Demographics of CKD and ESRD in Children

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Introduction

Irreversible kidney damage or so-called chronic kidney disease (CKD) has become a major public health problem worldwide. The adult population has been the subject of extensive epidemiological research [1, 2] but fewer data are available about CKD in children [3]. Despite major scientific advances resulting in substantial improvement in the care of children with CKD, some will still progress and require kidney replacement therapy (KRT). ESKD is a devastating disorder causing substantial mortality and morbidity (most notably cardiovascular, cancer and infection), but this is compounded by specific problems which occur in children such as impaired growth and psychosocial adjustment [4], all of which severely impact upon quality of life [5]. Understanding of the epidemiology of CKD in children is required in order to make a precise and early diagnosis, identify preventable or reversible causes of progression, predict prognosis, and aid the counseling of children and their families.

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Part I: CKD (Stages I–4)

Definition of CKD

Precise data on the epidemiology of CKD in children allowing the evaluation of the incidence and prevalence of CKD and the comparison between countries is lacking. This was in part due to the lack of a universal definition of CKD. For example, the ItalKid Project and North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) defined CKD as having a glomerular filtration rate (GFR) of below 75 mL/min/1.73 m^2 [6, 7]. Others based their definition on serum creatinine levels themselves or on other thresholds of GFR [8–10]. In 2002, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) published a classification of CKD applicable to children [11]. CKD was defined by the persistence for more than 3 months of morphological, histological or biological abnormalities of the kidneys and/or a glomerular filtration rate (GFR) below 90 mL/min/1.73 m^2. This classification grades CKD in five stages from stage 1 with normal GFR to end-stage kidney disease (ESKD, stage 5). The K/DOQI classification was revised in 2012 by the KDIGO (Kidney Disease: Improving Global outcomes) to reflect the risk of progression to ESKD and is based on both GFR and albuminuria [12]. Of note, some pediatric specificities need to be considered when using this classification: a) the criteria for duration >3 months

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does not apply to newborns or infants <3 months of age, (b) the criteria of a GFR <90 mL/min/1.73 m^2 does not apply to children <2 years of age as neonates are born with lower GFR, which increases to normal values in the first 2 years of life, (c) a urinary total protein or albumin excretion rate above the normal value for age may be substituted for albuminuria ≥30 mg/24 h. A similar classification based on the same GFR cut-offs and on the urine protein-creatinine ratio and specifically validated in two large pediatric cohorts (CKID in the USA and ESCAPE in Europe) has been developed recently (Fig. 54.1; Table 54.1) [13].

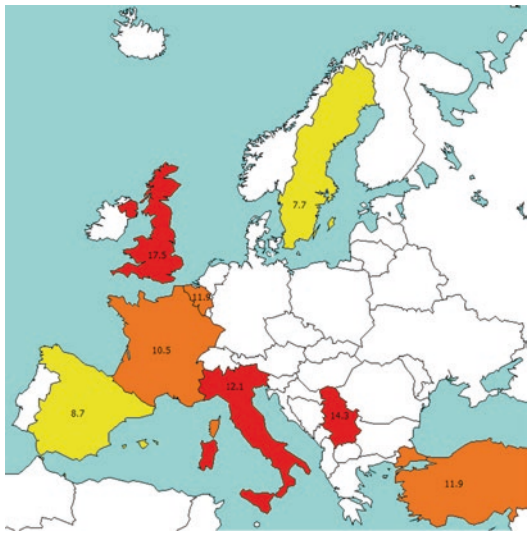

Fig. 54.1 Reported incidence (pmarp) of CKD in children in Europe

The new classification was widely adopted after its introduction; however, its limitations and possible modifications have been a matter of extensive discussions. Moreover, despite efforts to standardize creatinine measurement (by using enzymatic methods instead of colorimetric methods) and GFR estimation, there are still ongoing debates on which eGFR equation should be used in various clinical conditions particularly in early stages of kidney injury [14–17]. In 2009, the bedside Schwartz formula using height and serum creatinine and a unique k coefficient was developed and remains frequently used in clinical practice [18]. Since then many equations have been published using serum creatinine or cystatine C or a combination of both. Recently, papers focused on developing formulas that perform consistently over the whole range of GFR from infants to young adults (FAS [19], CKID U25 [20]).

