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EDITORIAL COMMENTARY

Urinary NGAL to define AKI in asphyxiated infants

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Abstract Acute kidney injury (AKI) is independently associated with poor outcomes in the critically ill patient. The standard kidney function biomarker, serum creatinine, shows a demonstrable rise in concentration many hours to days after insult to the kidney. Thus, creatinine-based AKI diagnosis is likely delayed, rendering treatments to mitigate or prevent AKI ineffective. Neonatal AKI is further confounded by the fact that infant serum creatinine concentrations reflect maternal levels. The past 15 years has seen a massive research effort to identify early damage markers of AKI, with the hope that earlier "sub-clinical" AKI diagnosis can lead to earlier initiation of AKI treatment, or to adjustment of care to mitigate the adverse effects of AKI until renal function recovery occurs. One of the most promising urinary AKI biomarkers, neutrophil gelatinase associated lipocalin (NGAL), has repeatedly performed well to predict AKI in many pediatric populations, including those post-cardiac surgery, critically ill mechanically ventilated children and children arriving to the emergency department. The study reported by Admani et al. uses NGAL not only to predict serum creatinine-based AKI, but also to define AKI to associate a Day 1 NGAL concentration above a specific threshold with clinical outcomes.

Keywords Acute kidney injury · Early damage markers · NGAL · Term infants · Asphyxiated infants

Introduction

Admani and colleagues [1] report on a prospective cohort evaluation of acute kidney injury (AKI)-associated outcomes in 108 asphyxiated newborns at two tertiary care centers in Nairobi, Africa. In their study, the authors use the novel urinary AKI biomarker, neutrophil gelatinase associated lipocalin (NGAL) not only to predict the development of serum creatinine (SCr)-based AKI, but also to define AKI, establishing an NGAL threshold concentration (250 ng/ml) to demonstrate that NGAL–AKI itself is associated with poor outcomes. This study adds to the growing evidence that subclinical AKI is an important entity that portends poor prognosis and that NGAL may be an important clinical marker in a previously unstudied population. This commentary will focus on the epidemic of AKI in the pediatric population, the further difficulty in defining AKI in infants and the work that still needs to be done to integrate novel AKI biomarkers into clinical practice with the hope of improving patient outcomes.

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The impact of AKI in children

The past 20 years has seen a shift in our understanding of the significant impact AKI has on short- and long-term outcomes in children. Prior to the 1990s, critically ill patients were thought to be dying "with" and not "from" AKI. The first critical step to advance the field was the observation that AKI more often results from another systemic illness (e.g. sepsis, cardiac surgery, liver disease) or treatment of that illness (e.g. nephrotoxic antibiotics), rather than the primary kidney injury itself [2–4]. The next advancement was the development of a standardized multidimensional AKI classification system; this was first validated in adults [5], then modified for children [6] and ultimately harmonized across all patient populations—except for newborn children and infants [7]. Since that time, the preponderance of epidemiological data support the concept that AKI is associated with mortality and morbidity in children, independent of underlying comorbidities and severity of patient illness [6, 8–10]. As a

result, the importance of AKI and its impact across the pediatric disease spectrum has become manifest and is now taken into account not only by nephrologists, but by all pediatric sub-specialists. These developments have led to the field of critical care nephrology being born.

Infants and AKI—the uncharted clinical research population

As noted above, the modern AKI classification systems have not, for the most part, been applied to neonates, term newborn children and infants. The notable exception is the post-cardiac surgery population, where the incidence of AKI (defined as a 50 % SCr concentration increase above baseline) is approximately 40 % [10–12]. The pediatric cardiac surgery population is an appealing target population for an AKI study since the timing of AKI is known (cardiopulmonary bypass), and the population has little co-morbidity. Aside from the cardiac surgery population, neonatal AKI research is challenged by a number of issues, including lack of systematic SCr surveillance in neonates and the contribution of maternal SCr to newborn SCr in the early post-natal period [13]. This led to the National Institute of Diabetes and Digestive and Kidney Disease convening a 1-day workshop in 2013 to highlight challenges facing neonatal AKI clinical research (http://www.niddk.nih.gov/news/events-calendar/Pages/neonatal-acute-kidney-injury-workshop.aspx). While white papers from this Workshop will be forthcoming, the recent high profile of neonatal AKI provides some encouragement that research in this area will be accelerated.

SCr as a late functional marker of AKI

The poor outcomes associated with SCr increases that were previously considered to be "modest" likely result from the fact that SCr is a late marker of kidney injury, analogous to electroencephalogram changes in the temporal evolution of the acute coronary syndrome. The past 15 years has also seen a huge research effort to find earlier, more sensitive markers of AKI to predict AKI development and severity. While a thorough review is beyond the scope of this commentary, and excellent reviews have been published recently [14, 15], novel AKI biomarkers have performed very well to predict AKI development in children after cardiac surgery [16], in critically ill children [17] and even in pre-term neonates [18]. Of these, urinary NGAL has been the most often studied biomarker in the pediatric population. Recent pooled analysis data also demonstrate that adults and children with "creatinine-negative, NGAL-positive" AKI have similarly poor outcomes as patients with "creatinine-positive/NGAL-positive" AKI, suggesting that sub-clinical AKI as evidenced by tubular damage is an entity that needs to be brought to the forefront [19, 20], as does the concept of that the AKI definition "might need reassessment". In addition, the combination of functional and damage AKI biomarkers has just been shown to predict, with great precision and better than SCr itself, just which children after cardiac surgery will develop transient versus persistent AKI [21]. Thus, the pediatric AKI field may be on the verge of integrating novel and functional biomarkers into the correct clinical context to identify which patients will have severe AKI and worse outcomes.

How does the current study by Amani et al. fit into the pediatric AKI research experience?

The study by Admani et al. [1] provides some novel information to the field. Similar to the cardiac surgery research paradigm, Admani et al. [1] leveraged the known perinatal timing of and exposure to asphyxia to prospectively assess for AKI development by SCr, as well as to assess the ability of NGAL to predict SCr-based AKI and to define AKI itself. These authors demonstrate that newborns' NGAL level has a moderate discriminatory power to predict SCr-based AKI with an AUC of 0.72. Importantly, the negative predictive value in their study was very high (95%), such that a NGAL level below their threshold was a strong predictor that AKI would not develop. This is of fundamental importance for the use of biomarkers, as capricious use with low sensitivity will lead to unnecessary interventions and resource utilization [22]. Further, the authors go on to demonstrate that a Day 1 NGAL concentration of >250 ng/ml is also predictive of the development of hypoxic ischemic encephalopathy and patient mortality. As noted above, elevated NGAL may be a manifestation of a sub-clinical AKI portending worse systemic disease. While only speculative, we and others have shown that fluid overload may dilute SCr and mask SCr-based AKI detection [23, 24]. One previous study used urinary NGAL—and not SCr—as the AKI definition in an AKI prevention study using fenoldopam versus placebo after cardiac surgery [25]. Given the confounding of maternal SCr, the low muscle mass of newborns and the developmental increase in GFR seen over the first year of life, the ability to detect AKI independent of SCr would be a major boon to pediatric care. Admani and colleagues [1] should be commended for extrapolating the previous AKI work into a new patient population, correctly focusing on a subset of the newborn population with an identifiable time of insult and high morbidity associated with AKI [26]. Further work should build upon theirs to ascertain whether or not we can define AKI, as they have, by novel AKI damage biomarkers in other newborn populations.

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