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EDITORIAL COMMENTARY

Acute kidney injury during the first week of life: time for an update?

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Introduction

Acute kidney injury (AKI) is a common and life-threatening complication in neonates admitted to neonatal intensive care unit (NICU), with incidence rates up to 30–40% [1]. Prematurity, perinatal asphyxia and other specific high-risk conditions make the newborn more vulnerable to AKI. In the Assessment of Worldwide Acute Kidney Epidemiology in Neonates (AWAKEN) study, first AKI events occurred most often during the first week after birth and, in term neonates, they were more likely associated with birth asphyxia [1]. Perinatal asphyxia can result in hypoxic ischemic encephalopathy (HIE) and concomitant injury to other organs [2]; in this setting, AKI per se has a negative prognostic role on several clinical long-term outcomes [2–4]. Therefore, it is necessary to recognize the early stages of neonatal AKI (nAKI) to prevent further progression of the renal injury and to reduce the impact of potentially associated severe comorbidities. However, the identification of neonates undergoing the early stages of AKI during the first week of life faces several challenges.

AKI is defined as a sudden decline in kidney function associated with structural kidney damage and is manifested by an acute decrease in the glomerular filtration rate (GFR) [4, 5]. In pediatric clinical practice, changes in GFR or AKI are determined by estimating the creatinine clearance (eCrCl) using several equations [6, 7] and/or detecting changes in serum creatinine (SCr) or urine output (UOP). The terms AKI and RIFLE (an acronym for Risk-Injury-Failure-Loss-End stage kidney) were coined simultaneously in 2004 to establish a consensus definition of AKI and define different progressive kidney injury stages in adults [8]. The rationale behind replacing the term acute renal failure for AKI was the perceived need to facilitate the early identification of structural kidney damage that occurs during AKI. It was anticipated that novel biomarkers (soon to be discovered) were going to be able to detect the early structural kidney injury before the changes in SCr occur. This rationale was based on the physiological principle that at normal GFR levels, a large drop in GFR is needed to increase the SCr (Fig. 1), and this process is delayed approximately 24 to 48 h in people with AKI. Unfortunately, despite the great progress made in the field of AKI during the last 20 years, we still do not have reliable biomarkers of nAKI during the first days of life and continue to use markers of renal function to assess kidney injury. Given these limitations, several definitions of AKI have been used in infants and newborns, including SCr levels > 1.5 mg/dl, a decline in UOP < 1 ml/kg/h [9], or > 50% rise in SCr over baseline [10]; additionally, the RIFLE [11], AKIN (Acute Kidney Injury Network) [12], and KDIGO (Kidney Disease Improving Global Outcomes) AKI criteria with adjustments specific to newborns have been employed [13]. However, it is unclear how sensitive and reliable all these definitions are during the first days of life, and until new biomarkers are developed [14], no perfect definition of AKI will be available for newborns.

Gutpa et al.'s approach to identify the early stage of AKI during the first week of life

In recognition of the limitations of the current AKI definitions for neonates, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) sponsored a workshop dedicated to nAKI in April 2013 [16]. A key outcome of this meeting was the formation of collaborative groups of neonatologists and nephrologists to develop new guidelines

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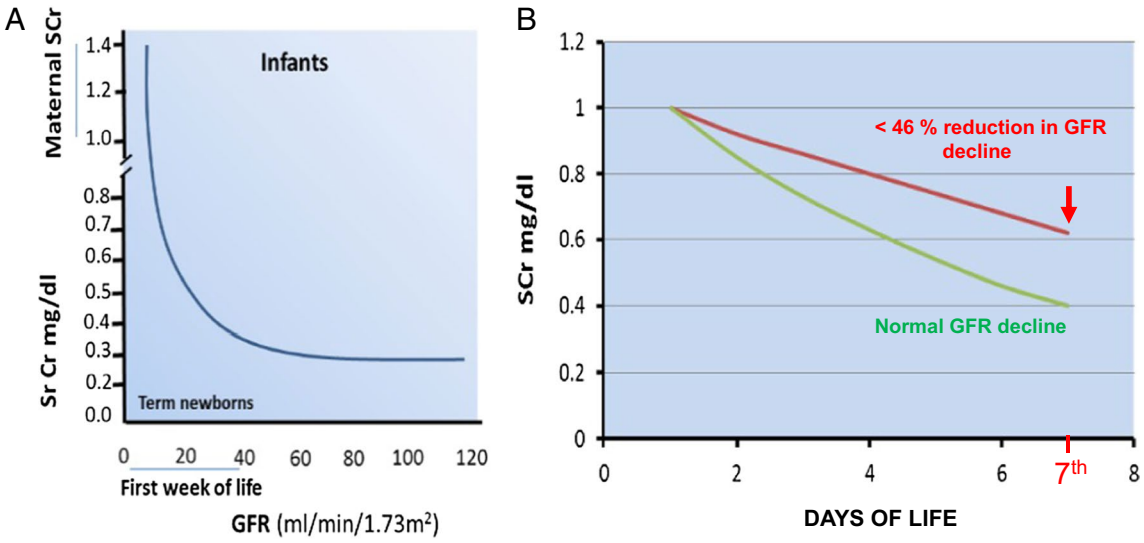