Screening for CKD

CKD screening and surveillance in adults, either population-based or targeted at risk populations, has become widely advocated and implemented in many countries worldwide, in an attempt to prevent ESKD and the progression of CKD. However, the benefit of screening for early-stage CKD is uncertain [21]. The benefit of such programs in children is even more uncertain [22]. Tests used for CKD screening in children

Table 54.1 CKD classification and estimated risk of progression adapted from (Furth et al. AJKD)

			Baseline UPCR		
			<0.5	[0.5, 2.0]	>2.0
Baseline GFR	I	≥ 90	IR = 2.3 (0.7, 7.0) per 100p-y	–	–
	II	[60–90)	IR = 1.5 (0.8, 2.6) per 100p-y	IR = 8.1 (4.8, 13.8) per 100p-y	IR = 14.2 (6.4, 31.6) per 100p-y
	IIIa	[45–60)	IR = 3.6 (2.5, 5.0) per 100p-y	IR = 6.4 (4.5, 9.1) per 100p-y	IR = 22.8 (13.7, 37.8) per 100p-y
	IIIb	[30–45)	IR = 5.9 (4.4, 7.8) per 100p-y	IR = 10.7 (8.1, 14.1) per 100p-y	IR = 32.0 (23.5, 43.6) per 100p-y
	IV	[15–30)	IR = 17.4 (12.8, 23.6) per 100p-y	IR = 24.8 (19.5, 31.6) per 100p-y	IR = 58.4 (44.5, 76.6) per 100p-y
	V	<15			

Based on baseline GFR and UPCR patients are classified in 6 groups (colors) based on their risk of progression. Incidence rates (IR) of 50% GFR decline or GFR < 15 mL/min/1.73 m^2 are reported

are usually limited to urinary dipstick protein instead of urine albumin/creatinine ratio or on creatinine-based calculation of estimated GFR as recommended for adults. There is also a large variation in the methods used and approaches taken by the different countries, and the findings have shown poor reproducibility [22].

The main studies about screening for CKD in children are summarized in Table 54.2 [23–34]. Mass screening programs to detect CKD in children have been undertaken for many years in several Asian countries such as Japan, Taiwan and Korea [23–25]. Conversely, screening programs have not been adopted in Europe or Australia but screening using urine dipsticks have routinely been performed in healthy children for decades in the United States. In 2000, the recommendations from the American Academy of Pediatrics were to screen the urine of preschool children and adolescents [35]. This policy has been revised in 2007 and this practice is no longer recommended [36]. Although a decrease in the incidence of ESKD has been observed in Japan and Taiwan, there is only limited evidence that early detection of kidney injury in children may lead to effective interventions to slow progression of CKD and further reduce the risk of developing ESKD [22]. Furthermore, some studies suggest that a urine dipstick is not a cost-effective strategy for screening in children [37] given the high prevalence of transient proteinuria in this population. Although some population-based studies assessing CKD epidemiology by GFR estima-

Table 54.2 Results from studies reporting screening programs from chronic kidney disease in children

Country [Reference]	Study period	Study population	Screening criteria	Main findings
Japan [23]	1974–2002	Population-based 6–14 years old	2 positive urine dipsticks	Prevalence of Pu: 0.07% in 6–11 years 0.35% in 12/14 years old
Taiwan [24]	1992–1996	Population-based 6–15 years old	Pu > 100 mg/dL CKD (SCr >1.7 mg/dL)	Prevalence Pu 0.06% Prevalence CKD 0.002%
Korea [25]	1998–2004	Population-based 6–18 years old	2 positive urine dipsticks	Prevalence Pu 0.2%
Australia [26]	2004–2008	Population-based (57% Arboriginal) 4–14 years old	Single assessment Urine dipsticks uACR≥3.4 mg/mmol	Prevalence of albuminuria at baseline 11.5%
India [27]	2013–2016	Population-based 8–18 years old	Single assessment Urine dipsticks	Prevalence of Pu 1.9% Prevalence of hematuria 5.2%
USA [28]	2009–2014	Population-based 12–18 years old	Albuminuria (uACR) eGFR (bedside Schwartz)	Prevalence of albuminuria: 13.7% Prevalence of persistent albuminuria 3.29% Prevalence of eGFR<60: 0.91%
Singapore [29]	1999–2000	Population-based 12 years old	Urine dipstick	Prevalence of Pu 1.3%
China [30]	2003–2005	Selected population School age children	2 positive urine dipsticks	Prevalence of Pu and/or Hu in 2 specimens: ~1%
Finland [31]	NA	Selected population 8–15 years old	4 urine samples (2 morning, 2 evening. Dipstick and measured Pu	Prevalence of Pu: 10.7% on at least 1 specimen 2.5% on 2 specimens 0.1% on 4 specimens
Iran [32]	NA	Selected population 6–7 years old	Urine dipsticks	Prevalence of Pu: 3.6% Prevalence of persistent Pu: 1.3%
Mexico [33]	2006–2007	Selected population 0–18 years old	Single assessment urine dipstick eGFR (Schwartz)	Prevalence of Pu 16.1% Prevalence of hematuria 17.5% Prevalence of eGFR<60: 1.7%
UK [34]	1967–1969	Selected population 5–16 years old	2 positive urine dipsticks	Prevalence of persistent proteinuria 0.8% on 2 specimens

