5 years, respectively[a]
Comorbidities
•High prevalence of (uncontrolled) hypertension, especially in HD and in age group 0–3 years
•High prevalence of hypertriglyceridemia, especially in PD
•Dyslipidemia associated with cyclosporine, steroids, low GFR and high BMI after transplantation
•53 % anemia in dialysis patients, most prevalent in HD
•Improvement in rate of growth retardation over time, but still 37 % reached final height below normal range in 2006–2011
•Limited prescription of rhGH despite severe growth retardation; 16 % of infants underweight and 41 % of adolescents overweight
Transplantation
•5–10 % graft loss due to recurrence of primary disease FSGS and MPGN as primary disease significantly associated with increased risk of graft loss
•11 % hyperphosphatemia after kidney Tx, associated with increased risk for graft loss
Rare diseases outcome
•Cystinosis: survival improvement over time to 100 % since 2000; later onset of RRT; better graft survival; sustained growth retardation
•Primary hyperoxaluria: threefold higher mortality risk than other RRT patients; 5-year kidney graft survival in combined liver–kidney Tx 76 %, vs. 85 % in non-primary hyperoxaluria Tx
CAKUT
•Most common primary renal disease in children, but accounts for only 2 % of all RRT patients
•Most CAKUT patients reach ESRD at adult age, median age of RRT is 31 years[b]
•Better survival compared to non-CAKUT

ESPN/ERA–EDTA, European Society for Paediatric Nephrology/European Renal Association–European Dialysis and Transplant Association; RRT, renal replacement therapy; CAKUT, congenital anomalies of the kidney and urinary tract; PD, peritoneal dialysis; HD, hemodialysis; Tx, transplantation; GFR, glomerular filtration rate; BMI, body mass index; rhGH, growth hormone; FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis; ESRD, end-stage renal disease

[a] Combined data from ANZDATA, Japanese Society for Dialysis Therapy, IPPN, ESPN/ERA–EDTA registries

[b] ERA–EDTA Registry

After transplantation, use of cyclosporine and steroids, low eGFR, and high BMI were positively associated with adverse lipid levels [19], but lipid levels still improved after transplantation, and as a result there was a lower prevalence of dyslipidemia in transplanted patients. Therefore, early transplantation might be a first step towards a better cardiovascular risk profile in children on RRT.

Anemia

Anemia is a common feature in children with CKD and ESRD and has been associated with increased morbidity and mortality and decreased quality of life [20, 21]. Studies from the ESPN/ERA–EDTA Registry have shown a high prevalence of anemia in children on RRT [22, 23]. Among dialysis patients, the target range of hemoglobin (Hb) levels has been defined as 10.5–12.0 g/dL in children aged <2 years and as 11.0–12.5 g/dL in children aged ≥2 years, based on a summary of various guidelines [22]. According to this definition, among >2,000 children on dialysis from 19 countries, 40 % of those aged <2 years and 50 % of those aged >2 years of age had Hb levels below the target. A total of 91 % of patients received an erythropoiesis-stimulating agent and 57 % were on iron therapy. Hb levels increased with age and were higher in patients receiving PD than in those on HD. Patients with CAKUT showed the highest Hb levels, and those with cystic

kidney diseases or metabolic disorders showed the lowest. Albumin, parathyroid hormone (PTH), and ferritin levels were independently associated with Hb levels. Children with anemia had a significantly higher systolic BP *z*-score than those who had Hb within the target range. The results of this study emphasize that optimal ferritin levels seem to be lower in children (25–50 ng/mL) than in adults and that other risk factors for anemia are dialysis modality and a high PTH level [22].

Among >3,600 pediatric kidney transplant recipients from 20 countries, 50 % were found to be anemic according to the NKF/KDOQI guidelines, while only 8 % were anemic according to the National Institute for Health and Care Excellence (NICE) UK guidelines [23]. Hb level was positively and strongly associated with graft function, and patients receiving tacrolimus had a higher Hb level than those on cyclosporine. Low Hb levels were also associated with a poorer patient and graft survival [23].

