Biomarkers for the prediction of acute kidney injury: a narrative review on current status and future challenges

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Abstract
Acute kidney injury (AKI) is strongly associated with increased morbidity and mortality in critically ill patients. Efforts to change its clinical course have failed because clinically available therapeutic measures are currently lacking, and early detection is impossible with serum creatinine (SCr). The demand for earlier markers has prompted the discovery of several candidates to serve this purpose. In this paper, we review available biomarker studies on the early predictive performance in developing AKI in adult critically ill patients. We make an effort to present the results from the perspective of possible clinical utility.

Keywords: AKI; biomarkers; ICU

Introduction
Acute kidney injury (AKI) represents an acute decline in renal function that leads to structural changes. AKI is associated with increased mortality, length of hospital stay and costs [1]. This unfavourable outcome might be tied to the late detection of AKI when the elevation of serum creatinine (SCr) is used. Many genes are up-regulated in the damaged kidney with the corresponding protein products appearing in plasma and urine. Some of these are candidate markers for more timely diagnosis of AKI. The purpose of this paper is to review the current state of epidemiological data concerning AKI, to evaluate available biomarkers for the prediction of AKI and to describe several potential therapeutic options.

Epidemiology of AKI in critically ill patients
The Beginning and Ending supportive therapy for the Kidney investigators study (BEST Kidney study) has provided recent global insight as to the prevalence of patients with AKI. The reported mortality rate is 60.3%, with sepsis and pre-morbid renal dysfunction being dominant causes. In this observation, 13.8% of the patients with acute renal failure (ARF) surviving until hospital discharge required chronic renal replacement therapy (RRT) [2]. AKI and AKI requiring RRT display increasing incidence due to the rising degree of comorbid conditions, increasing age and severity of illness in critically ill patients [3]. However, there seems to be a steady-state decline in annual in-hospital mortality (from 41.3% in 1988 to 28.1% in 2002). Despite the observed reduction in mortality rates, the rising incidence of AKI comes at a price. Patients tend to survive the intensive care unit (ICU) but will be discharged with various degrees of chronic kidney disease (CKD), which will increasingly strain the health care system [4]. These data are supported by observations from Australia, where the 10-year trend in the incidence of AKI and the crude hospital mortality rates adjusted for illness severity were likewise investigated. In this study, 5.2% of the patients have AKI with an increased incidence over the past decade; however, the multivariate adjusted odds of death associated with AKI show a declining trend. The increased risk of death associated with AKI persisted with the adjustment for several relevant covariates. ARF exerts an independent, profound and specific effect on morbidity and mortality in critically ill patients [5]. Furthermore, outcomes are directly related to the severity of AKI: even small changes in SCr have a detrimental impact on patient long-term survival [1, 6].

Biomarkers for the prediction of AKI
The ability of biomarkers to predict AKI has been studied intensely in several different clinical settings. For a sound interpretation of the reported results, it is important to realize that the studies present a mixture of ‘AKI diagnosis confirmation’ in patients with established AKI and ‘AKI early prediction’ in patients with developing AKI. Obviously, these are two different entities with different clinical impacts. For the clinical application of a new biomarker, it should prove to be more accurate with earlier detectability than the current gold standard SCr, which implies ‘early prediction’ only. Therefore, this review focuses on the prediction of developing AKI in adult critically ill patients. There are four major categories of biomarkers (Table 1).
**Table 1. Biomarkers for AKI**

| Biomarker types                  | Biomarkers                                      |
|----------------------------------|------------------------------------------------|
| Functional markers               | SCr and plasma/serum CyC                       |
| Up-regulated proteins            | NGAL, KIM-1, L-FABP and IL-18                  |
| Low-molecular weight proteins    | Urine CyC                                      |
| Enzymes                          | NAG, α-GST, β-GST, GGT and AP                  |

**Functional markers**

**Serum creatinine (SCr).** Serum creatinine (SCr) is a degradation product of muscle cells and represents a surrogate for the efficiency of glomerular filtration. It has poor predictive accuracy for renal injury, particularly, in the early stages of AKI [7]. In the case of critical illness, SCr concentrations are subject to large fluctuations due to a patient’s induced diuretal volume status, the catabolic effects of critical illness, the likelihood of concentration decreases in septic conditions and the increased tubular excretion with diminished renal function. Furthermore, after an injurious event, the rise in SCr is slow. Therefore, detection of the earliest evidence of AKI necessitates the use of other plasma or urinary biomarkers.