tion have been performed and indicate that a certain proportion of asymptomatic children have CKD, no systematic national screening program based on GFR assessment in children is currently ongoing.

Demographics of CKD

There is limited information on the epidemiology of early stages of CKD in children. As CKD is usually asymptomatic in its early stages, providing precise epidemiological data is difficult so CKD in children is likely to be underestimated and underreported. Although some pediatric CKD registries using the K/DOQI classification are beginning to emerge, only a few reports on the epidemiology of CKD stages 2–5 in children are available. Due to lack of resources and national renal registries, we know even less about the incidence and prevalence in low income countries. For these countries, data are mostly obtained from reports of major tertiary care referral centers, but the validity of this data is variable.

Europe

The largest population-based study in Europe on the epidemiology of pediatric CKD is the ItalKid project. This study in Italy has been collecting data since 1990 on the epidemiology of childhood CKD, describing the natural history of the disease, and identifying factors that influence its course [6]. So far, nearly 1198 patients have been registered. Other nation-wide European studies are the Serbian CKD registry [38], collecting data on over 336 patients since 2000, the Belgium CKD registry which started in 2001 and has over 143 patients [39], and the data from the Swedish Pediatric Nephrology Association [40]. Also regional studies have taken place in Spain [41], the South-East of the UK [42] and Lorraine in France [8].

Several pediatric nephrology societies from European countries have provided data on the early stages of CKD. Even though age categories and definition of CKD differed between countries, incidence in Europe was consistent, ranging from 8 to 14 per million age-related population (pmarp) for CKD stages 2–5, and being around 8 pmarp for CKD stage 4–5 (Fig. 54.1). The incidence was highest (17.5 pmarp) in a report from the United Kingdom but the study was hospital-based leading to potential referral filter bias and there may be some uncertainty about the covered geographical area [42].

While an increase in incidence since the 1970s was seen in France [8], this was not seen when comparing two time periods in Sweden [9, 40]. Two studies from Serbia and the UK also suggested an increase in incidence in the past 10 years [38, 42]. Prevalence ranged from about 55–60 to 90–95 pmarp in Spain, Italy, UK and Serbia, depending on the clinical definition of CKD that was used in each study.

In Turkey, the CREDIT study reported a prevalence of CKD stage 3–5 of 2600 pmarp in children aged 5–18 years old in 2007 [43].

North America

In Northern America most of the information on CKD in children derives from two large sources of information namely the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) [44] and the Chronic Kidney Disease in Children Prospective Cohort Study (CKiD) [45]. Both studies are collecting data on a voluntary basis and are not population based.

Population-based data are available in adolescents since the NHANES study investigated albuminuria and GFR in a nationally representative sample of the US population including 9225 adolescents aged 12–18 years over 3 study periods. They found a prevalence of 0.91% [95% CI 0.58–1.42%] for CKD stage 3–5 and a prevalence of persistent albuminuria of 3.29% [95% CI 1.94–4.63%] in the 2009–2014 survey [28].

Latin America and the Caribbean

In Chile, a national survey of pediatric nephrologists estimated an incidence of CKD (GFR <30 mL/min/1.73 m^2) in children aged less than 18 years of 5.7 pmarp and a prevalence of 42.5 pmarp in 1996 [46]. Among these patients, half were on conservative treatment and the others were on KRT. Very similar results were found in Argentina, with an incidence of 6.5 pmarp, but with a lower prevalence

(15.4 pmarp) [47]. Fifty-eight percent of this population had ESKD and started with dialysis. In Jamaica, the estimated incidence of CKD was 4.6 pmarp and 28% of them were already in ESKD, without having access to KRT [48].

