

Leading Article

Urinary Biomarker – A New Dimension for Quick Detection of Acute Kidney Injury (AKI)

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Acute kidney injury (AKI) in paediatric patients is characterized clinically by rapid loss of glomerular filtration rate (GFR) resulting in failure to excrete end products of nitrogen metabolism and to maintain fluid volume and electrolyte and acid base homeostasis.^{1,2} The incidence of AKI is rising in children both in developed and developing country with significantly increased mortality and morbidity in paediatric population as well as in paediatric intensive care unit (ICU).^{3,4} In a few studies, it has been observed that incidence of AKI varies from 30-50% in children undergoing cardiac surgery and even may go upto 82% in critically ill children with multiple organ failure.⁵

Till now due to lack of consensus on the definition of AKI, the incidence of AKI in the paediatric group of population is yet to be remain unknown in the developing country. But in the industrilized countries the incidence of AKI in hospitalized children is rising and the etiology of peadiatric AKI is dramatically changing from isolated acute renal disease to multiple organ failure. So to make a consensus on the definition of AKI in 2004 the acute dialysis quality initiative (ADQI) proposed RIFLE criteria for defining AKI based on risk, injury, failure, loss of kidney function and end stage renal disease (RIFLE). Three years

later acute kidney injury network (AKIN) modified RIFLE criteria for paediatric patient (pRIFLE) based on estimated creatinine clearance (eCCL) and urine output considering body weight of the patient.⁶

In clinical practice, traditionally serum creatinine (Cr), serum creatinine clearance (CCr) and urine output are used as the primary test to diagnose paediatric acute kidney injury⁵. Serum creatinine takes 24-48 hours to rise after initial renal insult which limits its early diagnostic value and potential for early intervention. In spite of this loophole there are also some limitations of serum creatinine as a diagnostic tool for AKI which are as follows:

- a) Serum creatinine do not reflect degree of renal injury but only renal function.
- b) Serum creatinine is affected by other non-renal factors like muscle mass, hydration status, sex, age, medication and bilirubin level.⁷
- c) The value of serum creatinine can not be used to distinguish from pre-renal cause of AKI to intrinsic renal failure or obstructive uropathy.⁵
- d) Small increase in serum creatinine may be mistaken as fluctuation remaining within normal limits.

Modified RIFLE criteria for paediatric patients (pRIFLE)

| RIFLE Criteria | Estimated CCL | Urine output |
|------------------------------|---|--|
| Risk (of renal dysfunction) | eCCL decrease by 25% | <0.5 ml /kg/hour for 8 h |
| Injury (to the kidney) | eCCL decrease by 50% | <0.5 ml /kg/hour for 16 h |
| Failure (of kidney function) | eCCL decrease by 75% or eCCL <35 ml/min/1.73 m ² | <0.5 ml /kg/hour for 24 h or anuric for 12 h |
| Loss (of kidney function) | Persistant failure > 4 weeks | |
| Endstage (kidney disease) | End-stage renal disease > 3 months | |

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- e) Increased serum creatinine might not be observed before the kidney have lost 25-50% of its function.
- f) Serum creatinine cannot be applied to neonates during first few weeks because serum creatinine reflects maternal kidney function during this period and does not reflect a marker of GFR in neonatal period.^{5,8}

Now a days, it is accepted that the serum creatinine is an insensitive and delayed measure of decreased kidney function following AKI.⁹⁻¹⁵ Multiple studies have focused on the development of the selective and specific biomarker of AKI.⁹ Most of the biomarkers are protein bound and indications of structural renal damaged rather than of decreased kidney function.⁵ Moreover an ideal AKI biomarker should be accurate, reliable, easy to measure with a standard assay, non-invasive, representable, sensitive and specific with defined cut off values.⁵

Urine represent an ideal body fluid for AKI biomarker assessment as it can be obtained noninvasively and repeatedly. from a spontaneously voided urine sample or from an indwelling bladder catheter^{5,8}. Multiple studies has focused on the development of sensitive and specific different biomarkers of AKI which are neutrophil gelatinase associated lipocalin (NGAL), cystatin C, kidney injury molecule-1 (KIM-1), b₂ microglobulin (b₂M), Interleukin 18 (IL-18) and urinary liver type fatty acid binding protein (L-FABP) show promise in both diagnostic and prognostic utility for AKI from various causes. In a nut shell, the use of newly discovered biomarkers for early diagnosis and intervention of AKI patients are described bellow:

