9-2-2011

The challenges of assessing acute kidney injury in infants

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Definitions of pediatric acute kidney injury (AKI) use changes of serum creatinine. There is a paucity of well-designed studies in infants because of creatinine age-dependency. The emerging role of cystatin C as a superior marker of renal dysfunction led to a carefully conducted study on AKI in infants by Zappitelli *et al.* This Commentary calls for the development of age-independent serum creatinine and estimated glomerular filtration rate *z* scores.

Kidney International (2011) **80,** 567–568. doi:10.1038/ki.2011.172

Acute kidney injury (AKI) is a serious condition that negatively affects the outcome of other conditions, particularly in neonates and infants. Infants with AKI have decreased survival compared with those without AKI.[1] There has been considerable debate about how best to define AKI, with over 30 different definitions.[2] To simplify this, a classification system called RIFLE—based on the criteria of risk, injury, failure, loss, and end-stage renal disease—has been proposed to standardize the definition of AKI in adults, and the criteria correlate with hospital mortality and adverse patient outcomes.[2] These criteria are based on serum creatinine (SCr), as a surrogate marker of glomerular filtration rate (GFR), and urine output. In children, variability of muscle mass, age, sex, diet, amount of creatinine filtered by the glomerulus, proximal tubule secretion, tubular reabsorption, and gastrointestinal elimination renders SCr problematic as a tool for GFR assessment.[3] Therefore, a modified pediatric definition was necessary, and the pRIFLE criteria were developed.[4] However, very few infants and no neonates were included in that study. In neonates, SCr reflects largely the maternal creatinine.[5] During gestation, GFR remains constant and SCr increases with the baby's length, but 24 hours after delivery, SCr drops progressively, and GFR increases threefold, then continues to increase slowly thereafter and reaches steady state at 18 months.[6] Thereafter, the absolute GFR increases with body length, and therefore GFR is normalized to body surface area, which makes it age-independent, while SCr continues to increase.[7] Even with normalization to body surface area, GFR increases from about 10 ml/min/1.73 m^2 in infants to 90–150 ml/min/1.73 m^2 in 2-year-old children. Figure 1 demonstrates these relationships between age and SCr, based on the new reference intervals by Boer *et al.*,[8] and between age and the new Schwartz estimated GFR,[9] based on the reference intervals of Boer *et al.* and standardized heights from the US Centers for Disease Control and Prevention (CDC) growth charts using the 2000 Third National Health and Nutrition Examination Survey (NHANES III) data.[10]

These developmental changes in SCr pose significant difficulties for the development of an AKI definition that is completely independent of age and sex. In view of these difficulties, a growing number of potential AKI biomarkers have been studied, such as neutrophil gelatinase-associated lipocalin, kidney injury molecule 1, liver fatty acid-binding protein, and cystatin C. It is timely to see a new report on a large cohort of 288 infants undergoing cardiac surgery in a multicenter study by Zappitelli *et al.*[11] (this issue). The authors studied cystatin C, a novel marker of renal function that is superior to creatinine,[7] in comparison with creatinine. They defined AKI as an abrupt (within 48 hours) reduction in kidney function, currently defined as an absolute increase in SCr of at least 0.3 mg/dl ($\geqslant$26.4 μmol/l), a percentage increase in SCr of at least 50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5 ml/kg per hour for more than 6 hours). They used a creatinine-based and urine output-based AKI definition and demonstrated nicely that cystatin C independently predicted morbidity and length of stay. But is their AKI definition, which is admittedly the result of a large consensus effort, really a good definition in view of the relatively dramatic evolution of renal function after birth?

