

---

## ICU Volume 13 - Issue 3 - Autumn 2013 - Cover Story: The Kidney

### Biomarkers for Acute Kidney Injury

---

#### Author

**Lakhmir S. Chawla, MD**

*Department of Anesthesiology and Critical Care Medicine*

*George Washington University Hospital*

*Washington DC, USA*

**John A. Kellum, MD**

*Professor and Vice Chair for Research*

*Department of Critical Care Medicine*

*University of Pittsburgh, Pittsburgh, USA*

[kellumja@ccm.upmc.edu](mailto:kellumja@ccm.upmc.edu)

Acute kidney injury (AKI) is a syndrome of decreased renal function associated with an increased risk of chronic kidney disease (CKD) and death. Recent advances in the field promise to improve AKI diagnosis and treatment.

AKI is a serious complication of acute illness, typically occurring as a result of underlying conditions such as sepsis, and is independently associated with decreased survival. It has become increasingly clear that AKI is associated with development of end-stage renal disease (ESRD) and chronic kidney disease (CKD) (Ishani et al. 2011; Chawla et al. 2011; Hoste et al. 2010). Individuals fortunate enough to survive a significant episode of AKI are therefore at risk of developing CKD-related disease.

Our understanding of AKI has advanced over the past decade, with a unified definition and standard criteria for staging, a quantification of renal replacement therapy (RRT) dosing, and the emergence of biomarkers related to AKI. These new markers provide clear and convincing evidence that AKI is indeed a very complex disorder. A study by Paragas et al., which examined the expression of neutrophil gelatinase-associated lipocalin (NGAL) using a luciferase reporter assay, clearly showed a very specific signal in the kidneys in response to lipopolysaccharide (LPS), whereas similar reductions in glomerular filtration rate (GFR) from dehydration showed no such signal (Paragas et al. 2011). Although NGAL has been shown in multiple large cohort studies to be a biomarker for early AKI diagnosis and for AKI prognosis (Shemin and Dworkin 2011), NGAL is expressed in multiple organs and is thus not kidney specific. Understanding how non-kidney sources of NGAL impact the urinary NGAL signal and establishing the sources of NGAL in AKI is essential.

Paragas and colleagues (2011) conducted their novel experiment by creating a reporter mouse for NGAL. They inserted a double-fusion reporter gene that encoded luciferase-2 and mCherry (Luc2-mC) in the locus for NGAL (lcn-2). In so doing, the investigators could assess endogenous NGAL message in real time and assess in which organs the message was being transcribed. In separate experiments, mice were subjected to unilateral or bilateral renal ischaemic models and nephrotoxic injury with cisplatin. In addition, the investigators tested whether NGAL-Luc2-mC was activated in prerenal azotaemia and ascertained the portion of the nephron responsible for urinary NGAL (uNGAL) production in AKI. The investigators determined that the principal or exclusive source of uNGAL was the thick ascending limb and collecting ducts of the nephron. In addition, in the prerenal azotaemia model, serum creatinine level rose, but NGAL-Luc2-mC was not activated and no increase in uNGAL level occurred. These data show that uNGAL is an appropriate kidney injury specific biomarker despite not being exclusively expressed in the kidney.

Another study involving NGAL displayed the range in which AKI biomarkers can assist clinicians caring for patients with AKI. NGAL has been primarily thought of as a biomarker for early diagnosis of AKI (Shemin and Dworkin 2011), but utility of this and other biomarkers may be much broader. Using a large multicentre cohort of patients with community-acquired pneumonia, Srisawat and colleagues (2011) examined plasma of patients on the first day they experienced severe AKI (RIFLE Failure level). In this study, recovery was defined as being alive and neither requiring RRT during hospitalisation nor having a persistent RIFLE Failure level classification at hospital discharge. The investigators found that elevated plasma NGAL levels were associated with renal non-recovery. Although the absolute predictive value of pNGAL alone was only fair (area under the receiver operating characteristic curve 0.74), the reclassification of risk of not recovering renal function was increased by 17%. These data are most notable for two reasons. First, because AKI can cause CKD and ESRD, decisions regarding long-term care (for example,

use of dialysis, vascular access, and follow-up) are often made in a piecemeal approach. If objective metrics coupled with clinical assessment can improve prognostic accuracy, a more informed decision can be made for survivors of AKI. Second, the association between plasma NGAL and renal non-recovery suggests that renal injury is ongoing, and even if a patient is undergoing dialysis therapies directed at mitigating ongoing injury may have a role in AKI treatment.

