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WORLD KIDNEY DAY 2016 AVERTING THE LEGACY OF KIDNEY DISEASE–FOCUS ON CHILDHOOD

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World Kidney Day 2016 focuses on kidney disease in childhood and the antecedents of adult kidney disease that can begin in earliest childhood. Chronic kidney disease (CKD) in childhood differs from that in adults, as the largest diagnostic group among children includes congenital anomalies and inherited disorders, with glomerulopathies and kidney disease in the setting of diabetes being relatively uncommon. Children born early or who are small-for date newborns have relatively increased risk for the development of CKD later in life. Persons with a high-risk birth and early childhood history should be watched closely in order to help detect early signs of kidney disease in time to provide effective prevention or treatment. Successful therapy is feasible for advanced CKD in childhood. Because there are disparities in access to care, effort is needed so that those children with kidney disease, wherever they live, may be treated effectively, irrespective of their geographic or economic circumstances. Our hope is that World Kidney Day will inform the general public, policy makers and caregivers about the needs and possibilities surrounding kidney disease in childhood.

"*For in every adult there dwells the child that was, and in every child there lies the adult that will be*."

John Connolly, *The Book of Lost Things*

INTRODUCTION AND OVERVIEW

The 11th World Kidney Day will be celebrated on March 10, 2016 and will focus on kidney disease in childhood and the antecedents of adult kidney disease, which can begin even in the perinatal period. This annual event, sponsored jointly by the International Society of Nephrology (ISN) and the International Federation of Kidney Foundations (IFKF), has become a highly successful effort to inform the general public and policymakers about the importance and ramifications of kidney disease.

Children who endure acute kidney injury (AKI) from a wide variety of conditions may have long-term sequelae that can lead to chronic kidney disease (CKD) many years later (Furth et al. 2006; Warady & Chadha 2007; Goldstein 2012; Harambat et al. 2012). Further, CKD in childhood, much of it congenital, and complications from the many non-renal diseases that can affect the kidneys secondarily, not only lead to substantial morbidity and mortality during childhood but also result in medical issues beyond childhood (Figure 1). Indeed, childhood deaths from a long list of communicable diseases are inextricably linked to kidney involvement. In addition, a substantial body of data indicates that hypertension, proteinuria and CKD in adulthood have childhood antecedents—from as early as in utero and perinatal life (see Table 1).

The prevalence of CKD in childhood is rare—and has been variously reported at 15-74.7 per million children (Warady & Chadha 2007). The World Health Organization (WHO) has recently added kidney and urologic disease to mortality information tracked worldwide, and should be a valuable source of such data over time — yet WHO does not post the information by age group (Health Statistics and Information Systems 2016). Databases such as the North American Paediatric Renal Trials and Collaborative Studies (NAPRTCS) (NAPRTCS 2016) the U.S. Renal Data System (USRDS) (Saran et al. 2015) and the EDTA registry (ESPN/ERA-EDTA Registry 2016) include data on paediatric ESRD, and some on CKD. Projects such as the ItalKid (Ardissino et al. 2003) and Chronic Kidney Disease in Children (CKiD) (Wong et al. 2012) studies, as well as registries that now exist in many countries provide important information, and more is required.

SPECTRUM OF PAEDIATRIC KIDNEY DISEASES

The conditions that account for CKD in childhood, with a predominance of congenital and hereditary disorders, differ substantially from those in adults. To date, mutations in more than 150 genes have been found to alter kidney development or specific glomerular or tubular functions (Eckardt et al. 2013). Most of these genetic disorders present during childhood, and many lead to progressive CKD. Congenital anomalies of the kidney and urinary tract (CAKUT) account for the largest category of CKD in children (Table 2) and include renal hypoplasia/dysplasia and obstructive uropathy. Many paediatric glomerulopathies are caused by genetic or acquired defects of the podocytes, the unique cell type lining the glomerular capillaries.