A study on the epidemiology of CKD conducted in several Latin American countries (Argentina, Brazil, Chile, Colombia, Mexico, Uruguay, and Venezuela) has shown a wide variation in incidence that ranged from 2.8 to 15.8 new cases pmarp [49]. Also an indirect estimation of the incidence of CKD in Mexico suggested a very high incidence, between 24 and 39 per million inhabitants, for which the differences within Mexico were explained by the level of social deprivation [50].

Asia

The estimated prevalence of CKD stage 3–5 among Japanese children in 2010 was 29.8 pmarp [51]. This lower prevalence of pre-dialysis CKD in Japan than in Europe was consistent with the lower prevalence of pediatric ESKD in Japan. Two reports from Vietnam and one from Thailand have suggested an annual incidence of hospitalization for CKD around 5 pmarp, most of patients had already reached ESKD [52–54]. Very little is known about pediatric CKD epidemiology in India and China. A survey conducted in 91 Chinese hospitals found a total of 1658 children aged <15 years with CKD stage 3–5 between 1990 and 2002 which suggests a very low incidence of treated CKD <0.5 pmarp [55]. Patients were referred late with advanced CKD or ESKD in 80% and in-hospital mortality was as high as 72%. Similarly, in India 58% of children had ESKD at the time of CKD diagnosis suggesting that children with CKD are underdiagnosed and referred late [55].

Middle East

The referral center for pediatric kidney diseases in Kuwait provided data on children aged 0–15 years with a GFR <50 mL/min/1.73 m^2 [10]. The mean incidence was found to be as high as 38 pmarp whereas the prevalence increased from 188 in 1996 to a rate as high as 329 pmarp in 2003. The marked difference in incidence between Kuwaiti children and non-Kuwaiti residents suggested the role of genetic factors. An incidence of 12 pmarp was found in a Turkish survey including children with a GFR <75 mL/min/1.73 m^2 [56]. An incidence of 11 pmarp and a prevalence of 51 pmarp have been reported in Jordanian children [57].

Africa

Single center studies from sub-Saharan Africa showed very low incidence of CKD estimated at 1–4 pmarp in Nigeria, Sudan, and South Africa [58–61]. Another single center report from Nigeria, however, found an annual incidence of CKD stage 1–5 of 11 pmarp and a prevalence of 48 pmarp [62], which was much higher than the 1.7 pmarp reported in 2004 [63].

Causes of CKD

Type 2 diabetes and hypertension are the leading causes of CKD in adults. The distribution of the causes of CKD in children are very different with major variations between countries. Indeed, congenital abnormalities of the kidney and the urinary tracts (CAKUT) account for 50–60% of CKD cases in children in Europe [6, 38, 39, 42], Japan [51] and the USA [44]. In Turkey and in the Middle East, CAKUT remains the first cause of CKD with often a higher proportion of hereditary nephropathies related to higher rates of consanguinity [10, 56, 57, 64]. Higher proportions of glomerular diseases are found in developing countries such as India, Southeast Asia [52–54], Latin America [48, 49] and Sub-Saharan Africa [58]. The latter may be related to the high prevalence of bacterial, viral and fungal infections in these regions.

Whereas CAKUT predominates in younger patients, glomerulonephritis is the leading cause in children older than 12 years of age. Causes of CKD vary across races, for example, focal segmental glomerulosclerosis, the main cause of glomerular disease, is three times more common in blacks than in whites (19 compared with 6%) and especially among black adolescents (35%) [65].

In general, there is a predominance of male gender (male/female ratio ranging from 1.3 to 3.0). This partly reflects the higher incidence of CAKUT in boys than in girls, but has also been reported in the regions with a high rate of glomerulonephritis.

Part II: KRT (CKD Stage 5D and 5 T)

Epidemiological data on ESKD treated by dialysis or transplantation is more robust thanks to the development of several national and international registries. Unfortunately not every country has such a registry, not all children are reported to the relevant registry, and some countries with registries do not regularly publish reports. Also, as KRT is expensive not all countries are able to offer KRT to children with ESKD. Approximately 80% of the children on KRT live in Europe, Japan or the United States. Dialysis and transplant registries only collect data on treated ESKD; untreated children with ESKD are not captured. However, at least in the developed world, the proportion of children with ESKD who do not receive KRT is likely to be very low [1].