**Plasma/serum cystatin C (CyC).** Cystatin C (CyC) is a 13-kDa non-glycosylated cysteine protease inhibitor produced by all nucleated cells at a constant rate. In healthy subjects, plasma CyC (pCyC) is excreted through glomerular filtration and metabolized completely by the proximal tubules. Furthermore, there is no evident tubular secretion. Several studies claim the superiority of pCyC against SCr to detect minor reductions in glomerular filtration rate (GFR) [8]. However, the interpretation of pCyC levels is biased by older age, gender, weight, height, cigarette smoking and high levels of C-reactive protein (CRP) [9, 10]. In addition, CyC levels are supposedly influenced by abnormal thyroid function [11, 12], the use of immunosuppressive therapy [13] and malignancies [14, 15]. In 318 patients included at ICU admission, pCyC predicted developing sustained AKI (n = 19) very modestly (area under the curve [AUC] = 0.65 [95% confidence interval (CI) 0.58–0.71]) in univariate analysis [16]. Herget-Rosenthal [17] described a cohort in whom sCyC was measured at admission in 85 patients with normal GFR. The reported AUC was 0.82 (CI 0.71–0.92) for acute renal failure 2 days prior to the event. A recent multicentre study in 151 subjects in a comparative setting found a poorer performance (AUC = 0.72 no CI provided) [18]. Metzger et al. [19] compared the classification performance of a set of urinary proteome analyses with sCyC in 20 general ICU patients, retrospectively, and found low classification accuracy (AUC = 0.67 CI not provided).

In cardio pulmonary bypass (CPB) cohorts, several studies explored the use of CyC for AKI prediction. Herget-Rosenthal et al. [20] described 100 cardiac surgical patients among whom 23 subjects were classified as patients without preoperative renal impairment. Their samples were measured at ICU arrival, and the reported AUC = 0.78 (CI 0.58–0.99) did not improve after 24 h. Koyner et al. reported on 72 patients who were admitted following CPB with 34 subjects developing AKI, which was defined as a 25% increase in PCr or the need for RRT (n = 7) within 3 days after surgery. PCyC measured at the time of ICU arrival was not a useful early predictor for the composite outcome AUC = 0.62 (0.49–0.75) [21]. A likely explanation is the applied unusual definition of AKI, which indicates less severe grades of AKI among the event group.

