Intensive Care Med
DOI 10.1007/s00134-017-4759-3

EDITORIAL

Have renal biomarkers failed in acute kidney injury? Yes

Jill Vanmassenhove[1*], Jan T. Kielstein[2] and Marlies Ostermann[3]

Introduction

Current diagnostic criteria for AKI are based on serum creatinine and urinary output, i.e. functional rather than specific injury markers. New biomarkers appeared to be flawless at least in selected patient populations such as children with few if any co-morbidities [1]. However, initial enthusiasm was curbed by subsequent studies revealing important shortcomings, especially in adults with comorbidities, and uncertainty about the exact timing of the renal insult [2].

Diagnosis of AKI

Biomarkers should differentiate between so-called pre-renal AKI and intrinsic AKI. Existing studies have been inconsistent and revealed large overlap in biomarker levels between both groups, even after excluding patients who were deemed unclassifiable according to standard criteria [3]. Needless to say, the latter are precisely the patients for whom biomarkers are needed most.

Blind faith in biomarkers has led to the existence of purely functional or pre-renal AKI being questioned. Several authors have demonstrated that biomarkers were detectable in pre-renal AKI and argued that patients with so-called pre-renal AKI also had a degree of tubular injury [4]. This gave rise to a new concept called subclinical AKI, characterized by an increase in biomarkers but no change in traditional markers [5]. Although these patients had a worse outcome than patients without a biomarker increase, it is not clear whether this was due to unrecognized renal damage or reflected associated non-renal conditions.

Prognosis of AKI

There is an urgent need for tools to identify AKI patients who will progress to severe AKI or may not recover renal function. BioMaRK (Biological Markers of Recovery for the Kidney) was an observational ancillary study to the Veterans Affairs/National Institutes of Health Acute Renal Failure Network trial, and focused on identifying new biomarkers to predict renal recovery at 60 days in survivors who had renal replacement therapy (RRT) [6]. Urinary hepatocyte growth factor (uHGF) at day 14 and relative change in uHGF over 14 days were found to be moderately predictive of RRT independence. However, when adding the two best performing individual markers [uHGF and neutrophil gelatinase-associated lipocalin (NGAL)] to a clinical model, the area under the receiver operating curve (AUC) only improved from 0.74 to 0.75. It should also be acknowledged that these observational data were derived from a highly selected patient group.

Data linking biomarkers to long-term outcomes including chronic kidney disease (CKD) and mortality are scarce. The Translational Research in Biomarker Endpoints in AKI cohort (TRIBE-AKI) investigators showed modest associations between biomarkers and mortality [7]. In a study by Coca et al. [7], mortality rates increased by tertiles of urinary biomarkers in AKI and no AKI strata. However, the addition of peak biomarker levels to a clinical model did not change the AUC for death.

Identifying patients with an unfavorable clinical course is pivotal for clinical management but also for intervention trials. Including AKI patients with a favorable course regardless of any intervention will reduce the power in these trials. To date, there is no clear evidence that any of the existing biomarkers are ready for this task.

Unmet needs

Biomarkers are only useful if they offer value above routinely available clinical data. One of the biggest challenges

*Correspondence: Jill.Vanmassenhove@ugent.be
[1] Renal Division, Ghent University Hospital, Ghent, Belgium
Full author information is available at the end of the article
For contrasting viewpoints, please go to doi:10.1007/s00134-017-4763-7
and doi:10.1007/s00134-017-4792-2.