Nutrophil Gelatinase Associated Lipocalin (NGAL): Nutrophil gelatinase associated lipoprotein (NGAL) is a 25 kDa protein bound to gelatinase from neutrophil¹⁶. NGAL is found to be one of the most rapidly induced protein in the kidney folling experimental AKI and NGAL appeared in the urine before other biomarker.^{10,11} The level of NGAL increased in plasma and urine hours of cardiac surgery in those who developed AKI compared to 2-4 days for increase in serum creatinine to occur.¹¹ NGAL is also shown to be an early predictor of contrast induced nephropathy in children.¹² But there is also some non-specificity of NGAL as biomarker of AKI because some other factors may influence the NGAL e.g NGAL acitivity is inhibited by endogeneous urea, nephrotoxins and heavy metals.¹⁷ Eleveted level of NGAL may be found

in Juvenile rheumatoid arthritis, impaired glucose tolerance and hypothyroidism.¹⁷ So this factors make the NGAL not specific to be used as a biomarker in AKI.

Interleukin 18 (IL-18):

It is a proinflammatory citokines is produced at the proximal tubular cells and it is identified as a very early biomarker of AKI in kidney transplant patients, acute respiratory distress syndrome and after cardiopulmonary bypass surgery.¹⁸ A major drawback limits the routine use of biomarker is their low individual sensitivity and specificity not exceding 70-75% for detection of early kidney damage.¹⁹ From different studies it was observed that IL-18 performed moderately well for detecting AKI in four different population, adults who underwent cardiac surgery, children who are critically ill, adults with acute lung injury and adults who received kidney transplantation.

Kidney injury molecule-1 (KIM-1):

It is a trnasmembrane protein produced by the proximal tubule following ischemic or toxin induced AKI. This urinary biomarker is investigated in patients undergoing cardiopulmonary bypass²⁰. In this situation it is proved more specific than NGAL but in some situation NGAL is more sensitive than KIM-1 in ischemic and nephrotoxic induced AKI.¹⁷

Cystatin C:

It is a protease inhibitor is relesed into the blood, filtered in the glomerulus and completely reabsorbed in the proximal tubule. In cardiac surgry patient a 50% increased in cystatine C could predict AKI 48 hour before changes in serum creatinine or creatinine clearance suggested renal dysfunction⁷. However NGAL is an earlier biomarker than cystatin C.¹⁷

b₂ microglobulin:

b₂ microglobulin are low molecular weight proteins freely filtered by the glomerulus.¹⁷ b₂ microglobulin concentration are less dependent on extra renal factors like creatinine.²⁰ In a cross sectional analysis, Herron-Morin and co-workers showed that cystatin C and b₂M was found to be largely superior to a creatinine clearance cutoff <80 ml/min/1.73 m² for detecting decreased glomerular rate in critically ill children.¹⁷

Urinary liver type fatty acid binding protein (L-FABP):

L-FABP is a small cytoplasmic protein has been shown to be a sensitive and early predictor of AKI in paediatric patients undergoing cardiac surgery.¹⁵ In a

prospective case control study by Portilua et al demonstrating for the first time that urinary excretion of L-FABP in paediatric patients undergoing cardiac surgery is significantly increased within the first hours whereas serum creatinine rises after 24-72 hours after cardiac surgery.^{18, 20}

Limitations of Biomarkers:

A major drawback limiting the routine use of biomarkers is their low individual selectivity and sensitivity not exceeding 70-75% for detecting early kidney damage.²⁰ One possible solutions might be the creation of a kit incorporating various biomarkers to allow quick and accurate diagnosis of AKI.^{21, 22} In a recent study, NGAL and serum creatinine derived GFR or both predicted development of severe AKI.²³ On the other hand in the presence of normal serum creatinin values, NGAL alone may remain predictive for AKI. At present the paediatric nephrologist are in an unprecedented level to deal with the newer biomarker such as NGAL, KIM-1, IL-18 and LFABP due to their low sensitivity and specificity individually. It is highly likely that these novel biomarkers alone or in-combination will be introduced over the next few years for early diagnosis and intervention of paediatric AKI patients.²⁴

References

1. Ellis DA, William EH, Patrick N, Norishige Y. Clinical evaluation of acute kidney injury in children. In: Sharon (ed), Paediatric Nephrology, 6th edition. Springer Verlag Barlin Heidelberg; 2009. 1603-1618.
2. Robert MK, Hal BJ, Richard EB, Bonita FS. Renal failure. In: Beth AV, Ellis DA (eds), Nelson textbook of paediatrics, 18 ed. Elsevier (Sauder) Philadelphia. 2011. P:2206-2209.
3. Barletta GM, Burchman TE. Acute renal failure in children and infants. *Acute renal failure in children and infants curr opin crit care* 2004; 10: 499-504.
4. Besolin N, Silva C, Hakal A, Toporouski J, Feruales V, Goes J et al. Prognosis for children with acute kidney injury in the intensive care unit. *Pediatr Nephrol* 2009; 24: 537-544.
5. Helmut Schiffli, Susane M Lang. Urinary biomarkers and acute kidney injury in children. The long road to clinical application. *Pediatr Nephrol* 2013; 28: 837-842.