**Up-regulated proteins**

**Neutrophil gelatinase-associated lipocalin.** Neutrophil gelatinase-associated lipocalin (NGAL) is a small protein linked to neutrophil gelatinase in specific leukocyte granules [22]. It is also expressed in a variety of epithelial tissues associated with anti-microbial defence [23–26]. In the normal kidney, only the distal tubules and collecting ducts stain for NGAL expression. NGAL’s composite molecule binds ferric siderophores, and furthermore, it is a potent epithelial growth inducer, has protective effects in ischaemia [27, 28] and is up-regulated by systemic bacterial infections [24, 29–32]. In the case of AKI, proximal tubule cells also stain for NGAL proteins, which is explained by megalin-cubilin-mediated re-uptake of NGAL present in the glomerular filtrate [33, 34]. Urinary NGAL originates from local production in the distal tubules and collecting ducts. However, uNGAL excretion is proportional to albumin excretion in mouse models of diabetic nephropathy and is thus augmented when the proximal transport maximum is exceeded [33, 35, 36]. Siew et al. [37] enrolled their patients within 24 h after admission and reported a receiver operating characteristic curve (ROC) AUC = 0.77 (CI 0.64–0.90) for developing AKI in a subgroup of patients with estimated glomerular filtration rate (eGFR) at admission >75 mL/min/1.73 m² for urine NGAL (n = 18 versus 257). Cruz et al. reported on the development of AKI within 48 h after first sampling an AUC = 0.78 (CI 0.65–0.90). However, the reported positive predictive value was low (24%), and within 5 days, the AUC was reduced to 0.67 (CI 0.55–0.79) [38]. The first sampling was performed within 24 h after ICU admission. De Geus et al. [39] came to roughly similar reports with samples at ICU admission in patients with eGFR >60 mL/min/1.73 m² for both plasma and uNGAL (AUC = 0.75 ± [standard error (SE)] 0.103) AUC NGAL = 0.79 ± (SE) 0.085. It is debatable whether the exclusion of patients with eGFR <75 or 60 mL/min/1.73 m² applied by Siew and de Geus et al. is useful in clinical practice because a biomarker should also be effective in patients with CKD. In patients with sepsis, the predictive performance for AKI seemed not to be affected, as reported by Martensson for both plasma and urine NGAL [respectively, AUCs = 0.85 (CI 0.67–1.0) and 0.86 (CI 0.68–1.0)] [40]. However, Bagshaw et al. [41] report a distinct influence on test characteristics in patients with sepsis. Several studies report results in CPB cohorts: Koyner et al. [21] measured both pNGAL AUC 0.526 (0.388–0.664) and uNGAL AUC = 0.705 (CI 0.581–0.829) at ICU admission. An additional analysis by the same authors stratified their patients according to attained RIFLE stage and reported increased performances when using the harder end point of failure AUC = 0.69 (0.57–0.80) and AKIN Stage 3 AUC = 0.79 (0.65–0.94) [42]. A large study (n = 426) in CPB patients demonstrated test performance association with the pre-surgery baseline eGFR. Interestingly, only in patients with an eGFR above 60 mL/min was NGAL predictive: AUC = 0.68 (CI 0.54–0.81) [43]. A much smaller study (n = 9 events) reported values for both pNGAL and uNGAL, corrected for urinary creatinine: AUC = 0.85 (CI 0.73–0.97) and AUC = 0.96 (CI 0.90–1.0), respectively [44]. Haase-Fielitz [20] compared the performance of conventional and novel markers for pNGAL in adult CPB patients, excluding patients with preoperative renal impairment NGAL: the results yielded AUC = 0.80 (CI 0.58–0.99). In another large study (n = 879) for pNGAL measured immediately after CPB with 75 events, the AUC reported was 0.641 (0.58–0.71) [45]. Wagener et al. performed a study in adult CPB patients: for urine NGAL,
the predictive performance was AUC = 0.573 (CI 0.506–0.640) directly after the operation and the performance increased until 18 h after ICU admission to a maximum of 0.611. In a study performed by Liangos et al. (46), these results were similar in 103 CPB patients 2 h after surgery: AUC = 0.50 (CI 0.33–0.68).47 Among general adult ICU patients, 82 subjects developed AKI within 48 h of admission, and the predictive performance for NGAL corrected for urinary creatinine concentration yielded AUC = 0.55 (CI 0.48–0.63) (48). Metzger et al. compared the classification performance of urinary proteome analysis with classical markers. For urine NGAL, the ROC analysis revealed low classification accuracy: AUC = 0.54 CI (not provided) (19). The only meta-analysis published to date assessed pNGAL’s ability to predict across different settings; when weighted for study sample size, this value yielded an overall AUC of 0.782 (CI 0.689–0.872) (49).

Kidney injury molecule-1. Kidney injury molecule-1 (KIM-1) is a Type I transmembrane glycoprotein with a cleavable ectodomain (90 kDa) which is localized in the apical membrane of dilated tubules in acute and chronic injury (50, 51). Kim-1 is believed to play a role in regeneration processes after epithelial injury and in the removal of dead cells in the tubular lumen through phagocytosis (50, 52). A reduction in proteinuria with renine angiotensin aldosteron blockade is accompanied by a reduction in urinary KIM-1 excretion (53, 54). Among general adult ICU patients, 82 subjects developed AKI within 48 h of admission, and the predictive performance for KIM-1 corrected for urinary creatinine concentration yielded AUC = 0.55 (CI 0.47–0.62) in the study of Endre et al. (48). Metzger et al. compared the classification performance of urinary proteome analysis with classical markers. For urine KIM-1, the ROC analysis revealed low classification accuracy (AUC = 0.71 CI, not provided) (19). Several studies report its diagnostic properties in adult CPB patients (42, 47, 55–57). Liang et al. reported an AUC for progressive AKI of 0.69 (CI 0.61–0.78) after 6 h of inclusion. Notably, adding KIM-1 to interleukin (IL)-18 [AUC for IL-18 for progressive AKI 6 h after inclusion was 0.87 (CI 0.80–0.93)] improved the model’s accuracy only minimally [AUC 0.88 (CI 0.82–0.93)]. Liangos et al. reported an AUC 2-h post-CPB surgery of 0.78 (CI 0.64–0.91); however, in multivariate regression analysis, the association of KIM-1 was attenuated after adjustment. Koyner et al. (42) found an AUC 0.56 (CI 0.46–0.67) for this prediction, which resulted in very moderate performance for the entire cohort with an improvement when predicting AKIN Stage 3 only [AUC = 0.69 (CI 0.44–0.93)].

