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

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General Introduction

END-STAGE RENAL DISEASE

Our kidneys are tasked with the vital responsibilities of filtering waste products from the blood, producing urine, regulating blood pressure, erythrocyte production, and controlling calcium, phosphate, and magnesium metabolism. Chronic kidney disease (CKD) is a general term for a diversity of disorders affecting the kidney and is characterized by a deterioration of kidney function over time. The final stage of CKD is end-stage renal disease (ESRD), a devastating condition that is associated with considerable morbidity, mortality, and a poor quality of life [1, 2]. In adults, ESRD is a leading cause of morbidity and mortality worldwide, with an estimated prevalence of 2.6 million patients receiving treatment in 2010, and a projected doubling of this number by 2030 [3]. In children, ESRD is considered a rare and complex condition caused by a variety of aetiologies, constituting approximately 1-2% of the total ESRD population. Compared to adults, where diabetes and hypertension form the leading causes of ESRD, the majority of paediatric patients suffer from a multiplicity of congenital anomalies, hereditary nephropathies, and glomerular defects [4, 5].

RENAL REPLACEMENT THERAPY IN CHILDREN

ESRD necessitates chronic renal replacement therapy (RRT) to sustain life. Prior to the start of paediatric RRT programs in the 1960s, ESRD in children was a death sentence. Since then, substantial advances in renal medicine have been achieved. The treatment modality choices for RRT consist of peritoneal dialysis (PD), haemodialysis (HD), and renal transplantation (Tx). Although the latter is considered the optimal modality choice with regard to patient survival, cognitive development, quality of life, and growth [6–10], approximately three-quarters of patients will initiate RRT on dialysis to bridge the preparation time needed for transplantation or will require dialysis after graft loss [11]. The provision of RRT to children is more expensive compared to adults, as children are ideally treated by an extensive and specialized multidisciplinary team, and often require expensive medications such as growth hormone. A Swiss study estimated the annual costs of approximately $200,000 for paediatric dialysis, $300,000 for the total cost of all care during the first year of a paediatric kidney transplant, and about $75,000 for each following year [12, 13].

THE ESPN/ERA-EDTA REGISTRY

Up-to-date, accurate, and detailed epidemiologic data regarding the paediatric ESRD population is vital for evidence-based policymaking and for informing patients, physicians, and healthcare providers. Accurate data on the demographics, such as on the number of existing (prevalence) and new cases (incidence) of children on RRT in Europe, are scarce. In addition, national or single-centre studies are often unable to provide sufficient statistical power to accurately assess treatment outcomes. Fortunately, over the past decades, various (inter)national registries have collected sufficient data to power statistically valid and clinically meaningful studies, and have been instrumental in advancing epidemiologic research and expanding the growing evidence base regarding treatment outcomes in this population. In 2007, the European Society for Pediatric Nephrology / European Renal Association – European Dialysis and Transplant Association (ESPN/ERA-EDTA) Registry was established to consolidate data collected by population-based European national renal registries on children with ESRD treated with RRT. Currently, the registry collects data annually from 36 European countries and holds records on over 10,000 paediatric patients. Given the large number of data, we are now able to accurately assess the recent epidemiology of paediatric RRT in Europe, which we will present in **chapter 2**.

EUROPEAN DISPARITIES REGARDING TREATMENT AND MORTALITY RATES IN THE PAEDIATRIC RRT POPULATION

One of the main focus points of the European health policy framework, *Health 2020,* is to significantly reduce health inequalities and ensure universal, equitable, and high quality health services across Europe [14]. Although all European Member States have made commitments towards this goal, considerable international disparities in treatment- and mortality rates have been described in the adult RRT population. Disparities in treatment rates have been attributed to the percentage of elderly, the prevalence of diabetes and hypertension in the general population [15–17], and factors affecting access to care [18, 19], whereas disparities in mortality rates have been explained by differences in country macroeconomics, general population mortality rates, patient demographics, the distribution of cause of renal disease, the quality of renal care, access to treatment, and attitudes regarding acceptance to and withdrawal from treatment [20–22].

It is difficult to extrapolate findings from the adult to the paediatric RRT population due to differing primary renal diseases, the rarity of paediatric ESRD, and the high costs involved treating children in mostly academic settings by a multidisciplinary team. Apart from a single non-population-based study which studied the influence of gross national income on paediatric PD prevalence and mortality rates [23], little is known about the extent of disparities in the European paediatric RRT population, and their underlying factors remain unknown.

