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EDITORIAL COMMENTARY

Inequalities in access to pediatric ESRD care: a global health challenge

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Abstract The increasing attention paid to chronic kidney disease (CKD) as a major cause of mortality and disability, as well as the advances in management of CKD in children, have created a growing demand for pediatric renal replacement therapy (RRT) worldwide. A study by Koch Nogueira and colleagues of children on the transplant waiting list showed large disparities in access to pediatric kidney transplantation between regions in Brazil. This finding raises a wider question about inequalities in access to CKD care in children. Here we review the available data on the global burden of end-stage renal disease in children, the need for pediatric RRT, and its actual provision worldwide. We focus on inequalities in access to renal care for children that currently exist between and within countries. Reduction in worldwide inequalities in access to RRT in children remains a challenge, which requires greater awareness and effective interventions and policies.

Keywords End-stage renal disease · Chronic kidney disease · Children · Health inequalities · Developing countries

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Introduction

Children with chronic kidney disease (CKD) are at risk of developing end-stage renal disease (ESRD), which requires renal replacement therapy (RRT). RRT is a life-saving yet high-cost treatment for ESRD. The use of RRT, through either dialysis or transplantation, varies widely between and within countries because of differences in population demographics, causes of CKD, prevalence of ESRD, and factors affecting both access to and provision of pediatric renal care [1].

In 2000, the Millennium Development Goals were established under the auspices of the United Nations (UN) with several targets by 2015 including the reduction of child deaths, which have indeed dropped dramatically. In September 2015, a set of Sustainable Development Goals to be accomplished over the next 15 years has been adopted by the UN as part of a new global development agenda [2]. Among these goals, one is to ensure healthy lives at all ages and another is to reduce inequalities in access to health and education. Global inequality has two dimensions: the inequalities that exist between countries and the inequalities within countries. Both apply to and must be taken into account in the care of children with kidney diseases.

In an article recently published in *Pediatric Nephrology*, Koch Nogueira and colleagues report striking disparities in access to kidney transplantation across Brazil with children from two regions having far lower chances of getting a deceased donor transplant than those from two other regions [3]. For the authors, these results are attributable to economic and organizational issues. This finding, along with emerging data from RRT registries, provides valuable insights into inequalities in pediatric ESRD care across the world.

Global burden of pediatric ESRD

The prevalence of CKD is estimated to be 8–12 % of the adult population [4] but prevalence of pediatric CKD worldwide is unknown. The scarce available population-based data suggest that CKD might affect up to 1 % of children and adolescents [5, 6]. The burden of CKD has led to rising global rates of ESRD and death from non-communicable diseases in adults [7, 8]. In a recently published systematic review, Liyanage and colleagues estimated that in 2010 the number of patients receiving RRT worldwide was 2.6 million, with almost 80 % of them on dialysis [9]. The same authors estimated the number of patients needing RRT from models of age-standardized data on prevalence from 20 high-income countries with robust renal registries [9]. On the basis of these models, they estimated the number of children and young people aged 0–19 years with ESRD to be between 200 and 300 per million age-related population (pmarp) [9]. For a worldwide population of 7.2 billion including about 35 % (2.5 billion) under the age of 20 in 2014, Liyanage and colleagues therefore estimated the number of children and young adults with ESRD who would need RRT if access were universal to be at least 500,000. However, this estimate contrasts with the available renal registry data and is likely to overestimate the needs in the pediatric population. Indeed, in renal registries worldwide, the reported RRT prevalence rates in children and adolescents are highly variable but almost systematically fall below 100 pmarp [1], a figure at least two times lower than the estimates of Liyanage and colleagues [9].