Nutrition and growth

Failure to thrive and poor growth remain major concerns in childhood ESRD. Growth reference charts are essential clinical tools for assessing normal growth and final height. The choice of an appropriate growth chart becomes of particular importance when the height of children from different countries is being studied, like in the ESPN/ERA–EDTA Registry. Considerable differences between existing growth charts were found. For this reason, we developed new growth charts for Northern and Southern Europe [24] which can be applied in future registry studies on growth and which may help physicians towards better decision-making in growth hormone (rhGH) therapy.

ESPN/ERA–EDTA Registry data on >1,600 patients from 20 countries demonstrated an improvement of final adult height by a standard deviation score (SDS) of 0.49 (0.73 SDS when adjusting for age at RRT and primary renal disease) in recent years, despite the acceptance of more complicated patients with more comorbid conditions to pediatric RRT programs [25]. The percentage of patients reaching a final height within the normal range increased from 50 % when reaching adulthood in the period 1990–1995 to 63 % when reaching adulthood between 2006 and 2011. Factors associated with higher final height SDS in that study were older age and higher height SDS at the start of RRT, cumulative time on a functioning graft, and a more recent period of commencing RRT. However, height SDS did not change significantly between onset of RRT and final measurement, suggesting that this improved growth outcome is mainly due to advances in the care and prevention of pre-ESRD-associated growth failure.

Despite improvement over time, overall 45 % of patients did not reach a final height of more than −1.88 SD. One explanation for these disappointing results might be some reluctance among physicians to prescribe rhGH in growth-retarded ESRD children. In a recent Registry survey on growth hormone policies in European pediatric RRT, the actual rhGH prescription rate in growth-retarded patients was remarkably low despite full reimbursement in most countries [26]. These findings suggest that interventions targeted at both doctors' and patients' attitudes towards rhGH are needed in order to offer ESRD children a chance to achieve better health and psychosocial outcomes. The current epidemic of childhood obesity also affects pediatric RRT, as shown by a Registry study on underweight, overweight, and obesity [27]. The prevalence of overweight and obesity was 21 and 13 %, respectively, and was thereby much higher than the prevalence of underweight (3.5 %). Large differences across the age groups were found; the prevalence of underweight was higher among infants (16 %), whereas adolescents were more likely to be overweight or obese (41 %). Dialysis treatment and young age were the main factors associated with being underweight. Among transplanted patients, short stature and steroid treatment were associated with a higher risk of being overweight or obese [27]. Furthermore, the BMI increased substantially after transplantation. These data highlight the need for weight management programs and for identifying the patients that would benefit from clinical intervention.

Outcomes of RRT

Among children who started RRT in Europe in the period 2007–2011, the mortality rate was 23 deaths per 1,000 patient-years, which is more than 50fold higher than in the general pediatric population [7]. Overall, the 4-year survival was almost 94 %. Children starting with dialysis had a sixfold increased risk of death compared to those receiving preemptive transplantation, and the risk of death was fourfold higher in the youngest age group (0–4 years) than in adolescents aged 15–19 years [7]. The mortality rate in Europe is similar to that found in the Canadian and the Australian and New Zealand registries, but approximately one half that reported in the USA by the U.S. Renal Data Ssystem [12, 28, 29]. Part of the difference might be explained by the greater incidence of RRT in the 0 - to 4-year age group in the USA.

Along with three other registries, namely, the International Pediatric Peritoneal Dialysis Network (IPPN), the Australia and New Zealand Dialysis and Transplantation Registry (ANZDATA), and the Japanese Society for Dialysis Therapy registry, the ESPN/ERA–EDTA Registry provided information on the largest cohort of neonates starting chronic dialysis to date [30]. Given the medical and ethical challenges that arise from this rare clinical situation, this study provided outcome data of critical importance. Among 264 patients who started RRT during their first month of life and followed up for a median time of 29 months, survival rate was 81 and 76 % at 2 and 5 years, respectively [30]. This finding suggests that

survival up to 2 years of age is similar to that reported in previous studies of RRT in neonates and infants but that it has apparently improved at a later age [31]. No determinants of survival could be identified—except the presence of neurological disorder which was associated with a significant fivefold increased risk of death. However, comorbidities and complications such as infections, growth failure, and hypertension remained highly prevalent. Despite uncertainties in the actual number of neonates with ESRD, including those who were not treated with chronic dialysis and those not recorded in RRT registries, this study will help clinicians to provide reliable prognosis and counseling to families [30, 31].