Incidence

The incidence of KRT in children varies greatly between countries but can be estimated between 5 and 10 pmarp [66–70] with extreme values ranging from 0 (Malta) to 17 pmarp (Kuwait) [71]. However, given that pediatric KRT is extremely rare, numbers in smaller countries are subject to random error. Moreover, variations in incidence may reflect variations in the incidence of CKD, differences in pre-ESKD care or differences in access to KRT. Among large countries with universal access to KRT, the US incidence is consistently high at around 12.9 per million population [72]. In Japan, incidence of pediatric KRT (4.0 pmarp) was consistently much lower than in other high income countries (Table 54.3).

Among lower income countries the incidence is typically lower, as was shown for the Eastern European countries in the ESPN/ERA-EDTA registry [73]. In developing countries where KRT is unaffordable for all but the very wealthy, incidence rates are either not available or were extremely low (<1 pmarp in Bangladesh and Nepal). Some of the variation in incidence may be due to differences in the timing of KRT initiation. In Europe, KRT was generally started at a median GFR of 10.4 mL/min/1.73 m^2 whereas mean GFR ranged from 11.3 to 13.6 mL/min/1.73 m^2 in the United States [72, 74] (Fig. 54.2).

Within-country variations occur by racial group. For example African American in the US, arboriginal children in Australia and New Zealand or children from South Asian origin in the UK [72, 75, 76] have a significantly higher incidence of ESKD than their white counterparts, although differences in the prevalence of other ESKD risk factors such as obesity or disparities in access to medical care may account for at least

Table 54.3 Incidence, prevalence and KRT modality distribution among children with ESKD

	Countries	Year	Age	Incidence/ prevalence	Treatment modality distribution		
					HD	PD	Transplantation
ESPN/ERA-EDTA	36 European countries	2018	0–14	4.9/29.8	43.8 15.9	37.9 17.9	17.8 66.2
USRDS	USA	2017	0–21	12.9/98.7	51.3 16.6	27.8 10	20.9 73.4
CORR	Canada	2014	0–19	7.7/65.1	29.5 10	16.4 7	54.1 83
JSPN Pediatric survey 2012	Japan	2006–2011	0–19	4/–	16 –	61.7 –	22.3 –
ANZDATA	Australia and New Zealand	2018	0–17	6–9/25–100	25 6	45 12	30 82

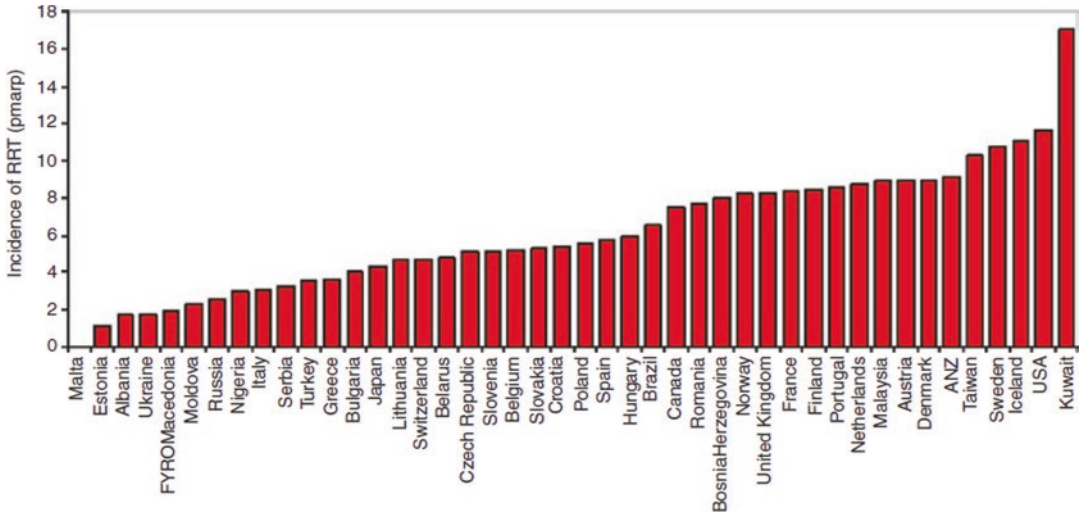

Fig. 54.2 Incidence of KRT in children aged 0–14 between 2008 and 2014

part of these differences. There are also large differences between age groups. The incidence has a typical U-shape distribution, with the highest incidence in the preschool children and in adolescents. Therefore, registries that include patients up to 20 years of age report higher incidence and prevalence data compared with registries excluding those over the age of 15.