In high-income countries including the European Union, Australia and New Zealand, Japan, Canada, and the USA (altogether 1 billion people, i.e., 14 % of the world population) where the vast majority of RRT is provided, the number of patients aged under 20 years currently treated for ESRD approaches 15,000. There were around 8000 pediatric patients on RRT in North America by the end of 2012 (RRT prevalence 83 pmarp in the USA and 63 in Canada) [10, 11], around 6000 in Europe with an average prevalence of 55 pmarp [12], and less than 1000 in Japan (dialysis prevalence 22 pmarp) [13], Australia and New Zealand together (RRT prevalence 64 pmarp) [14]. Contrary to the adult population, kidney transplantation is the most common RRT modality among prevalent pediatric ESRD patients [1]. Despite the numerous pediatric patients treated by RRT in other high-income economy regions (for example South Korea, Singapore, Saudi Arabia) and in populated middle-income countries with a variable access to RRT, like Brazil, Mexico, Iran, Russia, and Turkey, the number of children and adolescents aged under 20 estimated to be receiving RRT worldwide might not exceed 25,000. These data suggest that possibly less than 10 % of children with kidney failure needing RRT worldwide actually receive it. The unmet need for RRT may be negligible in the United States and Western Europe, but is huge in China, India and Pakistan, South Asia, sub-Saharan Africa, and Oceania. The likely consequence of this burden of untreated kidney failure within these regions is that hundreds of thousands of children died in the past few years as a result of ESRD.

Global inequalities in provision of RRT

A distinction should be made between countries providing universal access to RRT and those that do not. In countries with universal access, such as in Western Europe or the United States, incidence rates of RRT have stabilized over the past 15 years after a period of growth driven by inclusion of younger and sicker patients into pediatric RRT programs [1]. However, pediatric RRT incidence remains highly variable in high-income countries from four pmarp in Japan [15] to 14 pmarp in the United States [10] in 2012. In Europe, the differences in RRT incidence are mostly explained by national wealth and health expenditure [16].

In countries that provide partial access to RRT, inequalities in ESRD care are considerable. A recent nationwide survey on pediatric ESRD in China reported around 500 children aged under 18 who started chronic dialysis in 28 centers between 2007 and 2012 [17], that is a yearly dialysis incidence of less than 0.5 pmarp. Only 10 % of these children had access to transplantation in China, which is performed so far in only one center. In India, approximately 350 children were receiving any form of RRT in 18 out of 23 pediatric nephrology units in 2014 (A. Bagga, pers. comm. Oct. 2015). Although underestimated, the prevalence of RRT in children <15 years was as low as 1 pmarp in India, suggesting that only a small minority of those with ESRD have access to RRT. Despite rapid economic growth and improved ability to provide pediatric nephrology services, the pediatric RRT gap remains immense in these two countries [18]. Conversely, state-funded RRT programs exist in middle-income Asian countries such as Malaysia and result in comparable or even higher incidence (ten pmarp) and prevalence rates of RRT (85 pmarp) than in Europe [19]. In Latin America, the provision of pediatric RRT is also variable (prevalence from ten pmarp in Paraguay to 40 pmarp in Argentina) and highly correlated with country income (Latin American Dialysis and Transplantation Registry, pers. comm. Oct. 2015). Prevalence of RRT is higher in Central America, especially in Nicaragua, which has the highest prevalence of the continent despite being one the poorest countries in Latin America. This may be due to the endemic Mesoamerican nephropathy of unknown etiology in young people combined with the availability of a comprehensive pediatric RRT program in the country. Indeed, a unique cooperation project between the Children's Hospitals of Managua and Milan, Italy, funded by private charity foundations and the government of Nicaragua, allows for sustainable treatments of children with CKD and ESRD (A. Edefonti, pers. comm. Oct.

2015). In Africa, available data are extremely limited due to the absence of renal registries. RRT for children is mainly provided in Egypt and South Africa. These countries have long-standing established dialysis and transplant programs [20]. The particular model of Sudan also deserves attention. Through the combination of a state-funded program, a private donation, and establishment of a center linked with a university hospital in the United Kingdom, all forms of RRT are provided for children in Khartoum, Sudan, with an annual incidence of around 3 pmarp [21]. Although there is some progress happening in Africa with emerging programs in pediatric nephrology units (often attached to adult units) offering dialysis and/or transplantation in Tunisia, Morocco, Kenya, Nigeria, or Tanzania (M. McCulloch, pers. comm. Oct. 2015), most of the continent cannot afford chronic RRT, or only to a very limited number of children.