Liver fatty acid binding protein. Fatty acid binding proteins are small (15 kDa) cytoplasmic proteins abundantly expressed in tissues with active fatty acid metabolism. Their primary function is the facilitation of long-chain fatty acid transport, the regulation of gene expression and the reduction of oxidative stress. Urinary liver fatty acid binding protein (L-FABP) is undetectable in healthy control urine, which is explained by efficient proximal tubular internalization via megalin-mediated endocytosis (58, 59). Under ischemic conditions, tubular L-FABP gene expression is induced; in renal disease, the proximal tubular re-absorption of L-FABP is reduced (59, 60). To date, there is one small study reporting on the early diagnostic performance of L-FABP in adult ICU patients. The reported ROC AUC value was 0.95, no CI provided. However, several uncertainties remain after disclosure of the study’s methodology. Firstly, patient selection (n = 25 with 14 AKI and 11 non-AKI) seems to have been a result of convenient sampling. Secondly, the ‘true early diagnosis’ remains very doubtful as peak SCR and L-FABP values are reported as having the same median value; no further clear information concerning timing is provided (61).

Interleukin-18. In animal models, IL-18 has proven to be an important mediator in the process of AKI. Therefore, its urinary release has been anticipated as a possible early marker; several studies have explored the clinical application of this hypothesis. Among general adult ICU patients, 82 subjects developed AKI within 48 h of admission, and the predictive performance for IL-18 corrected for urinary creatinine concentration was AUC = 0.55 (CI 0.47–0.62) (48). Metzger et al. compared the classification performance of urinary proteome analysis with classical markers. For urine IL-18, the ROC analysis revealed low classification accuracy (AUC = 0.57 CI not provided) (19). Nevertheless, in a large cohort of mixed patients (n = 451), Siew et al. enrolled patients within 24 h after ICU admission: 86 developed AKI. The overall predictive performance reported was AUC = 0.62 (CI 0.54–0.69); this value increased slightly in patients with an eGFR above 75 mL/min/1.73 m² [AUC = 0.67 (CI 0.53–0.81)]. There seemed to be a strong association with sepsis (62). In patients with acute lung injury, uIL-18 predicted progression to AKI within 24 h with an accuracy of AUC = 0.731 (CI not provided) with substantial overlap between cases and controls in urine concentrations (63). In CPB patients, 2 h after CPB time, the optimal performance was reported to yield an AUC = 0.66 (CI 0.49–0.83) (47).

Low-molecular weight proteins

Urine cystatin C. The urinary excretion of CyC (uCyC) specifically reflects tubular damage because systemically produced cystatin C is normally not found in urine (64). However, recent insights show that urinary CyC excretion is augmented by albuminuria (65). In patients without AKI on ICU entry, uCyC was not predictive of AKI occurring within 48 h with AUC = 0.54 (CI 0.46–0.62) (66). Liangos et al. (47) used uCyC for this prediction, which resulted in very moderate performances 2-h post-CPB surgery with ROC AUC = 0.50 (CI 0.27–0.72) in a cohort of 103 patients with 13 events of AKI. In a study in patients undergoing CPB, Koyner et al. demonstrated that uCyC measured at ICU admission reached a maximum performance with an AUC of 0.693 (CI 0.567–0.818) (21, 48). Among general adult ICU patients, 82 subjects developed AKI within 48 h of admission and the predictive performance for urine CyC corrected for urinary creatinine concentration yielded AUC = 0.55 (CI 0.48–0.63). Another study performed by Koyner et al. demonstrated the predictive value of uCyC at ICU admission for any stage of AKI with AUC = 0.72 (CI 0.61–0.83). For the prediction of AKIN Stage 3 versus the rest of the cohort, the predictive performance increased to AUC = 0.84 (CI 0.68–0.99) (42). Royakkers et al. (18) regarded uCyC as a predictor for AKI 2 days prior to the first day of AKI and found no diagnostic value (AUC = 0.49 no CI provided).