Around 20% of patients receive a pre-emptive kidney transplant. In patients starting on dialysis, dialysis modality is strongly dependent on age; while peritoneal dialysis is the treatment of choice in the majority of young children, this pattern decreases with age, with typically higher rates of HD from the age of 10 onwards [75]. Finally, the relative proportion of HD and PD is quite variable between countries and between centers presumably reflecting differences in clinician preference and funding models [77].

Prevalence

The prevalence of treated ESKD is completely dependent on access to KRT in each country. In countries with available data on KRT, the IPNA global registry reports prevalences ranging from less than 1% in some African and Asian countries to 98.7 pmarp in the United States [72, 78]. Indeed, 80% of prevalent ESKD patients live in Europe, North America and Japan, while the prevalence of treated ESKD remains very low in many countries with the highest CKD burden [79]. Within Europe, there are also large differences, with high income countries reporting prevalence rates over 55 pmarp similar to Australia/New Zealand with 56.7 cases per million population [69], while middle income European countries report prevalences around 40 pmarp (Fig. 54.3).

In many countries the prevalence is rising due to the combination of a fairly steady incidence and improved patient survival on KRT. In the United States, the adjusted annual incidence of ESKD in the pediatric population rose slowly during the 1980s then increased marginally from 14 to 15 pmarp between 1990 and 2011 [80]. In contrast, the adjusted prevalence increased from 60 to 85 in between 1990 and 2011. Similar trends were observed in Australia and New Zealand, where the incidence has remained constant at about 8 pmarp over the past 25 years, while the prevalence of KRT increased from approximately 30–50 pmarp [69]. A report from the ERA-EDTA registry on patients aged 0–19 years starting KRT between 1980 and 2000 in 12 Western European countries showed that the incidence of KRT rose from 7 pmarp in 1980–1984 to 10 pmarp in 1985–1989 and remained stable thereafter [81], while the preva-

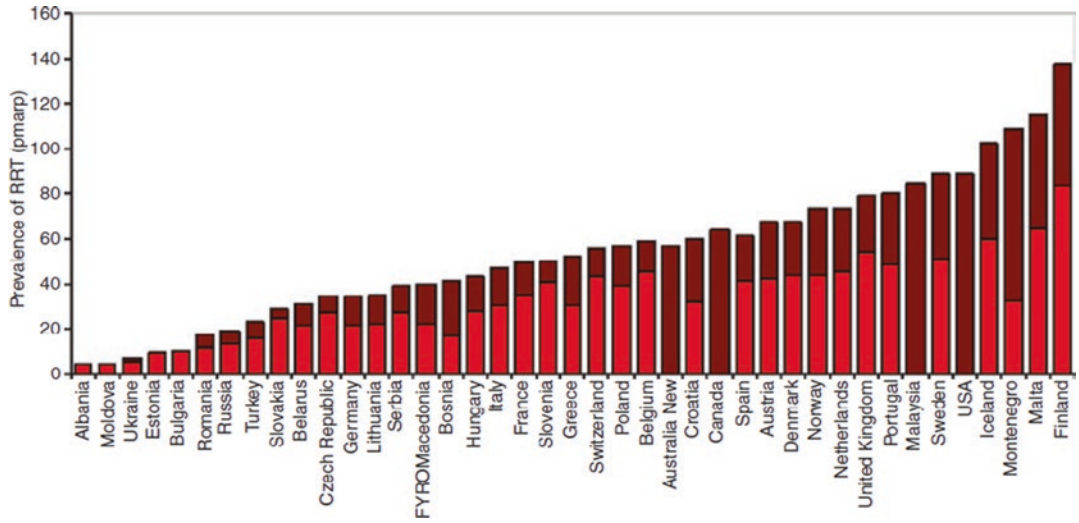

Fig. 54.3 Prevalence of KRT in children on 31st of December 2011 (2012 for Australia and New Zealand and Malaysia). The light bar corresponds to the prevalence in children aged 0–14 years, the sum of the light and the dark bars corresponds to the prevalence in children aged 0–19 years

