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### Learning From Kids

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### Learning From Kids



Children are not just little adults. This adage is universally recited to medical students during their pediatric clerkships to emphasize that the pathophysiology, manifestations, and outcomes of diseases are often different in children. Consequently, diagnostic approaches and therapeutic interventions developed and catered to adults may not be appropriate. Moreover, despite the iteration of this axiom and virtual acceptance as fact borne of evidence, it is not. Paradoxically, contemporary management guidance for children, including dosing of therapeutic agents, has largely been extrapolated from studies in adults. Plus, clinical trials in children were long viewed as nihilistic, given the barriers of low incidence and prevalence of disease, notwithstanding societal concerns about studies in children. Fortunately, with strong and steadfast advocacy from the pediatric community, patients, and families, regulatory and funding agencies in the United States have increasingly recognized the importance of clinical research in children.

Efforts to first incentivize and then require drug studies in children, such as the enactment of the Best Pharmaceuticals for Children Act in 2002 and the Pediatric Research Equity Act in 2003, have resulted in studies of safety and dosing for hundreds of medications in children.<sup>1</sup> Funding agencies, including the National Institutes of Health, have targeted funding for pediatric studies and encouraged inclusion of children in clinical trials and cohort studies. Funding has hit its targets several times, and the Chronic Kidney Disease in Children (CKiD) study and two, large, prospective, cohort studies of nephrotic syndrome and glomerulonephritis in adults and children, NEPTUNE and CureGN are funded.<sup>2,3</sup> These bull's eyes are important for the pediatric community as this research has and will continue to provide crucial information to optimize care and outcomes for children. But, internists should regard the increase in clinical research in children with more than passing interest, since studies in children may provide important information that directly impacts the understanding and treatment of disease in adults.

The contention that research in children may inform adult care typically includes two lines of reasoning: (1) events or diseases that occur exclusively in childhood

may impact the development of disease in adulthood and (2) adult diseases, including cardiovascular disease, may have their origins in childhood. Nevertheless, the investigation of childhood disorders is quite distinct from so-called analogues experienced by adults. One of these is CKD, and investigations thereto may provide important information regarding the pathophysiology and outcomes from disease onset and during disease progression, absent the concomitant and confounding comorbidities and risk factors associated with adult CKD.

There is an enlarging evidence base which demonstrates that many disease processes that occur exclusively in childhood may impact morbidity and mortality in adulthood. There is no stronger case for this argument than the association between nephron endowment, which is established by 32- to 36-week gestation, and risk for cardiovascular and kidney disease in adulthood.<sup>4,5</sup> First postulated by Brenner and colleagues, this risk is now so uniformly accepted that birth weight and gestational age, hitherto irrelevant beyond infancy and early childhood, are now routinely collected in clinical studies of cardiovascular and kidney disease in adults.<sup>4,5</sup> Recent, more quantitative methods that determine nephron endowment include magnetic resonance imaging. With appropriate software manipulation nephron number and size in whole human kidneys is calculable *ex vivo*.<sup>6</sup> Ongoing efforts to enumerate endowment in infancy have the potential to allow early identification of at-risk individuals for intervention and monitoring, with the potential to improve childhood and adult health—a two-fer! Although childhood obesity is a condition that frequently extends into adulthood, there is evidence to support that even transient obesity in adolescence is associated with increased risk for disease and premature death during adulthood, independent of obesity during adulthood.<sup>7,9</sup> Therefore, ongoing efforts to characterize risk for and prevention of obesity in children are imperatives to minimize morbidity and mortality in adults.

Hypertension and cardiovascular disease are prominent examples of adult conditions that may have their origins in childhood. That childhood high blood pressure may predict hypertension in adulthood was first demonstrated by the Muscantine Study in the late 1980s.<sup>10</sup> Autopsy findings from the Bogalusa Heart Study and the Pathobiological Determinants of Atherosclerosis in Youth study convincingly demonstrated that early findings of atherosclerosis are present in children and young adults.<sup>11,12</sup> A more recent study from the Bogalusa Heart Study demonstrated that childhood hypertension was associated with an increased risk of adult hypertension, heightened pulse wave velocity, increased carotid intima-media thickness, and left ventricular hypertrophy.<sup>13</sup> Therefore, ongoing studies to improve the recognition of hypertension in children are important to allow early intervention, thereby minimizing the risk for hypertension and cardiovascular disease in adults.