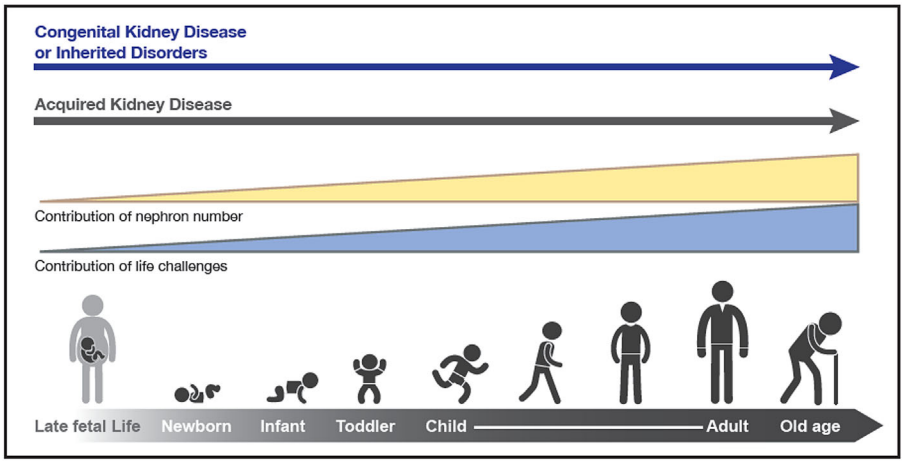

Figure 1: The types and risks of kidney disease change across the lifecycle. The contribution of nephron number increases over the life cycle, in concert with events that provide direct insults and challenges to kidney health.

CONGENITAL KIDNEY DISEASE AND DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE, RENAL ENDOWMENT AND IMPLICATIONS

In regions where antenatal fetal ultrasounds are routine, many children with urologic abnormalities are identified antenatally, which permits early intervention. However, in much of the world, children with structural abnormalities are not identified until much later, when symptoms develop. Both diagnosis and therapy of kidney disease in childhood have matured over the past several decades. While generalized screening for proteinuria, hematuria and urinary tract infections are carried out in some countries and regions, there is a lack of consensus as to its effectiveness. However, there is general agreement that children with antenatal ultrasound studies indicating possible genitourinary anomalies, children with a family history of kidney disease, and children with signs such as failure to thrive or a history of urinary tract infection, voiding dysfunction or an abnormal appearing urine should be examined. Initial screening would include a focused physical examination and a urine dipstick, formal urinalysis and a basic chemistry panel, followed by a more focused evaluation if indicated.

Depending on the diagnosis, definitive therapy may be indicated. However, the evidence that therapy will slow progression of CKD in childhood remains limited. Angiotensin converting enzyme inhibitors, angiotensin receptor blockers, antioxidants and, possibly, dietary changes may be indicated,

Perinatal Period-	22 completed weeks of gestation to Day 7 of postnatal life
Neonatal Period-	Birth to Day 28 of postnatal life
Infancy	Birth to 1 year of age
Childhood	1 year of age to 10 years of age
Adolescence	10 years of age to 19 years of age

Table 1: Definitions of stages of early life.

Notes: The data in this table are as defined by the World Health Organisation. The perinatal period is defined as 22 completed weeks of gestation to Day 7 of life; the neonatal period, as up to 28 days of life; infancy as up to one year of age; childhood as year 1 to 10; and adolescence from 10 years to age 19. There is variation worldwide in how these stages of early life are defined. Some would define "young people" as those age 24 or less. In the United States, childhood is as a whole defined as going to age 21.

CKD Aetiology	Percentage (Range)	ESRD Aetiology	Percentage (Range)
CAKUT	48–59%	CAKUT	34–43%
GN	5–14%	GN	15–29%
HN	10–19%	HN	12–22%
HUS	2–6%	HUS	2–6%
Cystic	5–9%	Cystic	6–12%
Ischemic	2–4%	Ischemic	2%

Table 2: Aetiology of chronic kidney disease in children.