As nearly all cases of paediatric ESRD consist of rare disorders of at least some genetic origin, we postulate that differences in treatment rates across Europe could partly be explained by geographical differences in genetic background [24]. On the other hand, non-medical country-level factors, such as macroeconomics, are likely to affect access to care and may also play a role in explaining the variation in paediatric RRT rates [23, 25]. In **chapter 3**, we therefore assess the factors that determine the incidence of RRT by exploring how much of the variance can be attributed to genetic factors, and how much can be attributed to disparities in access to renal care.

Similarly, European disparities regarding mortality rates in the paediatric RRT population may be explained by both patient-level factors, such as renal disease distribution, and by country-level factors, such as the number of paediatric treatment centres. In **chapter 4**, we aim to determine the magnitude of variation in country mortality rates, and disentangle both patient- and country-level factors to understand which mechanisms may be responsible for these geographical disparities.

SURVIVAL IN THE PAEDIATRIC RRT POPULATION

Although other patient-related outcomes such as growth and quality-of-life are crucial, prolongation of patient survival may be arguably the most relevant clinical goal. Mortality in the paediatric RRT population is multifactorial, owing to the complex nature and diversity of ESRD. In **chapter 5**, we touch on several factors which have been shown to affect the mortality risk in the paediatric RRT population, including age at RRT initiation, time on RRT, primary renal disease (PRD), the presence of comorbidities, and initial treatment modality [26].

Transplantation is considered the optimal modality choice with regard to patient survival, however, most patients will initiate RRT on dialysis to bridge the preparation time needed for transplantation [11]. In the adult dialysis population, a large number of observational studies have investigated survival differences between patients starting on HD and PD. Although comparisons between studies are hampered by differences in case-mix adjustments and analysis techniques, in Western countries there seems to be a consistent trend showing a survival advantage for patients initiating dialysis on PD during the initial years on dialysis, and in younger, healthier, and non-diabetic patients [27–32].

In children, the few studies that have explored the effect of dialysis modality on mortality risk show conflicting results [8, 33–35]. In Europe, no such study has previously been undertaken on an international scale, and the rarity of paediatric ESRD has limited exploration of the heterogeneity of treatment effects across patient subgroups and time-dependent treatment effects, as have been demonstrated in the adult population. Therefore, in **chapter 6**, we describe the mortality risk in the paediatric dialysis population, and compare the mortality risk between patients starting RRT on haemodialysis and peritoneal dialysis. Furthermore, as it is generally believed that in infants HD should only be reserved for cases where PD is not feasible, we will answer the same questions focusing specifically on the infant dialysis population in **chapter 7**.

GRAFT FAILURE RISK IN DIFFERENT DONOR AND RECIPIENT AGE COMBINATIONS

It has been well established that renal transplantation offers better patient outcomes compared to dialysis [6–9]. Nonetheless, 10 years after transplantation, approximately 40% of paediatric transplant recipients will have lost their graft [10]. Moreover, returning to dialysis after graft failure has been associated with a 4.4-fold increase in mortality risk [36]. Recipient and donor age are amongst the many factors that influence graft survival. In most European countries, a deceased donor-recipient 'young-for-young' matching policy has been implemented, where young donor grafts are preferentially allocated to children [37–44]. These donor-allocation policies aim to reduce waiting times and provide high-quality grafts to the best-matched recipients in order to improve graft survival. However, earlier reports have shown a higher risk of graft loss in recipients of the youngest donors due to surgical

complications, high rates of graft thrombosis, early rejection, and hyperfiltration injury [39, 40, 45–47]. Furthermore, although it is known that living donation offers better long-term graft survival compared with deceased donation [11, 48, 49], it remains unknown whether utilizing kidneys from elderly living donors, should be preferred over kidneys from age-matched deceased donors. As it remains unclear which organs should be ideally allocated to children, donor-allocation policies continue to differ between countries, hampering equal access to renal transplantation for children across Europe [42]. Consequently, to help optimize kidney donor allocation policies, in **chapter 8** we examine how the relationship between donor age and recipient age affects graft survival in paediatric kidney transplant recipients.

AIM

This thesis aims to reveal health inequalities and improve outcomes in the European paediatric RRT population by determining the epidemiology of the paediatric RRT population across Europe, exposing international disparities in treatment rates and mortality risk in this population, and investigating factors that may explain these differences. Lastly, this thesis aims to help define the optimal donor kidney allocation policy by examining the relationship between donor age and graft loss.