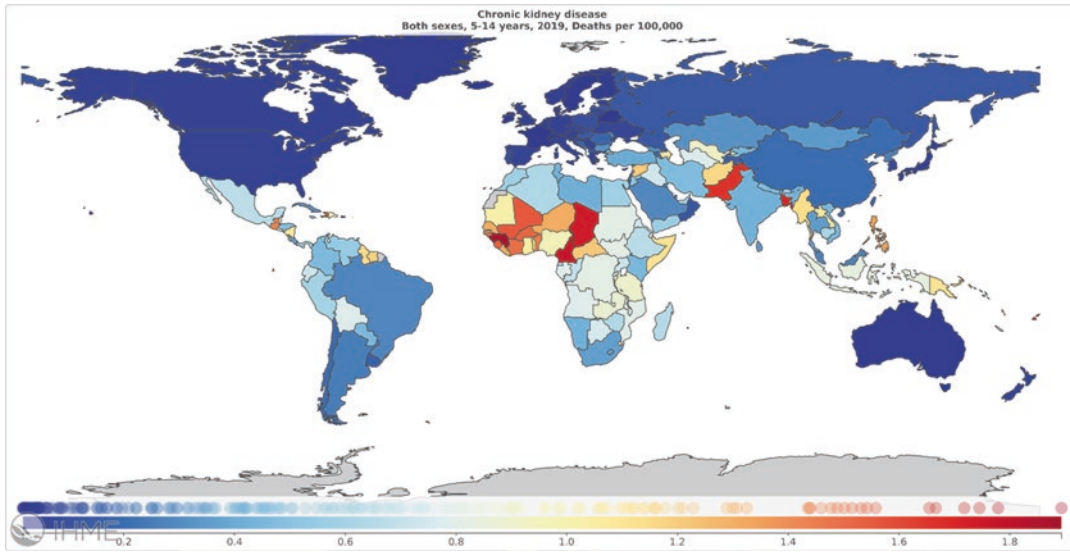

Fig. 54.4 CKD-related death rates in children aged 5–14 years (Global Burden of Disease [83])

lence increased from 22.9 pmarp in 1980 to 62 pmarp in 2000. The increases in prevalence were explained by improved survival and treatment of younger children, while the prevalence was relatively constant for the pubertal age groups.

In developing countries, a lower prevalence of children with ESKD is explained by a low access to KRT [78] and by lower patient survival. Figure 54.4 presents the death rates per country caused by CKD in children aged 5–14 years old in 2019. As expected, this map perfectly matches maps reporting access to KRT by countries [82].

Transplantation is by far the most common treatment modality in most countries, accounting for 60–80% of patients receiving KRT (Table 54.3). Here again, differences among

countries are substantial. For example, fewer than 10% of children on KRT are maintained with a kidney transplant in Belarus, compared with over 90% in Japan and Finland [84]. Recent data show that differences among countries were explained by factors such as the deceased donor rate, the pediatric priority from deceased donor programs, the living donation rate, and healthcare funding models [85]. Compared to adults, children are much more likely to be treated by transplantation due to a combination of fewer comorbidities, higher availability of living donors and, in some cases, preferential allocation of deceased donor kidneys.

Causes of ESKD

the distribution of primary kidney diseases in children reaching ESKD is different than the distribution in children with CKD. Although CAKUT is the most prevalent cause also in children with ESKD, a relatively higher proportion of ESKD cases is caused by glomerular diseases reflecting the faster progression and higher risk of ESKD of this disease group. However, a recent large cohort study from Israel demonstrated that young adults (16–25 years old) with a medical history of kidney disease in childhood but with normal serum creatinine, blood pressure and no proteinuria presented a four-fold increased risk of ESKD over a 30 year follow-up [86]. This underlines the impact of kidney diseases in childhood on ESKD in adulthood and supports long-term follow up of these patients.

There are also very specific local factors. For example, congenital nephrotic syndrome of the Finnish type, explains the very high prevalence of childhood KRT in Finland. Finally, the difference in the distribution of the causes of ESKD in children vs. adults and especially the absence of diabetes or hypertension induced ESKD explains the moderate increase in the prevalence of ESKD in children (+16.6%) in contrast with the major growth experienced by the entire ESKD population (+77%) between 2000 and 2017 in the US [72].

Conclusion

CKD and ESKD in children is a significant public health burden worldwide. Despite significant effort to collect data on children with CKD, the incidence and prevalence of CKD are underestimated in many parts of the world and further studies aiming at improving early CKD diagnosis and at developing effective strategies to slow down CKD progression are needed. For children reaching ESKD, the main challenge is the access to KRT and especially transplantation that remain unavailable to the majority of children with ESKD worldwide.

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