Fig. 1 Panel **A** shows the relationship between the serum creatinine (SCr) and the glomerular filtration rate (GFR). At high levels of kidney function (high GFR), large changes in GFR result in small or no changes in SCr. In contrast, at lower GFR levels, as seen in neonates during the first week of life [7], small changes in the SCr decline are associated with more significant changes in GFR. This model supports the hypothesis that the rate of SCr decline during the first week of life can be used as a surrogate marker to assess changes in GFR. Panel **B** shows the predicted SCr decline in healthy term newborns (normal SCr decline) and those with impaired kidney function (IKF) as reported by Gupta et al. [15]. The figure was modified from a figure published by Gupta et al. [15] and reproduced with the authorization of the authors and journal

for assessing the kidney function of newborns. The approach developed by Gupta et al. in 2016 [15] was tested in 106 term newborns treated with hypothermia for HIE at Children's National Hospital in Washington DC. Based on the notion that the SCr levels during the first day of life reflect the maternal SCr levels, they used the rate of SCr decline as a surrogate marker to assess the kidney function of neonates during this time (Fig. 1). They also established cutoff values for the normal SCr decline of term infants on the third, fifth, and seventh days of life and demonstrated that neonates who failed to reach the expected SCr decline cutoff values required more days of mechanical ventilation, used more vasopressor drugs, and showed higher gentamicin levels, more fluid overload, more prolonged hospital stay, and lower urinary levels of epidermal growth factor, when compared to those who had a normal SCr decline rate and no AKI. In this manner, the criteria, established by Gupta et al. [15], allowed the early identification of more neonates with an impaired kidney function (IKF) (19%), who were at high risk of developing more severe complications and were missed by the KDIGO nAKI definition.

Results of Ahn et al.'s study

In the current issue of the journal, Ahn et al. [17] reported the results of a retrospective single center study in 225 term or late preterm neonates with moderate to severe HIE who were treated with hypothermia at Stanford University from 2008 to 2020, according to National Institute of Child Health and Human Development (NICHD) guidelines [18]. They found that 28% of neonates who met the nAKI KDIGO definition, and 31% who met Gupta et al.'s criteria but did not meet nAKI-KDIGO criteria, had increased mortality, developed more severe brain injury, needed more respiratory support, and showed a longer hospital stay, when compared to those who did not develop AKI [17]. These findings are highly significant from the clinical point of view, since they confirm, in a large group of neonates treated recently in a different and state-of-the-art US neonatal center, that the KDIGO nAKI definition misses a significant number of neonates who have an IKF and are at high risk of dying or developing more severe complications in subsequent days. Six neonates (2.6%) only developed early AKI based on KDIGO SCr criteria, but subsequently showed a normal SCr decline and normal SCr levels by the seventh day of life. This outcome suggests that either the neonates had a rapid recovery of AKI or that the SCr was elevated due to other functional but not structural causes. In a similar manner, 12 neonates (5.3%) developed AKI based on the KDIGO UOP criteria only, but showed normal SCr decline and normal SCr levels by the seventh day of life. The clinical outcome of these newborns was not described in detail, probably because this group is too small to derive statistically relevant conclusions, and therefore, it is unclear whether neonates who meet KDIGO UOP criteria only during the first week of life

develop similar clinical complications compared to those with abnormal SCr changes. In addition, Ahn et al. also confirmed the results of previous perinatal asphyxia studies, which revealed that neonates with AKI develop more significant neurological damage [2, 19, 20]. One potential limitation of these studies is that clinical neurological outcomes were assessed by structural changes in brain on MRI. However, in infants with HIE receiving therapeutic hypothermia, the instrumental evaluation of encephalopathy can be an inaccurate predictor of disability in early childhood in case of mild/moderate brain injuries compared with the longitudinal evaluation of the neurodevelopmental outcome [3].

All these findings provide a compelling argument to re-evaluate the approach that is currently being used to assess the kidney status of critically ill newborns during the first week of life. Furthermore, since the SCr decline approach has been validated currently in three different studies that included more than 600 critically ill newborns [15, 17, 21], it is probably the right time to consider implementing this approach in clinical practice.

