



## EDITORIAL

### In time: averting the legacy of kidney disease – focus on childhood



### Em tempo: evitando as consequências da doença renal – foco na infância

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“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, around the globe. 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. In 2016, World Kidney Day will be dedicated to kidney disease in childhood and the antecedents of adult kidney disease, which can begin in earliest childhood.

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.<sup>1–4</sup> 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. Indeed, childhood deaths from a long list of communicable diseases are inextricably linked to kidney involvement. For example, children who succumb to cholera and other diarrheal infections often die, not from the infection, but because of AKI induced by volume depletion and shock. 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](#) for definitions of childhood). World Kidney Day 2016 aims to heighten general awareness that much adult renal disease is actually initiated in childhood. Understanding high risk diagnoses and events that occur in childhood have the potential to identify and intervene preemptively in those people at higher risk for CKD during their lifetimes.

Worldwide epidemiologic data on the spectrum of both CKD and AKI in children are currently limited, though increasing in scope. The prevalence of CKD in childhood is rare – and has been variously reported at 15–74.7 per million children.<sup>3</sup> Such variation is likely because data on CKD are influenced by regional and cultural factors, as well as by the methodology used to generate them. The World Health Organization (WHO) has recently added kidney and urologic disease to mortality information tracked worldwide, and

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**Table 1** Definitions of stages of early life.

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

Notes: The data in this table are as defined by the World Health Organization.

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.

should be a valuable source of such data over time – yet WHO does not post the information by age group.<sup>5</sup> Databases such as the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS)<sup>6</sup> the U.S. Renal Data System (USRDS)<sup>7</sup> and the EDTA registry<sup>8</sup> include data on pediatric end-stage renal disease, and some on CKD. Projects such as the Italkid<sup>9</sup> and Chronic Kidney Disease in Children (CKiD)<sup>10</sup> studies, the Global Burden of Disease Study 2013, as well as registries that now exist in many countries provide important information, and more is required.<sup>11</sup>

AKI may lead to CKD, according to selected adult population studies.<sup>12</sup> The incidence of AKI among children admitted to an intensive care unit varies widely – from 8% to 89%.<sup>1</sup> The outcome depends on the available resources. The results from projects such as the AWARE study, a five-nation study of AKI in children are awaited.<sup>13</sup> Single center studies, as well as meta-analyses indicate that both AKI and CKD in children account for a minority of CKD worldwide.<sup>2,3</sup> However, it is increasingly evident that kidney disease in adulthood often springs from a childhood legacy.

## Spectrum of pediatric 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.<sup>14</sup> 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 (see Table 2) and include renal hypoplasia/dysplasia and obstructive uropathy. Important subgroups among the renal dysplasias are the cystic kidney diseases, which originate from genetic defects of the tubuloepithelial cells’ primary cilia. Many pediatric glomerulopathies are caused by genetic or acquired defects of the podocytes, the unique cell type lining the glomerular capillaries. Less common but important causes of childhood CKD are inherited metabolic disorders such as hyperoxaluria and cystinosis, and atypical hemolytic uremic syndrome, a thrombotic microangiopathy related to genetic abnormalities of complement, coagulation or metabolic pathways.

In various classifications it is not clear how to categorize children who have suffered AKI and apparently recovered,

**Table 2** Etiology of chronic kidney disease in children.<sup>2</sup>

CKD		ESRD	
Etiology	Percentage (range)	Etiology	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%

CKD, chronic kidney disease; ESRD, childhood onset end-stage renal disease; CAKUT, congenital anomalies of the kidney and urinary tract; GN, glomerulonephritis; HN, hypertension; HUS, hemolytic uremic syndrome. Rare causes include congenital NS, metabolic diseases, cystinosis. Miscellaneous causes depend on how such entities are classified.

Chronic Kidney Disease data are from North American Pediatric Renal Trials and Collaborative Studies, the Italian Registry and the Belgian Registry. Childhood onset end-stage renal disease data are from ANZDATA, ESPN/ERA-EDTA, UK Renal Registry and the Japanese Registry.

or how and whether to include those children who have had perinatal challenges, likely resulting in a relatively low nephron number.

Among children with childhood-onset end-stage renal disease (ESRD) glomerulopathies are slightly more and congenital anomalies less common (Table 2), due to the typically more rapid nephron loss in glomerular disease. However, recent evidence suggests that many patients with milder forms of CAKUT may progress to ESRD during adulthood, peaking in the fourth decade of life.<sup>15</sup>

There are national and regional differences in the types and course of both AKI and CKD during childhood and beyond. Death from kidney disease is higher in developing nations, and national and regional disparities in care and outcome must be addressed. Further, access to care is variable, depending on the region, the country and its infrastructure. By focusing on kidney disease in childhood, cost-effective solutions may be reached, as treating disease early and preemptively may prevent later, more advanced CKD. Expectations depend on the availability of care and management. Treating children, even from infancy, who have AKI and CKD that requires renal replacement therapy can be effective in mitigating the burden of kidney disease in adulthood. Doing so requires resources that focus on the most expeditious and cost-effective ways to deliver acute RRT in childhood.

## 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

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