Are we ready for the clinical use of novel acute kidney injury biomarkers?

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Abstract Acute kidney injury (AKI) is a common event in several neonatal populations, and those neonates with AKI have poor outcomes. Serum creatinine (SCr)-based definitions of AKI are not ideal and are additionally limited in neonates whose SCr reflects the maternal creatinine level at birth and normally drops over the first weeks of life dependent on gestational age. Recent studies show that urine and serum biomarkers may provide a better basis than SCr on which to diagnose AKI. In this month's issue of *Pediatric Nephrology*, Sarafidis et al. show that urine neutrophil gelatinase-associated lipocalin (uNGAL), serum NGAL (sNGAL), and urine cystatin c (uCysC) are highest in those neonates with asphyxia who have elevated SCr. Furthermore, those with asphyxia without a concomitant rise in SCr levels have elevated levels of biomarkers compared to controls, suggesting a dose response. Once the SCr level returns to normal, the levels of novel AKI biomarkers continue to be elevated. While these findings strengthen the argument for the clinical use of these AKI biomarkers, further work is needed before they can be implemented in clinical practice. Large-scale observational multi-center studies are needed to test these biomarkers against hard clinical endpoints. In addition, randomized intervention trials which use biomarkers to define AKI need to be performed.

Keywords Acute kidney injury · Ngal · Cystatin c · Asphyxia · Newborn · Neonates

Over the last few years our understanding of the incidence and outcomes in neonates who have acute kidney injury (AKI) has improved. The findings of single-center prospective studies in very low birth weight (VLBW) infants [1], infants who undergo cardiopulmonary bypass [2, 3], infants requiring extracorporeal pulmonary oxygenation [4, 5], and infants with perinatal birth asphyxia [6] suggest that neonatal AKI is common and associated with poor outcomes [7, 8]. To define AKI, these studies have used serum creatinine (SCr) alone, or SCr and urine output criteria. Although SCr is currently the most available method to define AKI, SCr-based AKI definitions are not ideal for numerous reasons. Firstly, because SCr is a measure of function (not injury), it is a late biomarker for an acute injury. Secondly, due to renal function reserve, more than 50 % of nephrons must be compromised before changes in SCr level are evident. Therefore, SCr is at best a late marker of significant renal dysfunction. In neonates, SCr-based AKI definitions are additionally complicated because at birth SCr reflects maternal creatinine, which improves over the first few weeks of life, dependent on gestational age [9]. For these and other reasons, newer definitions of a neonatal AKI using noninvasive serum and urine biomarkers are greatly needed.

Studies in VLBW infants [10, 11], infants who undergo cardiopulmonary bypass surgery [3, 12–17], and other sick newborns admitted to a neonatal intensive care unit [18] suggest that such biomarkers can detect those infants who will later have a rise in SCr and that they may also predict hard clinical endpoints, such as mortality. However, there are several challenges in validating urine AKI biomarkers. One of the main challenges is that novel biomarkers are tested against SCr, which as outlined above is not the ideal

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marker to serve as a gold standard for AKI. In this month's *Pediatric Nephrology*, Sarafidis et al. [19] report data on serum and urine AKI biomarkers in asphyxiated neonates that not only shed light on the potential use of urine biomarkers in this population, but also emphasize how SCr is an imprecise measure of AKI.

Specifically, these authors present three important findings. First, they eloquently show that compared to infants with perinatal asphyxia whose SCr does not acutely rise, urine neutrophil gelatinase-associated lipocalin (uNGAL), serum NGAL (sNGAL), and urine cystatin c (uCysC) are elevated in similar infants whose SCr rises shortly after birth. Second, they show that asphyxiated newborns who do not have elevated SCr have elevated uNGAL, sNGAL, and uCysC compared to healthy controls. These findings suggests a dose response of these biomarkers whereby those with asphyxia but without a change in SCr sustain a mild injury, and those with more severe injury (elevated SCr) have higher elevations of these urine biomarkers.

A third major finding highlights how SCr and urine biomarkers differ as AKI improves/resolves. The authors demonstrate that SCr levels 1 week after birth were similar in those who had an acute SCr rise and those who did not. However, the AKI biomarkers described continued to be elevated 1 week later. This development implies one of several things: either the glomerular filtration rate improves faster than tubular repair, or SCr is not sensitive enough to detect complete recovery of kidney function. To what degree these biomarkers, both at the time of insult and during AKI recovery, predict the progression and development of chronic kidney disease needs to be explored.

These findings highlight crucial gaps in our ability to reliably detect AKI in pediatric populations. In order for us to be able to improve outcomes of infants with AKI, neonatologists, nephrologists, and pediatric intensivists must work together to develop better definitions of AKI using newer biomarkers, perhaps in conjunction with SCr, urine output, and clinical criteria. To accomplish this task, validation of these biomarker studies needs to be performed in different critically ill populations. Large-scale observational multi-center studies in which these biomarkers are tested against hard clinical endpoints (such as need for dialysis provision, mortality, lengths of stay, and long-term evidence of chronic kidney disease) must be performed. In addition, AKI prevention studies using novel biomarkers to define AKI are needed, such that if an intervention is shown to reduce AKI incidence or severity (as defined by AKI biomarkers), it would lend support to that biomarker's clinical utility. Lastly, studies are needed in which AKI biomarkers are used to identify AKI early

in the disease process; once the AKI is identified, randomized interventions can be tested.