Tubular enzymes

Alpha-glutathione s-transferase and pi-glutathione s-transferase. Alpha-glutathione s-transferase (α-GST) and pi-glutathione s-transferase (π-GST) are both members of a multigene family of detoxification enzymes present in
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many organs including the kidney. Distribution across the entire nephron of structurally and functionally distinct isoforms has been demonstrated. In urine, these enzymes are normally not present. After injury, α-GST is primarily detected in the proximal cells, whereas π-GST is observed in the distal parts [67]. Westhuyzen et al. studied the predictive performance of tubular enzymes and their combination in adult critically ill patients. Four patients developed AKI defined as a 50% SCR increase or more. At the time of ICU admission, α-GST and π-GST measured and indexed to urine creatinine provided AUCs of 0.893 (CI 0.688–0.975) and 0.929 (0.740–0.990), respectively, [68]. However, the patients with AKI seemed to have established AKI at study inclusion with a median creatinine clearance of 38.1 mL/min. Walse et al. reported that in patients with developing AKI and sepsis admitted to the general ICU, both enzymes were bad predictors. They suggested that sepsis might be the confounder triggering the production of these enzymes [69]. Finally, a study by Kayner et al. in 123 adult CPB patients reported AUC = 0.59 (CI 0.47–0.71) and 0.54 (0.42–0.66) for the prediction of AKI Stage 1 for α-GST and π-GST measured at ICU unadjusted for urine creatinine arrival, respectively, with similar test performances when using the harder end point of AKIN Stage 3 AUC = 0.58 (0.31–0.83) and AUC = 0.70 (0.50–0.90) [42].

N-acetyl-β-D-glucosaminidase. N-acetyl-β-D-glucosaminidase (NAG) is a lysosomal enzyme (> 130 kDa) that is localized in the renal tubules. Due to its large molecular weight, it precludes glomerular filtration, implying that urinary elevations have a tubular origin. Increased activity suggests injury to its cells but may also reflect increased lysosomal activity without cell disruption. NAG catalyses the hydrolysis of terminal glucose residues in glycoproteins.

Westhuyzen et al [68] reported on the ability to predict developing AKI in four cases in general ICU patients with AUC = 0.845 (CI 0.639–0.955); however, these patients seem to have established AKI with reduced creatinine clearance at the time of study inclusion. In adult CPB patients, 13 cases of developing AKI were reported: and the 2-hr post-operative prediction for NAG was very moderate: AUC = 0.62 (0.41–0.83) [47] (See Table 3 for a summary of all cited studies).

**Treatment of AKI**

The pathogenesis of AKI is very complex with multiple mechanisms underlying its course. Furthermore, critically ill patients do not generally die from AKI as such but more from the multiple organ dysfunction syndrome (MODS) associated with it. Given the multiple interactive pathways underlying AKI, it might be a mistake to concentrate therapeutic effects on one single part of the interrelated cascades. Therapies may need to target multiple sites in the pathophysiological pathways of AKI and MODS in order to be of any benefit for patients. Such combination therapies must involve agents with potential beneficial effects on vascular tone, tubular obstruction and inflammation. Furthermore, it is unlikely that targeting events that occur late in AKI will be effective. Pharmacological therapy in the prevention and treatment of AKI has been largely unsuccessful despite proven benefits as seen in pre-clinical studies. A number of drugs and investigational compounds seem promising in pre-clinical studies. There are six major categories of treatment strategies: anti-inflammatory agents, anti-apoptotic agents, iron scavengers, anti-oxidants, vasodilators and growth factors (Table 2).