The ESPN/ERA–EDTA Registry also allows evaluation of several outcomes of kidney transplantation. Recurrent disease is an important cause of graft dysfunction and eventual graft loss. The risk of recurrence of the disease that caused the initial renal damage is relatively high after renal transplantation in children and may lead to graft loss, representing 5–10 % of all graft failures [32]. A Registry study determined the actual graft survival for many rare diseases known to recur in the kidney transplant. Such diseases were associated with either a significantly (focal and segmental glomerulosclerosis, membranoproliferative glomerulonephritis) or a non-significantly [hemolytic uremic syndrome (HUS), Henoch Schönlein purpura/IgA nephropathy, lupus] higher risk of graft loss than renal hypoplasia and/or dysplasia taken as reference [33]. Probably due to the anticipation of such risk or to heavy proteinuria requiring bilateral nephrectomy, preemptive transplantation was performed less often in patients with these recurrent diseases than in those with hypoplasia and/or dysplasia. Although the Registry data did not make a distinction between typical and atypical HUS, graft survival among children with HUS dramatically improved between the periods 1995–1999 and 2005–2009, suggesting growing disease recognition and risk assessment by physicians [33].

Another outcome of special relevance to pediatric kidney transplantation is bone mineral metabolism. A recent Registry study among >1,200 pediatric kidney transplant recipients showed that post-transplant mineral abnormalities are common [34]. Serum phosphorus levels were abnormal in 25 % of the patients (14 % hypo- and 11 % hyperphosphatemia), serum calcium was abnormal in 30 % (19 % hypo- and 11 % hypercalcemia), and hyperparathyroidism was found among 41 % of the patients. Serum phosphorus levels showed a significant inverse association with eGFR. Surprisingly, serum phosphorus above recommended targets was associated with a more than twofold increased risk of graft failure, independent of the eGFR [34]. However, it should be noted that due to the observational nature of the Registry, cause–effect relationships are not clear. Nevertheless, these results underline the importance of controlling mineral metabolism after pediatric kidney transplantation to ensure optimal linear growth and prevent cardiovascular complications.

Rare diseases

One of the great opportunities of having a large registry is the possibility to study rare diseases. Nephropathic cystinosis is the most common form of cystinosis, a rare inherited metabolic disorder leading to ESRD. Because of its rarity, long-term renal outcome data are limited to major referral centers [35]. The ESPN/ERA–EDTA Registry provided data on 245 children with cystinosis from 18 countries [36]. Between 1979 and 2008, the mean age at the start of RRT among children with cystinosis increased significantly from 8.8 to 12.7 years, whereas this change was not observed in non-cystinosis children. Five-year patient survival on RRT dramatically improved in cystinosis patients, from 86 % before 1990 to 100 % since 2000. Furthermore, 5-year graft survival was better (94 % vs. 84 %) in patients with cystinosis than in matched RRT children. Although height at start of RRT slightly improved during the past decade, children with cystinosis remained significantly shorter than non-cystinosis children on RRT [36]. This demonstration of a delayed onset of ESRD and a better patient and renal survival after the start of RRT in a large cohort of children with cystinosis, together with the greater proportion of patients with cystinosis reaching ESRD during adulthood [37], is most likely the consequence of cysteamine treatment.