References

1. Koralkar R, Ambalavanan N, Levitan EB, McGwin G, Goldstein S, Askenazi D (2011) Acute kidney injury reduces survival in very low birth weight infant. *Pediatr Res* 69:354–358
2. Blinder JJ, Goldstein SL, Lee VV, Baycroft A, Fraser CD, Nelson D, Jefferies JL (2012) Congenital heart surgery in infants: effects of acute kidney injury on outcomes. *J Thorac Cardiovasc Surg* 143:368–374
3. Krawczeski CD, Woo JG, Wang Y, Bennett MR, Ma Q, Devarajan P (2011) Neutrophil gelatinase-associated lipocalin concentrations predict development of acute kidney injury in neonates and children after cardiopulmonary bypass. *J Pediatr* 158:1009–1015
4. Askenazi DJ, Griffin R, McGwin G, Carlo W, Ambalavanan N (2009) Acute kidney injury is independently associated with mortality in very low birthweight infants: a matched case-control analysis. *Pediatr Nephrol* 24:991–997
5. Gadepalli SK, Selewski DT, Drongowski RA, Mychaliska GB (2011) Acute kidney injury in congenital diaphragmatic hernia requiring extracorporeal life support: an insidious problem. *J Pediatr Surg* 46:630–635
6. Kaur S, Jain S, Saha A, Chawla D, Parmar VR, Basu S, Kaur J (2011) Evaluation of glomerular and tubular renal function in neonates with birth asphyxia. *Ann Trop Paediatr* 31:129–134
7. Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL (2007) Modified RIFLE criteria in critically ill children with acute kidney injury. *Kidney Int* 71:1028–1035
8. Zappitelli M, Parikh CR, Akcan-Arikan A, Washburn KK, Moffett BS, Goldstein SL (2008) Ascertainment and epidemiology of acute kidney injury varies with definition interpretation. *Clin J Am Soc Nephrol* 3:948–954
9. Askenazi DJ, Ambalavanan N, Goldstein SL (2009) Acute kidney injury in critically ill newborns: what do we know? What do we need to learn? *Pediatr Nephrol* 24:265–274
10. Askenazi DJMA, Hunley H, Koralkar R, Pawar P, Shuaib F, Liwo A, Devarajan P, Ambalavanan N (2011) Urine biomarkers predict acute kidney injury and mortality in very low birth weight infants. *J Pediatr* 159:907–912
11. Lavery AP, Meinen-Derr JK, Anderson E, Ma Q, Bennett MR, Devarajan P, Schibler KR (2008) Urinary NGAL in premature infants. *Pediatr Res* 64:423–428
12. Portilla D, Dent C, Sugaya T, Nagothu KK, Kundi I, Moore P, Noiri E, Devarajan P (2008) Liver fatty acid-binding protein as a biomarker of acute kidney injury after cardiac surgery. *Kidney Int* 73:465–472
13. Zappitelli M, Krawczeski CD, Devarajan P, Wang Z, Sint K, Thiessen-Philbrook H, Li S, Bennett MR, Ma Q, Shlipak MG, Garg AX, Parikh CR (2011) Early postoperative serum cystatin C predicts severe acute kidney injury following pediatric cardiac surgery. *Kidney Int* 80:655–662
14. Hall IE, Koyner JL, Doshi MD, Marcus RJ, Parikh CR (2011) Urine cystatin C as a biomarker of proximal tubular function immediately after kidney transplantation. *Am J Nephrol* 33:407–413
15. Parikh CR, Devarajan P, Zappitelli M, Sint K, Thiessen-Philbrook H, Li S, Kim RW, Koyner JL, Coca SG, Edelstein CL, Shlipak

- MG, Garg AX, Krawczeski CD (2011) Postoperative biomarkers predict acute kidney injury and poor outcomes after pediatric cardiac surgery. *J Am Soc Nephrol* 22:1737–1747
16. Nguyen MT, Dent CL, Ross GF, Harris N, Manning PB, Mitsnefes MM, Devarajan P (2008) Urinary aprotinin as a predictor of acute kidney injury after cardiac surgery in children receiving aprotinin therapy. *Pediatr Nephrol* 23:1317–1326
17. Ramesh G, Krawczeski CD, Woo JG, Wang Y, Devarajan P (2010) Urinary netrin-1 is an early predictive biomarker of acute kidney injury after cardiac surgery. *Clin J Am Soc Nephrol* 5:395–401
18. Askenazi DJ, Koralkar R, Hundley HE, Montesanti A, Parwar P, Sonjara S, Ambalavanan N (2012) Urine biomarkers predict acute kidney injury in newborns. *J Pediatr*. doi:[10.1016/j.jpeds.2012.02.007](https://doi.org/10.1016/j.jpeds.2012.02.007)
19. Sarafidis K, Tsepkentzi E, Agakidou E, Diamanti E, Taparkou A, Soubasi V, Papachristou F, Drossou V (2012) Serum and urine acute kidney injury biomarkers in asphyxiated neonates. *Pediatr Nephrol*. doi:[10.1007/s00467-012-2162-4](https://doi.org/10.1007/s00467-012-2162-4)