Springer

Table 1 Biomarkers of AKI in humans

Type of biomarker	Examples	Diagnostic relevance	Potential role as AKI biomarker	Important confounders	Limitations
Proteins produced predominantly by non-renal cells	Cystatin C Neutrophil gelatinase-associated lipocalin (NGAL) α_1 microglobulin (α_1 MG) β_2 microglobulin (β_2 MG) Retinol binding protein (RBP)	Systemic production and released into urine following glomerular filtration α_1 MG, β_2 MG and RBP are reabsorbed and fully catabolised by proximal tubular cells	Diagnosis of AKI Severity of AKI	Systemic inflammation Sepsis Malignancy Diabetes Thyroid disorder Glucocorticoid disorders CKD HIV disease UTI	Commercial assays only available for cystatin C, NGAL and [IGFBP-7]-[TIMP-2) Lack of agreement on specific cut-offs for diagnosis of AKI
Proteins/peptides produced by renal cells	Neutrophil gelatinase-associated lipocalin (NGAL) Netrin-1 Kidney injury molecule–1 (KIM-1) Monocyte chemoattractant peptide-1 (MCP-1)	Released into urine following after tubular cell injury	Diagnosis of AKI Severity of AKI Prognosis of AKI Mortality	Systemic inflammation Malignancy Pancreatitis COPD CKD UTI	No information about aetiology of AKI Some biomarkers have not been validated outside the critical care or post-operative setting
Cytosolic proteins in renal and non-renal cells	Calprotectin Chitinase 3-like protein 1 α glutathione S-transferase (α GST) π glutathione S-transferase (π GST) Liver-type fatty acid-binding protein (L-FABP)	Released into urine following tubular cell injury/ intrinsic AKI	Diagnosis of AKI Severity of AKI Prognosis of AKI Mortality	Inflammatory bowel disease UTI CKD Malignancy Connective tissue disease Liver disease Sepsis Anemia	No agreement on whether biomarker concentrations in urine should be corrected for urinary creatinine
Lysosomal enzymes	*N*-acetyl-*β*-D-glucosaminidase (NAG)	Released into urine after tubular injury	Diagnosis of AKI prognosis of AKI	Diabetes	
Enzymes located on the brush border of proximal tubular cells	Alanine aminopeptidase (AAP) Alkaline phosphatase (ALP) γ-glutamyl transpeptidase (γ-GT)	Detectable in urine following proximal tubular cell injury	Diagnosis of AKI		
Growth factors	Angiopoietin-1 Angiopoietin-2	Upregulated in glomerular disease	Diagnosis of glomerular AKI	Systemic inflammation Sepsis Diabetes Malignancy	
Cytokines	Interleukin-18 (IL-18) Hepatocyte growth factor (HGF)	Released into urine following tubular cell injury	Diagnosis of AKI Prognosis of AKI Mortality	Inflammatory diseases COPD Liver cirrhosis Connective tissue disease Cardiovascular disease	
Peptide hormones	Hepcidin Proenkephalin	Detectable in urine following glomerular filtration	Diagnosis of AKI Severity of AKI	Systemic inflammation	
Cell cycle arrest markers	Insulin-like growth factor binding protein-7 (IGFBP-7) Tissue metalloproteinase-2 (TIMP-2)	Released into urine after tubular cell stress	Diagnosis of AKI Prognosis of AKI Mortality	Diabetes	
Single-stranded non-coding nucleotides	microRNA	Upregulated following tubular cell injury; detectable in plasma and urine	Diagnosis of AKI AKI progression Mortality	Sepsis	
Immunoglobulin superfamily of receptors	Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1)	Detectable in urine following systemic and renal production	Diagnosis of sepsis–associated AKI	Systemic inflammation sepsis	

AKI acute kidney injury, *CKD* chronic kidney disease, *COPD* chronic obstructive pulmonary diseases, *HIV* human immunodeficiency virus, *UTI* urinary tract infection

for new AKI biomarkers is that they need to perform well in patients with chronic comorbidities, including impaired renal function. Unfortunately, most existing biomarkers seem to be confounded by the presence of CKD (Table 1).

In a recent study, evolution to AKI was better predicted by the response in urinary output to a furosemide stress test than by markers such as NGAL, interleukin-18, kidney injury molecule-1 and cell cycle arrest markers [8]. This underlines the fact that in our 'quest for the holy grail', the value of traditional diagnostic tests such as urinary analysis and urinary output should not be underrated [9–11].

It is utopian that one single 'magic bullet' biomarker will cover the complex spectrum of AKI and will perform well for both diagnosis and prognosis, but combining biomarkers has also yielded rather disappointing results. On the other hand, it is fair to state that no biomarker can perform well against an imperfect gold standard such as serum creatinine. Rather than trying to find a troponin-like biomarker, it is important to focus on the synergistic role of biomarkers and standard parameters in order to improve the outcome for AKI patients [10]. Biomarkers should never replace clinical judgement and should only be used as add-on tools.

Furthermore, several important technical issues related to biomarkers need clarification before implementing them in clinical practice. Clear cut-offs between "AKI" and "no AKI" need to be determined, and assays need to be calibrated accordingly. In addition, agreement is necessary as to whether or not biomarker levels should be normalized for urinary creatinine [12].

To date, four studies have used biomarkers as a clinical decision tool [13–16]. In the EARLY-ARF trial [13], which investigated the potential benefit of early treatment with erythropoietin to prevent AKI, biomarkers failed to identify patients at high risk for AKI. Two trials [14, 15] compared early versus late start of RRT in critically ill patients, and used biomarkers to enrich their study population. However, in one of these studies, NGAL levels were not different between patients treated with RRT and those who recovered spontaneously in the standard group [14]. Meersch et al. [16] recently compared standard care versus application of a KDIGO care bundle to prevent AKI post-cardiac surgery and used [TIMP-2*IGFBP7] to identify high-risk patients. They found a decrease in AKI incidence and in marker levels in the intervention group but no difference in mortality or need for RRT. Larger multicenter studies in a more heterogeneous setting are necessary to validate these results.

More awareness of the potential harm from non-critical use of biomarkers is crucial. New diagnostic tests should only be implemented if they are cost-effective, outperform a clinical model based on traditional markers and improve patient outcome.

Author details
[1] Renal Division, Ghent University Hospital, Ghent, Belgium. [2] Academic Teaching Hospital Braunschweig, Medical Clinic V Nephrology, Hypertension and Blood Purification, Brunswick, Germany. [3] Department of Critical Care and Nephrology, King's College London, Guy's and St Thomas' Foundation Hospital, London, UK.

Compliance with ethical standards

Conflicts of interest
The authors declare that there is no conflict of interest.