6. Bresolin N, Patricia AB, Alberton CH. Paediatric acute kidney injury assessed by Prifle as a prognostic factor in the intensive care unit. *Pediatr Nephrol* 2013; 28: 485-492.
7. Boer DP, de Rijke YB, Hop WC, Crausborg K, Dorrestein EM. Reference values of serum creatinine in children younger than 1 year of age. *Pediatr Nephrol*, 2010; 25: 2107-2113.
8. Waiker SS, Liu KD, Chertow GM. Diagnosis Epidemiology and Outcomes of Acute Kidney Injury. *CJASN* May 2008; 3: 3844-3861.
9. Devarajan P. Emerging biomarkers of AKI. *Contrib Nephrol*, 2007; 156: 203-312.
10. Mishra J, Ma Q, Prada A. Neutrophil Gelatinase-associated lipocalin as a novel urinary biomarker for ischemic injury. *J Am Soc Nephrol* 2003; 4:2534-2543.
11. Mishra J, Dent C, Tarabishi R. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury following cardiac surgery. *Lancet* 2005; 365: 1231-1238.
12. Hirsch R, Bent C, Pfreim H. NGAL is an early predictive biomarker of contrast nephropathy in children. *Pediatr Nephrol* 2007; 22: 2089-2095.
13. Han WK, Waikar SS, Johnson A. Urinary biomarkers in the early diagnosis of acute kidney injury. *Kidney Int* 2008;73: 863–869.
14. Koyner JL, Bennett MR, Worcester EM. Urinary cystatin C as an early biomarker of acute kidney injury following adult cardiothoracic surgery. *Kidney Int* 2008;74:1059–1069.
15. Portilla D, Dent C, Sugaya T. Liver fatty acid-binding protein as a biomarker of acute kidney injury after cardiac surgery. *Kidney Int* 2008;174:465–472.
16. Honore PM, Jacobs R, Boyak OJ, Verfaillie L, Regt JD, Gorp VV et al. Biomarkers for early diagnosis of AKI in the ICU; ready: ready for prime time use at the bedside? *ANN Intensive Care*, 2012;2:24.
17. Herrero-Morin JD, Malaga S, Fernandez N, Rey C, Dieguez MA, Solis G et al. Cystatin C and b2 microglobulin: markers of glomerular filtration in cretically in children. *Crit care*. 2007;11:59.
18. Parikh CR, Jauj A, Mishra J, Ma Q, Kelly C, Barash J et al. Urine NGAL and IL-18 are

- predictive biomarker for delayed graft function following kidney transplantation. *Am J transplant.* 2006;1639-1645. Doi: 10.1111/J.1600-6143.2006.01352.x [PubMed/ (cross ref)]
19. Cruz DN, de Zeeuw D, van Boven E, et al. Biomarker strategies to predict need for renal replacement therapy in acute kidney injury. *Semin Dial.* 2011;24: 124-131/ doi: 10.1111/J.1525-1392.2011.00830(pubmed)
 20. Binachi C, Donadio C, Tramonti G, Cousani C, Lorusso P, Rossi G. Reappraisal of serum b2 microglobulin as marker of GFR. *Ren Fail.* 2001;23:419-429.doi:10.1081/Joi-100104725.[Pub Med] [CNBS ref]
 21. Bagshaw SM, Laugenberg C, Haase M, van L, May CN, Bellomo R. urinary biomarkers in septic acute kidney injury. *Intensive Care Med.* 2007;33:1285-1296.doi:10.1007/800134-007-0656-5 [Pub Med] [CNBS Ref]
 22. Molitoris BA, Melnikov VY, Okusa MD, Himelfarb J. Technology Insight: biomarker development in acute kidney injury – what can we anticipate? *Nat Clin Pract Nephrol.* 2008;4:154-165.doi:10.1038/nepneph0723.review [Pub Med][CNBS Ref]
 23. de Geus, Bakker J, Lesatre EM, Le Noble JL. Neutrophil Gelatinase-associated lipocalin at ICU admission predictors for acute kidney injury in adult patients. *Am J Respir Crit Care Med.*2011;183:907-914. doi:10.1164/reem.200908-12140c.[Pub Med][CNBS Ref]
 24. Kashai K, Al khataji A, Ardiles T, Artigab A, Bagshaw SM, Bell M et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *crit care.*2013;17: R25.