**Conclusions**

In the quest for earlier markers for the recognition of AKI, several biomarkers have been investigated. The reported AUCs are disappointing ranging from 0.50 to 0.84, with one or two exceptions, which can be explained by statistical or methodological differences in study design. The discriminatory function in heterogeneous populations is poor and influenced by pre-existing renal function and time of sample collection with respect to the renal insult [48]. Clinical appraisal of a patient using standard parameters such as SCR and diuresis remains the cornerstone for now [70]. Therefore, it seems reasonable to perhaps shift our views and using biomarkers together with other parameters such as traditional clinical characteristics to optimize the accuracy of prediction of developing AKI might be an interesting option. Ultimately, the potential of new therapeutic agents can be tested and their use evaluated.

**Table 2. Therapeutic agents for the treatment of AKI**

| Therapeutic agents category | Agents |
|----------------------------|--------|
| Anti-inflammatory agents    | j1 Integrin antagonist, adenosine receptor antagonist, mesenchymal stem cells, C5a receptor antagonist, IL-10, IL-6 antagonist, statins, erythropoietin, α-melanocyte stimulating hormone, heme oxygenase-1 inducers (rapamycin), activated protein C, toll like receptor (TLR) blockers (Eritoran), sphingosine 2A agonist, fibrates, statins, peroxisome proliferator activated receptor (PPAR)-γ agonist, minocycline, inducible nitric oxide (iNOS) inhibitor, insulin, ethyl pyruvate, C3-antagonists, alkaline phosphatase |
| Anti-apoptotic agents       | NGAL, adenosine receptor antagonist, mesenchymal stem cells, erythropoietin, α-melanocyte stimulating hormone, caspase inhibitors, minocycline, nuG acute, pifithrin-α, poly ADP ribose polymerase (PARP) inhibitor, NGAL, apotransferrin, deferoxamine |
| Iron scavengers             | Reactive oxygen species scavengers |
| Anti-oxidants               | Erythrophilin, C5a receptor antagonist, CO-releasing compounds, fenoldopam, anti natriuretic peptide (ENAP), erythropoietin, hepatocyte growth factor |

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Gammaglutanyl transpeptidase and alkaline phosphatase. Gammaglutanyl transpeptidase (GGT) and alkaline phosphatase (AP) both are tubular brush border enzymes that are released into urine when there has been significant damage to the brush border membrane with loss of the microvillus structures. Few clinical studies are available, but Westhuyzen et al. [68] report data on four cases with developing AKI respectively of AUC = 0.950 (CI 0.789–0.999) and AUC = 0.863 (CI 0.676–0.973). However, these results should be interpreted with caution because the cases must be considered as established AKI at study inclusion according to their reported creatinine clearance. In general adult ICU patients, 82 subjects developed AKI within 48 h of admission and the predictive performance for urine GGT and urine AP corrected for urinary creatinine concentration AUC = 0.57 (CI 0.50–0.64) and AUC 0.56 (CI 0.49–0.63), respectively [48].

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**Table 3. Conclusions**

- In the quest for earlier markers for the recognition of AKI, several biomarkers have been investigated. The reported AUCs are disappointing ranging from 0.50 to 0.84, with one or two exceptions, which can be explained by statistical or methodological differences in study design.
- The discriminatory function in heterogeneous populations is poor and influenced by pre-existing renal function and time of sample collection with respect to the renal insult [48].
- Clinical appraisal of a patient using standard parameters such as SCR and diuresis remains the cornerstone for now [70].
- Therefore, it seems reasonable to perhaps shift our views and using biomarkers together with other parameters such as traditional clinical characteristics to optimize the accuracy of prediction of developing AKI might be an interesting option. Ultimately, the potential of new therapeutic agents can be tested and their use evaluated.
Conflict of interest statement. None declared.