There are multiple causes for global inequality in provision of ESRD care in children. Despite its increasing impact on global health, CKD has not yet been targeted as a public health priority in many countries. Yet, its prevalence is higher in individuals from low- and middle-income countries [4], and among disadvantaged populations in high-income countries, including children. Besides genetic background, this is partially driven by infectious diseases, low birth weight and early malnutrition, poor sanitation, pollutants, and traditional medications [22, 23]. Another major contributor to the burden of CKD is acute kidney injury (AKI). Each year, 85 % of about 13 million episodes of AKI overall occur in low- and middle-income countries, and possibly result in 1.7 million deaths [24]. In developing countries, AKI predominantly affects children and young people, due to diarrhea and hypovolemia, infections, toxins, or obstetric complications, and is associated with high mortality and long-term renal consequences including CKD and ESRD [24].

The lack of human and financial resources in developing countries leading to inequities in overall health care systems, medical education, patient information, access to diagnostics and treatment, but also religious and cultural issues, have hampered pediatric nephrology programs. Moreover, in many countries, health authorities have prioritized adults over children for renal care. This concerns not only the ability to provide chronic RRT but also the management of the early stages of CKD. The low number of health care providers including pediatric nephrologists in many places around the world drives a vicious circle of worse CKD outcomes. There are for instance only two pediatric nephrologists in the Democratic Republic of Congo (vs. ~1000 in the United States), a country with a population of approximately 80 million, half of whom are children. The lack of health care resources results in poor detection and prevention of childhood onset CKD. Children from low- and middle-income countries more often have unrecognized and untreated CKD, and are more likely to progress to ESRD. In poor countries without universal access to health care, RRT remains unaffordable for the majority, and its out-of-pocket cost can be unbearable for those families who have access to it. Once initiated, often in a context of AKI suspicion, providers may be constrained to stop RRT when there is no more money left, even if AKI is not resolved. When ESRD is the initial diagnosis, pediatric nephrologists may face the ethical dilemma of whether it is appropriate to start RRT in a child who will most probably discontinue therapy and die after depleting all the family's resources. In a hospital-based study of children presenting with ESRD in Nigeria, 80 % of whom started dialysis, the median survival was less than 2 months and there was virtually no one alive 6 months after presentation in the hospital in the absence of chronic RRT [25]. Even in developing countries where chronic dialysis is available, mortality is strongly associated with country income, which further reduces RRT prevalence [26].

Inequalities in access to transplantation

In high-income countries with specialized pediatric transplantation centers, kidney transplantation is the primary choice of care for ESRD because it offers a longer life expectancy and a better quality of life than chronic dialysis. Pediatric kidney transplantation is now performed in more than 60 countries worldwide but may cover no more than 10 % of global needs. The transplant incidence rate was above ten pmarp in 2012 in the United States [10]. In Europe, the median incidence rate of pediatric kidney transplantation was around six pmarp in 2008 (ranging from 0 to 13) and was strongly associated with country income [27]. In the developing world, incidence rates of transplantation depend on country income even more. Pediatric transplant rates are <1–2 pmarp in Pakistan, Arab countries, and South Africa, and <4 pmarp in Brazil, suggesting that a limited number of ESRD children have access to transplantation [20, 28–30]. Transplantation outcome is generally poorer in low-income countries, although a small minority of referral centers in these countries also show excellent results [28].

Access to pediatric transplantation can also vary substantially within the same country. Despite being the world's 7th largest economy and having experienced social progress in the past decades, Brazil, like many other Latin American countries, still has to overcome extreme inequalities that leave more than 20 % of its population below the poverty line. In an effort to investigate potential inequalities in access to pediatric kidney transplantation in Brazil, Koch Nogueira and colleagues examined the probability of receiving a deceased donor transplant using competing risks regression models [3]. In an article recently published in *Pediatric Nephrology*, they report that, despite a nationally regulated allocation system, children from the North and the Midwest macroregions of Brazil have a 3–4 times lower probability of

getting a deceased donor transplant than children from the South and Southeast macroregions [3]. It is argued that this is not compensated by a higher living donor transplant rate and nor does it completely reflect the underlying disparities in pediatric ESRD incidence [31]. Although the authors found an association between gross domestic product per capita and access to transplantation, the differences were only partly related to regional wealth. Koch Nogueira et al. rather attributed the disparities to a matter of supply and demand. The disadvantaged macroregions indeed have a low-density population and are medically deprived areas in terms of pediatric nephrology services, suggesting that training the existing transplant staff may be a cost-effective way to cut down these inequalities in Brazil.