Moving into the future

More work is needed to establish the best approach to identify the early stages of AKI in newborns during the first week of life. However, there are several barriers to accomplish this goal. The most relevant ones are that the GFR and SCr are not in a steady-state balance, the volume of SCr distribution is changing, and neither the old nor the updated Schwartz formulas have been validated in newborns. In addition, as demonstrated by Ahn et al. [17], given the maternal SCr load at birth, a kidney injury event that could potentially increase the mortality risk, does not necessarily increase the SCr by ≥ 0.3 mg/dl, as required by the KDIGO nAKI criteria. In support of this notion, a retrospective very large multicenter study, done by members of the AWAKEN group, showed that smaller changes in SCr during the first week of life (≥ 0.1 mg/dl) were associated with higher mortality [22]. However, such small changes in SCr may fall within the standard deviation (SD) of the SCr measurements, may reflect hemoconcentration due to fluid losses, and/or fall within the SD of the normal SCr values for term newborns [15]. Thus, they are unreliable to make clinical decisions in individual neonates. This issue also highlights the importance of establishing normal SCr cutoff values before using the SCr decline approach [15, 21], since changes in SCr decline that occur below the normal SCr levels are not clinically relevant. Alternatively, nAKI definitions that rely only on the UOP criterion only (< 1 ml/kg/h) may be problematic as well. The quantification of the UOP in newborns is cumbersome and is affected by diuretics, IV fluid administration, fluid losses, and the use of other drugs. In addition, previous studies showed that nAKI can occur without oliguria, and that the UOP is not a sensitive clinical marker of nAKI [23]. Furthermore, the clinical outcome of AKI defined by the UOP criterion, does not always match the outcome of AKI defined by the SCr criterion [24]. As shown by Ahn et al. [17], very few newborns (~5%) fell in this group category, and their clinical outcome remains uncertain. Finally, as discussed above, we need reliable early biomarkers of AKI for first week of life [14].

The SCr decline approach was also used by Gupta et al. [15] to identify newborns at high risk of developing AKI and those undergoing the injury stage of AKI during the first week of life, mimicking the kidney "risk" and "injury" stages of the original RIFLE criteria in adults. In addition, they reported that newborns who showed a rise in SCr ≥ 0.3 mg/dl within 48 h developed more severe complications and therefore were considered undergoing the "failure" AKI stage [15]. For this reason, comparing the number of patients who fulfill KDIGO but not Gupta's criteria, as done by Ahn et al. [17], although necessary to determine the clinical outcome of both groups independently, could be confusing, since the Gupta criteria were developed to identify newborns undergoing the early stages of AKI during the first week of life. Both approaches provide complementary information and should be merged into one nAKI definition as described previously by Gupta et al. [15]. Alternatively, considering that the SCr decline is a marker of renal function, not injury, a follow-up study done by Perazzo et al. [21] used the term IKF to group all neonates who met the SCr decline criteria but not the KDIGO nAKI criteria during the first week of life. They also tested the SCr decline criteria in preterm infants with other critical illnesses up to ≥ 31 weeks of gestational age and showed that the KDIGO nAKI definition also missed many neonates at risk of dying or developing worse clinical outcomes [21]. It should be mentioned that the term IKF will include neonates undergoing dehydration, hemoconcentration, immature kidneys, hemodynamic changes associated with poor kidney perfusion, drug-induced toxicity, kidney malformations, as well as those undergoing early nAKI. Although all these factors may contribute to precipitate nAKI, not all neonates with IKF will develop AKI. On the other hand, all neonates, who meet the KDIGO nAKI definition, should have IKF, based on the required KDIGO changes in SCr and UOP. Thus, the term IKF appears to be a more accurate and practical term to group all neonates at high risk of dying or developing more severe complications during the first week of life [15, 17, 21]. Given that the prevalence of nAKI varies significantly among different high-risk groups and because of limitations of kidney function biomarkers in neonates, the use of risk prediction scoring systems based on a combination of SCr and UOP with clinical markers of illness severity has also been proposed. Recently, the "STARZ score" resulted useful

to predict, with a high diagnostic accuracy, the risk of AKI in a heterogeneous group of patients admitted to the NICU [25].

Finally, the rationale for using the SCr decline as a surrogate marker of renal function during the first week of life is supported by solid renal physiological principles and studies [26–30]. During the first hours of life, the GFR reflects the kidney function in utero, when the fetal excretory function is performed mainly by the placenta [30], and the SCr levels are determined by the immature renal function plus the load of maternal creatinine. The kidney function increases rapidly during subsequent days of life (Fig. 1), and given the low GFR values of newborns [28], the SCr can change exponentially with smaller changes in GFR (Fig. 1). This situation mimics the clinical status of people with chronic kidney failure after a successful kidney transplant, in whom the SCr decline also predicts their kidney function. Overall, it is remarkable how the SCr decline of term newborns reflects the kidney maturational changes characteristic of the first week of life and provides a very simple tool to estimate their kidney function.

Conclusions

As discussed above, developing a perfect definition of nAKI will depend on the discovery of specific biomarkers of kidney injury, including those able to detect a moderate tubular injury that might not even affect the GFR. However, until these biomarkers are developed and validated, the SCr decline and KDIGO approaches combined, as discussed by Gupta el. [15] and validated by Ahn et al. [17] in a large group of newborns, can facilitate the early recognition of all term newborns with HIE who are at higher risk of dying or developing more severe clinical complications due to an IKF. This approach should provide opportunities to initiate more timely therapeutic interventions during the first days of life and prevent the progression of neonatal kidney injuries.

Declarations

Conflict of interest The authors declare no competing interests.

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