References

1. Chertow GM, Burdick E, Honour M et al. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol* 2005; 16: 3365–3370

2. Uchino S, Kellum JA, Bellomo R et al. Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA* 2005; 294: 813–818

3. Bagshaw SM, George C, Bellomo R. Changes in the incidence and outcome for early acute kidney injury in a cohort of Australian intensive care units. *Crit Care* 2007; 11: R68

4. Waikar SS, Curhan GC, Wald R et al. Declining mortality in patients with acute renal failure, 1988 to 2002. *J Am Soc Nephrol* 2006; 17: 1143–1150

5. Metnitz PG, Krenn CG, Steltzer H et al. Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. *Crit Care Med* 2002; 30: 1143–1150

6. Uchino S, Bellomo R, Bagshaw SM et al. Transient azotemia is associated with a high risk of death in hospitalized patients. *Nephrol Dial Transplant* 2010; 25: 1833–1839
Biomarkers for AKI: a clinical review

7. Waiker SS, Betensky RA, Bonventre JV. Creatinine as the gold standard for kidney injury biomarker studies? Nephrol Dial Transplant 2009; 24: 3263–3265
8. Dhamdhereka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. Am J Kidney Dis 2002; 39: 221–226
9. Knight EL, Verhove JC, Spiegelman D et al. Factors influencing serum cystatin C levels other than renal function and the impact on renal function measurement. Kidney Int 2004; 65: 1416–1421
10. Okura T, Jotoku M, Irita J et al. Association between cystatin C and inflammation in patients with essential hypertension. Clin Exp Nephrol 2010; 14: 584–588
11. Fricker M, Wiesli P, Brandle M et al. Impact of thyroid dysfunction on serum cystatin C. Kidney Int 2003; 63: 1944–1947
12. Manetti L, Pordini E, Genovesi M et al. Thyroid function differently affects serum cystatin C and creatinine concentrations. J Endocrinol Invest 2005; 28: 346–349
13. Manetti L, Genovesi M, Pordini E et al. Early effects of methylprednisolone infusion on serum cystatin C in patients with severe Graves’ ophthalmopathy. Clin Chim Acta 2005; 356: 227–228
14. Keller CR, Odden MC, Fried LF et al. Kidney function and markers of inflammation in elderly persons without chronic kidney disease: the health, aging, and body composition study. Kidney Int 2007; 71: 239–244
15. Kos J, Stabuc B, Cimerman N et al. Serum cystatin C, a new marker of glomerular filtration rate, is increased during malignant progression. Clin Chem 1998; 44: 2556–2557
16. Nejat M, Pickering JW, Walker RJ et al. Rapid detection of acute kidney injury by plasma cystatin C in the intensive care unit. Nephrol Dial Transplant 2010; 25: 3283–3289
17. Herget-Rosenthal S, Marggraf G, Husing J et al. Early detection of acute renal failure by serum cystatin C. Kidney Int 2004; 66: 1115–1122
18. Royakkers AA, Korevaar JC, van Suijlen JD et al. Serum and urine cystatin C are poor biomarkers for acute kidney injury and renal replacement therapy. Intensive Care Med 2011; 37: 493–501
19. Metzger J, Kirsch T, Schiffer E et al. Urinary excretion of twenty peptides forms an early and accurate diagnostic pattern of acute kidney injury. Kidney Int 2010; 78: 1252–1262
20. Aa Haase-Fieltz A, Bellomo R, Devarajan P et al. Novel and conventional serum biomarkers predicting acute kidney injury in adult cardiac surgery—a prospective cohort study. Crit Care Med 2009; 37: 553–560
21. Koyner JL, Bennett MR, Worcester EM et al. Urinary cystatin C as an early biomarker of acute kidney injury following adult cardiothoracic surgery. Kidney Int 2008; 74: 1059–1069
22. Borregaard N, Sehested M, Nielsen BS et al. Biosynthesis of granule proteins in normal human bone marrow cells. Gelatinase is a marker of terminal neutrophil differentiation. Blood 1995; 85: 812–817
23. Cowland JB, Borregaard N. Molecular characterization and pattern of tissue expression of the gene for neutrophil gelatinase-associated lipocalin from humans. Genomics 1997; 45: 17–23