In the US, despite a highly regulated organ allocation system, disparities in access to transplantation persist. Ethnic minorities, women, older adults, patients with lower socioeconomic status, and those on dialysis at a for-profit center are less likely to undergo kidney transplantation. Among pediatric patients, ethnic minorities tend to have reduced access to the transplant waiting list, have reduced access to deceased donor transplantation once on the waiting list [32], and to living-donor preemptive transplantation [33]. Although ethnicity and social deprivation are closely related, socioeconomic status does not explain all ethnic differences in access to pediatric kidney transplantation in the US [32]. A change in the national allocation policy in 2005, which gave a higher priority to pediatric candidates, has attenuated, but not eliminated, these ethnic disparities [34]. Ethnic disparities have also been identified outside the US. Indigenous children are less likely to receive a preemptive or a living-donor transplant in Australia [35], non-Western European origin is associated with reduced access to transplant in Belgium and the Netherlands [36], and ethnic minorities have lower rates of preemptive transplantation in the UK [37]. The reasons for these inequalities, including any contribution from underlying inequities, are subject to ongoing research [38].

Furthermore, there are many steps from the development of ESRD in a child to the receipt of a kidney transplant, each of which can be affected by inequalities in access. These include country- or region-level factors (availability of RRT facilities and pediatric transplant programs), center-level factors (specialized pediatric nephrology services, education about transplant, referral, listing, acceptance of a deceased donor, or identification of a living donor), and patient-level factors (age, ethnicity, co-morbidities, residence location, socio-economic, educational, and cultural issues) [38–41].

What's next?

A realistic key target to reduce renal care inequalities in children is to fight against AKI. Treating and preventing malnutrition and diarrheal disease in developing countries by water and sanitation interventions should be a public health priority to reduce child mortality but also global CKD prevalence. The 0by25 initiative of the International Society of Nephrology aims at achieving no preventable and treatable deaths from AKI by 2025 [42]. Raising awareness of AKI, performing inexpensive, easy, and accurate diagnostic tests (measurement of serum creatinine, assessment of urinary sediment and volume status), improved clinical nephrology training, appropriate fluid administration, and availability of affordable, usually peritoneal, dialysis, will be needed to achieve this ambitious goal. Another major aspect to tackle inequalities in pediatric renal care is the implementation of early CKD detection and intervention programs. Once CKD is detected, relatively simple and inexpensive measures can substantially slow disease progression and minimize the burden of pediatric ESRD. Increased funding and government awareness of CKD and its consequences at all ages are needed to support public health education and to develop local expertise in pediatric nephrology. The dissemination of such prevention programs could dramatically improve patient and renal survival rates in developing countries. Finally, development of models of pediatric dialysis and transplantation programs in emerging countries remains particularly challenging and cost intensive [20]. Establishment of publicly supported RRT programs and organ sharing frameworks, improvement of clinical dialysis and transplant training, and provision of cheaper dialysis supplies and lifelong immunosuppressive drugs are required to further facilitate access to, and success of, pediatric RRT worldwide. However, this may only be achievable in the long run. In high-income countries, possible interventions which may help to improve access to transplantation have been previously discussed in this journal [38].

Renal societies, such as the International Pediatric Nephrology Association (IPNA) and the International Society of Nephrology (ISN) also play a crucial role in narrowing the inequality gap. This consists of assisting in education and training courses, supporting visiting fellowship programs in excellence centers around the world, and promoting successful models of cooperation between well-established and emerging pediatric nephrology units (sister center program) similar to that of Nicaragua or Sudan (www.ipna-online.org/education/).

In conclusion, there remain major challenges to equally providing optimal care for children with ESRD worldwide. World Kidney Day 2016, dedicated to children, will help to deliver this message to governments, health-policy makers, the medical community, and the public at large.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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