Unfortunately, the diagnosis of hypertension in children is not straightforward. Although the results of recent trials have led to modifications in the target for blood pressure control in certain populations of hypertensive adults, the guidelines for adults provide a single systolic blood pressure threshold for diagnosis of hypertension.<sup>14,15</sup> For children, the blood pressure thresholds are functions of sex-, age- and height-specific percentiles. Consequently, the crafting of a seemingly simple diagnosis of hypertension becomes a cumbersome and error-prone process.<sup>13,16,17</sup> Some electronic health records are now able to calculate blood pressure percentiles automatically, and these "alerts" have been shown to increase identification of hypertension, but these systems are not widely distributed.<sup>18</sup> Recently published guidelines for the recognition and treatment of hypertension in children have provided simplified tables to optimize the recognition of elevated blood pressure by busy clinicians.<sup>17,18</sup>

It should also be acknowledged that the blood pressure thresholds used to diagnose hypertension in children are based on statistical methods, not outcomes.<sup>13,16,17</sup> Therefore, in addition to ongoing efforts to optimize the diagnosis of hypertension, longitudinal studies are necessary to identify associations between various blood pressure thresholds and outcomes. This requires cooperation between the pediatric and adult nephrology community as many outcomes will not manifest until adulthood. For example, the aforementioned Bogalusa study is comprised of nearly 3 decades of follow-up data since childhood.<sup>13</sup> Longitudinal studies of childhood hypertension may also support the development of strategies to treat and potentially reverse the complications of hypertension and ultimately prevent their development altogether.

While the value of studies of childhood disorders that potentially eventuate in adult disease or continue into adulthood may be readily apparent to internists, the contribution of studies of childhood CKD to the care of adults with CKD may be less apparent. CKD in children is quite different than in adults, most notably, because congenital anomalies of the kidney and urinary tract are the leading cause of CKD in children. In addition, the

risk for disease progression and ramifications of kidney disease is influenced by the demands of the growing and developing child.

However, in kids, CKD is often primary rather than secondary, and studies of the impact of progression of CKD on cardiovascular disease and CKD bone and mineral metabolism disturbances (CKD-MBD) are less likely to be confounded by preexisting underlying causes of CKD (eg, preexisting hypertension, diabetes, and/or systemic inflammatory disease) and/or other preexisting comorbidities. As such, studies that describe risk factors for and the pathophysiology of the ramifications of CKD may provide unique insight for those processes regardless of age. For example, studies of intact arteries from children which have provided mechanistic insights into vascular calcification in CKD advance knowledge not only for children, but adults with CKD.<sup>19,20</sup> The Cardiovascular Comorbidity in Children with CKD (4C) study has recently described the prevalence of surrogate markers for cardiovascular disease in a large cohort of children with CKD as well as associations with potentially modifiable risk factors such as hypertension, physical activity, body mass index, and serum phosphorus.<sup>21</sup> Interestingly, in a recent analysis of patients enrolled in CKiD, arterial stiffness, as measured by carotid-femoral pulse wave velocity, was comparable in children with mild kidney dysfunction and normal children.<sup>22</sup> Longitudinal study of the children enrolled in these studies will not only provide important information about the impact of CKD progression on these outcomes, but also the potential to identify therapeutic targets.

Similarly, studies of cognitive function in adults with CKD are often limited by the confounding impact of cerebrovascular disease and other comorbid conditions less frequently seen in children, such as diabetes.<sup>23,24</sup> In fact, while advanced CKD in children is associated with risk for significant neurocognitive impairment, a cross-sectional analysis from the CKiD study suggests that, in general, the children in the CKiD cohort with mild-to-moderate kidney disease fall within age-appropriate expectations for IQ, academic achievement, and attention/executive functioning.<sup>25</sup> However, at the individual level, a large percentage of the children had dysfunction that placed them at risk for poor long-term outcomes.<sup>25</sup> This longitudinal study is poised to examine the effect of variables that may become increasingly more apparent with CKD progression, such as anemia, hypertension, and chronic kidney disease–mineral and bone disorder on neurocognitive function.

The global nephrology community acknowledged the importance of pediatric kidney disease by dedicating World Kidney Day 2016 to kidney disease in childhood and the antecedents of adult kidney disease. This recognition should not be viewed as altruistic by the internal medicine nephrology community, nor should this be a limited endorsement. Ongoing advocacy and cooperation are required to continue to increase clinical research in childhood kidney disease, which should be buoyed by the recognition that the benefits are not limited to the care of children. We can all learn from kids.

## END QUOTATION

“... the world needs ‘childish’ thinking; bold ideas, wild creativity and especially optimism. Kids’ big dreams deserve high expectations, she says, starting with grownups’ willingness to learn from children as much as to teach.”

— Adora Svitak

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