Within the advancing field of AKI, the oldest known biomarker is urine output. The precise utility of oliguria has been controversial, and within the Acute Kidney Injury Network (AKIN) staging system, there has been discussion on the precise definition of oliguria over time (for example, consecutive hours of oliguria versus average urine output over a period of time). To understand this further, Macedo and colleagues (2011) utilised high-fidelity urimeters to compare various definitions of oliguria in critically ill patients. In their study 317 patients had specialised high-accuracy urimeters placed on their urinary catheters in order to measure their urine output hourly. Serum creatinine was measured every 12 hours, and definitions of AKI based on urine output were compared with those based on serum creatinine. Urine output was classified in three ways: consecutive hours of oliguria (oligo6-cons), an average amount of oliguria over a fixed block of time ( $<3$  ml/kg in the period from 6.00 am to 12.00 midday), or any episode of oliguria over a set period of time ( $<3$  ml/kg for any 6-hour period). Of these variables, oligo6-cons was the most specific when compared with the AKIN stage I serum creatinine standard (sensitivity 34%, specificity 71%). The other two metrics, oliguria 6-hour fixed (oligo6-fixed) and oliguria 6-hour floating (oligo6-float), were more sensitive, but less specific (sensitivities 47% and 53%, and specificities 62% and 54%, respectively). Of the patients with oliguria for 6 hours, 79% of oligo6-cons advanced to AKIN stage II, while 64% of oligo6-fixed and 52% of oligo6-float advanced to AKIN stage II. Using the urine output definition of AKI increased the observed incidence of AKI to 52% as compared with an AKI incidence of 24% using serum creatinine definitions alone. The mortality rate of patients with AKI defined by urine output alone was comparable to that of patients with AKI defined by serum creatinine alone (8.8% versus 10.4%). Moreover, oliguria was a more sensitive marker of AKI, and tended to occur earlier than did change in serum creatinine. These data endorse current consensus Kidney Disease: Improving Global Outcomes (KDIGO) definitions (based on RIFLE - Risk, Injury, Failure, Loss, and End-stage kidney disease)/ AKIN - Acute Kidney Injury Network) that incorporate changes in both urine output and serum creatinine (Kidney Disease: Improving Global Outcomes 2012).

An alternative interpretation was offered by Ralib and colleagues (2013), who analysed records from 725 consecutive admissions to a general ICU over a 12 month period. For a 6-hour urine output collection they found a threshold of 0.3 ml/kg/h to have the greatest accuracy for predicting in-hospital mortality or dialysis. A threshold of 0.3 ml/kg/h exhibited hazard ratios for in-hospital and one-year mortality of 2.25 (1.40 to 3.61) and 2.15 (1.47 to 3.15) respectively after adjustment for age, body weight, severity of illness, fluid balance, and vasopressor use. By contrast, the 0.5 ml/kg/h threshold used by the KDIGO criteria was not as strongly associated with these outcomes (hazard ratios: 1.48 (0.89 to 2.45) and 1.43 (0.96 to 2.13)) and not statistically significant in this small cohort. However, it is our view that the urine output threshold should be set not on the basis of hazard ratios for mortality but to be a sensitive indicator for AKI. In any case a hazard ratio of 1.48 is clearly clinically important, even if the study by Ralib and colleagues (2013) was under-powered to detect it.

At the other end of the timeline, entirely new biomarkers are emerging. Munshi and colleagues (2011) reported a study where potential biomarker candidates were chosen from urinary excretion of injury-induced mRNAs. The investigators posited that the resulting proteins of these mRNAs might be good AKI biomarkers, and may offer pathogenic information in addition to diagnostic information. Munshi et al. (2011) quantified the urinary excretion of the mRNAs for one of these candidate proteins, monocyte chemoattractant protein-1 (MCP-1). The investigators conducted multiple preclinical studies wherein various forms of AKI were induced, and MCP-1 was compared with a known representative AKI biomarker, NGAL. In the models of AKI, MCP-1 protein and mRNA increased more than corresponding increases in NGAL. Uraemia, without kidney injury, induced the NGAL gene, but not MCP-1, which suggests that MCP-1 may be more specific for AKI. These findings were tested in a candidate cohort of Acute Physiology and Chronic Health Evaluation (APACHE)- II-matched critically ill patients with and without AKI. In these patients, MCP-1 levels were significantly higher in those with AKI.

More recently, tissue inhibitor of metalloproteinases (TIMP)-2 and insulin-like growth factor-binding protein-7 (IGFBP7) were discovered and subsequently validated for their ability to predict the manifestation of moderate- severe (KDIGO stage 2-3) AKI within 12 hours (Kashani et al. 2013). Interestingly, not only do these biomarkers out-perform all other available AKI biomarkers, but their relationship to cell cycle arrest informs on a novel mechanism for AKI (Yang et al. 2010).

In our view, existing biomarkers such as NGAL and newly discovered biomarkers are beginning to shape clinical practice. This ongoing process of new discovery and reinvention of existing tools, including those as timeworn as urine flow, will advance the field further and we will eventually emerge with a set of tools that will not only help us diagnose AKI, but will also help us determine its cause, monitor its course and predict response to therapy. We eagerly await this bright future.

#### Acknowledgements

L. S. Chawla declares associations with the following companies: Alere, Astute Medical.

J. A. Kellum declares associations with the following companies: Abbott, Alere, Astute Medical, Roche.



Published on : Wed, 2 Oct 2013