Including an increase of SCr would account for the age-dependency of SCr, but an increase of 26.4 μmol/l would overestimate the degree of AKI in newborns compared with 1-year-olds. Normal median SCr falls from 55 μmol/l on day 1 to 21 μmol/l at 1 year,[8] which means that the same cutoff would be half as important for the 1-year-old. Zappitelli *et al.*[11] acknowledge these difficulties by excluding infants less than 1 month of age. Indeed, it is most questionable what it would mean if an SCr increases by 26.4 μmol/l on day 2, when SCr is still mostly the maternal creatinine.[5] An increase of 50% is equally problematic in view of the not-normally-distributed SCr concentrations across all ages (Figure 1). The problem is reduced by limitation of study participants to greater than 1 month and less than 2 years. However, congenital heart disease may require open-heart surgery much earlier than at 1 month of age, and clearly these patients are at risk for

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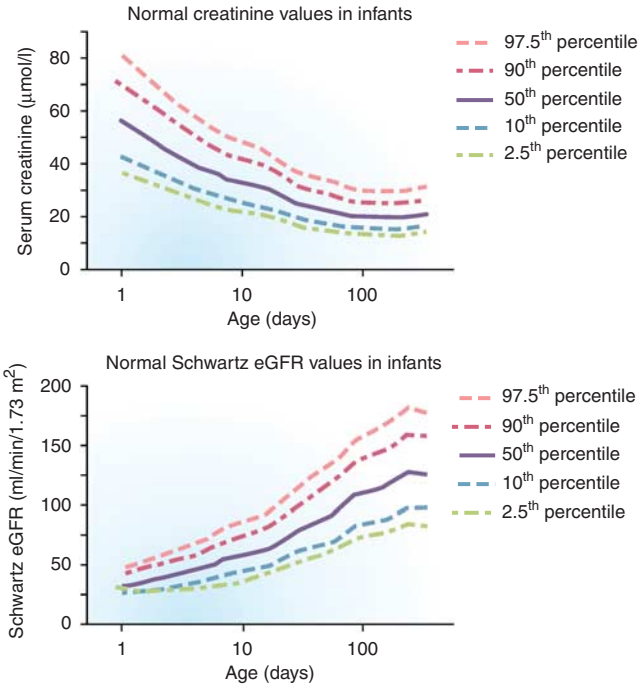

Figure 1 | Normal creatinine values by age. Taken from a recent publication on serum creatinine reference intervals[8] and the modified new Schwartz estimated GFR (eGFR),[9] based on standardized heights from the US Centers for Disease Control and Prevention growth charts using the 2000 Third National Health and Nutrition Examination Survey (NHANES III) data (file no. 2, LENAGEINF, in ref. 10).

postoperative AKI. We need a definition that is suitable across all ages.

To further address this issue, Zappitelli *et al.*[11] also used nuclear-medicine GFR values from a previous study on 651 people to generate percentile curves. They then plotted the study subjects into these curves. Although this is certainly an improvement over the definition used above, a separate validation of the new Schwartz formula[9] in a large cohort of infants against gold-standard GFR measurement remains elusive. Nonetheless, this approach offers significant advantages over an approach based merely on creatinine increase and percentage increase.

In pediatric practice, we are faced with age-dependency of reference intervals all the time, and we use charts to determine percentiles. A better way still are age-independent *z* scores. Given a large enough sample size (usually >5000 to account for both sexes and to cover all ages), methodologies such as Box–Cox transformations can be used to develop *L*, *M*, and *S* variables for each age (in months) to calculate age-independent *z* scores. The CDC website[10] offers a wealth of such approaches for height, weight, body mass index (>2 years of age), weight for height, blood pressure, and so on. It is surprising that the pediatric nephrology community has not embraced this mathematical approach and uses an AKI definition based on changes of the *z* scores for either SCr, cystatin C, or any estimated GFR. Expressing GFR and SCr as age-independent *z* score will also allow for better recognition of impaired kidney function, because a newborn's SCr or cystatin C cannot be properly interpreted without consultation of appropriate normative charts. The laboratories are not assisting pediatricians and pediatric nephrologists by providing age-dependent reference intervals for every day of life. Perhaps it is time that we use modern information-technology support to report all laboratory parameters as age-independent *z* scores, and to change the definitions accordingly.

In conclusion, the study by Zappitelli *et al.*[11] definitely adds to the medical literature and establishes the prognostic value of cystatin C as an AKI marker in infants at risk for AKI. The study also demonstrates the limitations of the current pediatric AKI definitions and raises the question of whether age-dependent parameters of renal function need to be expressed in a different form, perhaps as age-independent *z* scores?

DISCLOSURE

The author declared no competing interests.

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