Primary hyperoxaluria (PH) is another rare cause of ESRD with an extremely high potential for recurrence and reported poor outcomes after transplantation. Data on management and outcomes of PH children with ESRD remain scarce. The ESPN/ERA–EDTA Registry investigated these issues in a cohort of >9,000 children aged <19 years from 31 countries who started RRT between 1979 and 2009, of whom 100 (1 %) had PH [38]. The study found that, despite the acceptance of more challenging patients with PH into RRT programs in Europe, outcomes of children requiring RRT for PH substantially improved over time. Indeed, PH children were significantly younger than non-PH children at the start of RRT, with a decrease in their median age from 9.8 years in 1979–1989 to 1.5 years in 2000–2009. Patient survival, however, remained lower in PH patients, resulting in a threefold increased risk of death over non-PH patients. Among PH patients with combined liver–kidney transplantation, 5-year kidney graft survival was 76 % (85 % in non-PH patients) and was far poorer in PH patients receiving a kidney transplantation alone (5-year graft survival <20 %) [38].

CAKUT are the most common cause of CKD in children [11] but account for only 2 % of all patients (children and adults) in the ERA–EDTA Registry who started RRT between 1990 and 2009 [39]. Although the incidence of RRT due to CAKUT was highest during adolescence and decreased from 20 years of age, a majority of patients progressed to ESRD during adulthood and required RRT at a median age of 31 years versus 61 years in the total ERA–EDTA registry

cohort [39]. In addition, the survival of patients with CAKUT was better than that in age-matched patients with other underlying causes of ESRD, which may be explained by a better preservation of residual renal function and therefore a better metabolic and cardiovascular profile. The subgroup of patients with neurogenic bladder, however, had a higher risk of death, possibly due to infectious, malignant, or neurologic complications [39].

Strengths and limitations of the Registry

A major strength of the ESPN/ERA–EDTA Registry is the inclusion of data from multiple countries throughout Europe. Currently, 37 different European countries are participating in the Registry and, consequently, the Registry represents almost the whole of Europe. This large European coverage also enables current national practices and variations in practice across Europe to be studied, as the ESPN/ERA–EDTA Registry is capable of identifying differences in practice that influence patient outcomes [15, 26]. The Registry is not only a key resource to compare incidence and prevalence [7, 10] and thus help healthcare facilities in their planning, but also to compare the quality-of-care indicators across countries (available in country-specific annual reports). Moreover, data are collected on an annual basis, which provides the opportunity to perform longitudinal analyses. The Registry is therefore a unique tool to monitor and understand temporal trends in pediatric RRT care that may occur for many reasons, including availability of a new drug or procedure, publication of key research findings, release of new guidelines, and changes in policy and/or reimbursement [7, 25, 30, 36, 38].

The voluntary basis of the Registry results in many missing values for a number of variables which, depending on the aim of the study, might lead to potential bias in that study. However, novel statistical techniques are available to partly deal with this bias. A difficulty occurring with most registry studies is the absence of a central laboratory for measuring clinical parameters. The different participating centres determin values according to local practice, which often involves the use of different bioassays. For the most part, these different methods yield similar results for the same measured variable; however, a high inter-method variability has been reported for some parameters (e.g., PTH and lipids). Although the result may have been variability in the measurements, it is likely that the effect is small and has mainly resulted in an underestimation of the reported effects (non-differential misclassification). Another caveat of this multinational RRT registry is that for some variables a large amounts of data are collected in some—but not in other—countries, resulting in potential selection bias when such variables are reported. Moreover, the collection of comorbidity data, which are critically relevant in children with ESRD, remains a challenging task for renal registries [40]. There is an important heterogeneity in availability, completeness, and reliability of comorbidity data between countries which hampers complete adjustment for case-mix in ESPN/ERA–EDTA Registry analyses.

In view of the observational nature of the Registry, its corresponding studies are hypothesis generating and cannot prove causality. Ideally, randomized controlled trials (RCTs) should be performed to study causal effects of therapies on outcome measures. Although this study design is considered the gold standard, RCTs are highly time-consuming and expensive, may induce selection bias and, in some cases, are not possible [41]. In such situations observational studies provide a very good alternative, as long as their limitations are taken into account. In pediatric RRT, the small and heterogeneous population hampers the ability to conduct sufficiently powered clinical trials, whereas large registries provide the opportunity to analyze potential risk factors in relation to patient outcomes.