Received: 1 February 2017 Accepted: 2 March 2017
Published online: 24 April 2017

References

1. Mishra J, Dent C, Tarabishi R, Mitsnefes MM, Ma Q, Kelly C, Ruff SM, Zahedi K, Shao M, Bean J, Mori K, Barasch J, Devarajan P (2005) Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet 365:1231–1238
2. Parikh CR, Coca SG, Thiessen-Philbrook H, Shlipak MG, Koyner JL, Wang Z, Edelstein CL, Devarajan P, Patel UD, Zappitelli M, Krawczeski CD, Passik CS, Swaminathan M, Garg AX (2011) Postoperative biomarkers predict acute kidney injury and poor outcomes after adult cardiac surgery. J Am Soc Nephrol 22:1748–1757
3. Singer E, Elger A, Elitok S, Kettritz R, Nickolas TL, Barasch J, Luft FC, Schmidt-Ott KM (2011) Urinary neutrophil gelatinase-associated lipocalin distinguishes pre-renal from intrinsic renal failure and predicts outcomes. Kidney Int 80:405–414
4. Nejat M, Pickering JW, Devarajan P, Bonventre JV, Edelstein CL, Walker RJ, Endre ZH (2012) Some biomarkers of acute kidney injury are increased in pre-renal acute injury. Kidney Int 81:1254–1262
5. Haase M, Devarajan P, Haase-Fielitz A, Bellomo R, Cruz DN, Wagener G, Krawczeski CD, Koyner JL, Murray P, Zappitelli M, Goldstein SL, Makris K, Ronco C, Martensson J, Martling CR, Venge P, Siew E, Ware LB, Ikizler TA, Mertens PR (2011) The outcome of neutrophil gelatinase-associated lipocalin-positive subclinical acute kidney injury: a multicenter pooled analysis of prospective studies. J Am Coll Cardiol 57:1752–1761
6. Srisawat N, Wen X, Lee M, Kong L, Elder M, Carter M, Unruh M, Finkel K, Vijayan A, Ramkumar M, Paganini E, Singbartl K, Palevsky PM, Kellum JA (2011) Urinary biomarkers and renal recovery in critically ill patients with renal support. Clin J Am Soc Nephrol 6:1815–1823
7. Coca SG, Garg AX, Thiessen-Philbrook H, Koyner JL, Patel UD, Krumholz HM, Shlipak MG, Parikh CR, Consortium T-A (2014) Urinary biomarkers of AKI and mortality 3 years after cardiac surgery. J Am Soc Nephrol 25:1063–1071
8. Koyner JL, Davison DL, Brasha-Mitchell E, Chalikonda DM, Arthur JM, Shaw AD, Tumlin JA, Trevino SA, Bennett MR, Kimmel PL, Seneff MG, Chawla LS (2015) Furosemide stress test and biomarkers for the prediction of AKI severity. J Am Soc Nephrol 26:2023–2031
9. Perazella MA, Coca SG, Kanbay M, Brewster UC, Parikh CR (2008) Diagnostic value of urine microscopy for differential diagnosis of acute kidney injury in hospitalized patients. Clin J Am Soc Nephrol 3:1615–1619
10. Molitoris BA (2015) Urinary biomarkers: alone are they enough? J Am Soc Nephrol 26:1485–1488
11. Vanmassenhove J, Glorieux G, Hoste E, Dhondt A, Vanholder R, Van BW (2013) Urinary output and fractional excretion of sodium and urea as indicators of transient versus intrinsic acute kidney injury during early sepsis. Crit Care 17:1–10
12. Ralib AM, Pickering JW, Shaw GM, Devarajan P, Edelstein CL, Bonventre JV, Endre ZH (2012) Test characteristics of urinary biomarkers depend on quantitation method in acute kidney injury. J Am Soc Nephrol 23:322–333

13. Endre ZH, Walker RJ, Pickering JW, Shaw GM, Frampton CM, Henderson SJ, Hutchison R, Mehrtens JE, Robinson JM, Schollum JB, Westhuyzen J, Celi LA, McGinley RJ, Campbell IJ, George PM (2010) Early intervention with erythropoietin does not affect the outcome of acute kidney injury (the EARLYARF trial). Kidney Int 77:1020–1030
14. Wald R, Adhikari NK, Smith OM, Weir MA, Pope K, Cohen A, Thorpe K, McIntyre L, Lamontagne F, Soth M, Herridge M, Lapinsky S, Clark E, Garg AX, Hiremath S, Klein D, Mazer CD, Richardson RM, Wilcox ME, Friedrich JO, Burns KE, Bagshaw SM, Canadian Critical CareTrials G (2015) Comparison of standard and accelerated initiation of renal replacement therapy in acute kidney injury. Kidney Int 88:897–904
15. Zarbock A, Kellum JA, Schmidt C, Van Aken H, Wempe C, Pavenstadt H, Boanta A, Gerss J, Meersch M (2016) Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial. JAMA 315:2190–2199
16. Meersch M, Schmidt C, Hoffmeier A, Van Aken H, Wempe C, Gerss J, Zarbock A (2017) Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. Intensive Care Med. doi:10.1007/s00134-016-4670-3