Rare causes include congenital NS, metabolic diseases, cystinosis/ Miscellaneous causes depend on how such entities are classified CAKUT: Congenital anomalies of the kidney and urinary tract; GN: Glomerulonephritis; HN: Hypertension; HUS: Haemolytic uremic syndrome *from Harambat et al. CKD data are from NAPRTCS, the Italian Registry and the Belgian Registry. ESRD data are from ANZDATA, ESPN/ERA-EDTA, UK Renal Registry and the Japanese Registry.

depending on the diagnosis. However, dietary changes need to permit adequate growth and development. The ESCAPE trial provided evidence that strict blood pressure control retards progression of CKD in children irrespective of the type of underlying kidney disease (Group et al. 2009).

Some very young children may require renal replacement therapy, even in early infancy. Recent data pooled from registries world wide indicate good survival, even when dialysis is required from neonatal age (Harambat et al. 2012; van Stralen et al. 2014). Kidney transplantation, the preferred renal replacement therapy in children, is suitable from the second year of life, with excellent patient and allograft survival, growth and development.

In addition to those children with congenital kidney disease, perinatal events may affect future health in the absence of evident kidney disease in early life (Hoy et al. 2010). Premature infants appear to be particularly at risk for kidney disease long after they are born, based both on observational cohort studies, as well as on case reports. Even very premature infants now survive, including many born well before nephrogenesis is complete (Flynn et al. 2014). The limited data available indicate that in the process of neonatal ICU care, such babies receive many nephrotoxins, and that those dying prior to discharge from the nursery have fewer and larger glomeruli (Rodriguez et al. 2004). Additionally, those surviving have evidence of renal impairment that may be subtle (Abitbol et al. 2003). Even more concerning, abundant epidemiologic data indicate that persons born at term but with relatively low birth weights may be at high risk for hypertension, albuminuria and CKD in later life (Hodgin et al. 2009). When direct measurements are pursued, such persons, as adults, may have fewer nephrons, thus a low cardiorenal endowment.

In focusing on children for World Kidney Day, we would note that it is key to follow kidney function and blood pressure throughout life in those persons born early or small-for-dates. By doing so, and avoiding nephrotoxic medications throughout life, it should be possible to avert CKD in many people.

RESOURCES AND THERAPEUTICS FOR CHILDREN–DIFFERENCES FROM THERAPEUTICS IN ADULTS

Disparities exist in the availability of resources to treat AKI in children and young people; consequently, too many children and young adults in developing nations succumb if AKI occurs. To address the problem the ISN has initiated the Saving Young Lives Project, which aims both to prevent AKI with prompt treatment of infection and/or delivery of appropriate fluid and electrolyte therapy, and to treat AKI when it occurs. This ongoing project in SubSaharan Africa and South East Asia, in which four kidney foundations participate equally (IPNA, ISN, ISPD and SKCF)[1], focuses on establishing and maintaining centers for the care of AKI, including the provision of acute peritoneal dialysis. It links with the ISN's 0 by 25 project, which calls on members to ensure by 2025 that nobody dies from preventable and acute kidney injury.

TRANSITION FROM PAEDIATRIC TO ADULT CARE

Transition of care for adolescents with kidney disease into an adult setting is critical both for patients and their caregivers. Non-adherence is a too-frequent hallmark of transition from paediatric to adult care for young patients with chronic disease states (Watson 2000; Jarzembowski et al., 2004; Aujoulat et al. 2011). Hence, considered steps combined with systematically defined procedures supported by validated pathways and credible guidelines must be in place to ensure successful outcomes.

CALL FOR GENERATING FURTHER INFORMATION AND ACTION

Given vulnerabilities of children with kidney disease including impact on growth and development and future life as an adult, and given the much greater proportion of children in developing nations facing resource constraints educating everyone involved is imperative in order to realign communications and actions (White et al. 2010; Gallieni et al. 2014). These efforts should foster regional and international collaborations and exchange of ideas between local kidney foundations, professional societies, other not-for-profit organisations, and states and governments, so as to help empower all stakeholders to improve the health, well-being and quality of life of children with kidney diseases and to ensure their longevity into adulthood.

1. The four partners are (in alphabetical order): IPNA (International Pediatric Nephrology Association), ISN (International Society of Nephrology), ISPD (International Society for Peritoneal Dialysis), SKCF (Sustainable Kidney Care Foundation).

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