Future directions

Until recently, the disease classification used by the ESPN/ERA–EDTA Registry was based on the existing ERA–EDTA PRD coding system which has remained unchanged since the 1980s and was lacking in diagnostic details, especially for rare diseases highly prevalent in the pediatric ESRD population. The adoption and distribution of a new set of PRD codes [42] will ensure both a more flexible and more accurate disease classification, and further improve the quality of epidemiological research by the ESPN/ERA–EDTA Registry.

Collecting more detailed data by specific questionnaires or conducting surveys has been needed to answer important questions [15, 26]. Although the heavy burden of work faced by registries' staff in collecting these data may be a daunting barrier, the ESPN/ERA–EDTA Registry seeks to explore more specific topics by using these methods in future research.

In the field of RRT there is an increasing demand for information that can be used to help decision-making and improve the quality of care [43]. By providing comparisons of clinical performance indicators between countries (i.e., benchmarking) or using clinical practice guidelines, the ESPN/ERA–EDTA Registry will contribute to the identification of areas that require changes in clinical management, ultimately leading to improved patient outcomes.

Future direction of the Registry may also be to stimulate pediatric nephrology national societies to create renal registries that collect data on CKD stages 3–5, with the aim of setting up an ESPN/ERA–EDTA CKD registry.

Finally, the Registry expects to expand its contribution towards supporting or refining clinical practice guidelines in pediatric nephrology care.

Conclusion

The ESPN/ERA–EDTA Registry is a leading source of up-to-date and comprehensive data on pediatric RRT practices and outcomes in Europe. We have learned from the sometimes surprising variations in clinical practice among European countries, and the Registry has yielded clinical research findings directly relevant to patients, physicians, and healthcare policy-makers.

Compliance with ethical standards

Conflict of interest The authors declare no conflict interests.

Multiple choice questions (answers are provided in backmatter, following the reference list)

1. A population-based registry (please select 2 answers):
   a. is an organized system that uses observational study methods to collect uniform data from a population defined by a particular disease
   b. must include both individuals with and without the disease
   c. allows an exhaustive registration of cases in order to provide reliable epidemiological data
   d. does not allow monitoring trends in incidence and prevalence of the disease over time
   e. is a superior methodology to randomized controlled trials in the hierarchy of evidence in therapy.
2. Registry data on patient characteristics, incidence and prevalence of RRT in Europe showed that (please select 2 answers):
   a. glomerulonephritis is the most common primary disease requiring RRT
   b. incidence of RRT has remained relatively stable around 6 pmarp in children <15 years
   c. incidence of pediatric RRT has constantly increased over the past 10 years
   d. considerable differences in incidence and prevalence exist between countries
   e. hemodialysis is the most common RRT modality among incident patients.
3. Patient survival on RRT (please select one answer):
   a. is the highest in the youngest age group (<5 years of age)
   b. is around 85 % at 4 years after the start of RRT
   c. is higher in children starting with dialysis than in preemptive kidney transplant recipients
   d. is >75 % at 5 years in those who started dialysis during the neonatal period
   e. is similar in Europe and in the USA.
4. Which of the following ESPN/ERA–EDA Registry findings regarding CKD complications are true? (please select two answers):
   a. high Hb levels are associated with low ferritin levels (25–50 ng/ml) among dialysis patients
   b. uncontrolled hypertension is more prevalent in PD than in HD patients
   c. hyperlipidemia is uncommon after successful kidney transplantation
   d. around a quarter of RRT children reach an adult height below the 3rd percentile
   e. more than one third of adolescents on RRT are overweight or obese.
5. In studies focusing on rare diseases, the ESPN/ERA–EDTA Registry found that (please select one answer):
   a. the onset of RRT for cystinosis has been delayed over time
   b. patient survival improved over time in children with cystinosis and in those with oxalosis
   c. kidney graft survival is poorer in children with oxalosis receiving a kidney transplantation alone as compared with liver–kidney transplantation
   d. the majority of patients with CAKUT who progress to ESRD will start RRT during adulthood
   e. all of the above.

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Responses

1. a, c
2. b, d
3. d
4. a, e
5. e