24. Friedl A, Stoez SP, Buckley P et al. Neutrophil gelatinase-associated lipocalin in normal and neoplastic human tissues. Cell type-specific pattern of expression. Histochem J 1999; 31: 433–441
25. Flo TH, Smith KD, Sato S et al. Lipocalin 2 mediates an innate immune response to bacterial infection by sequestering iron. Nature 2004; 432: 917–921
26. Goetz DH, Holmes MA, Borregaard N et al. The neutrophil lipocalin NGAL is a bacteriostatic agent that interferes with siderophore-mediated iron acquisition. Mol Cell 2002; 10: 1033–1043
27. Yang J, Goetz D, Li JY et al. An iron delivery pathway mediated by a lipocalin. Mole Cell 2002; 10: 1045–1056
28. Mishra J, Mori K, Ma Q et al. Amelioration of ischemic acute renal injury by neutrophil gelatinase-associated lipocalin. J Am Soc Nephrol 2004; 15: 3073–3082
29. Fjaertoft G, Foucard T, Xu S et al. Human neutrophil lipocalin (HNL) as a diagnostic tool in children with acute infections: a study of the kinetics. Acta Paediatr 2005; 94: 661–666
30. Nielsen BS, Borregaard N, Bundgaard JR et al. Induction of NGAL synthesis in epithelial cells of human colorectal neoplasia and inflammatory bowel diseases. Gut 1996; 38: 414–420
31. Shapiro N, Trzeck G, Hollander J et al. A prospective, multicenter derivation of a biomarker panel to assess risk of organ dysfunction, shock, and death in emergency department patients with suspected sepsis. Crit Care Med 2009; 37: 96–104
32. Xu SY, Pauksen K, Venge P. Serum measurements of human neutrophil lipocalin (HNL) discriminate between acute bacterial and viral infections. Scand J Clin Lab Invest 1995; 55: 125–131
33. Mori K, Lee HT, Rappoport D et al. Endocytic delivery of lipocalin-siderophore-iron complex resolves the kidney from ischemia-reperfusion injury. J Clin Invest 2005; 115: 610–621
34. Hvidberg V, Jacobsen C, Strong RK et al. The endocytic receptor megalin binds the iron transporting neutrophil-gelatinase-associated lipocalin with high affinity and mediates its cellular uptake. FEBS Lett 2005; 579: 773–777
35. Schmidt-Ott KM, Mori K, Kalenda G et al. Neutrophil gelatinase-associated lipocalin-mediated iron traffic in kidney epithelia. Curr Opin Nephrol Hypertens 2006; 15: 442–449
36. Schmidt-Ott KM, Mori K, Li JY et al. Dual action of neutrophil gelatinase-associated lipocalin. J Am Soc Nephrol 2007; 18: 407–413
37. Siew ED, Ware LB, Grebeshadk T et al. Urine neutrophil gelatinase-associated lipocalin moderately predicts acute kidney injury in critically ill adults. J Am Soc Nephrol 2009; 20: 1823–1832
38. Cruz DN, Le Cal M, Garzotto F et al. Plasma neutrophil gelatinase-associated lipocalin is an early biomarker for acute kidney injury in an adult ICU population. Intensive Care Med 2010; 36: 444–451
39. de Geus HR, Bakker J, Sartafre EM et al. Neutrophil gelatinase-associated lipocalin at ICU admission predicts for acute kidney injury in adult patients. Am J Respir Crit Care Med 2011; 183: 907–914
40. MacLennan J, Bell M, Oldner A et al. Neutrophil gelatinase-associated lipocalin in adult septic patients with and without acute kidney injury. Intensive Care Med 2010; 36: 1333–1340
41. Bagshaw SM, Bennett M, Haase M et al. Plasma and urine neutrophil gelatinase-associated lipocalin in septic versus non-septic acute kidney injury in critical illness. Intensive Care Med 2010; 36: 452–461
42. Koyner JL, Vaidya VS, Bennett MR et al. Urinary biomarkers in the clinical prognosis and early detection of acute kidney injury. Clin J Am Soc Nephrol 2010; 5: 2154–2165
43. McLlroy DR, Wagener G, Lee HT. Neutrophil gelatinase-associated lipocalin and acute kidney injury after cardiac surgery: the effect of baseline renal function on diagnostic performance. Clin J Am Soc Nephrol 2010; 5: 211–219
44. Tuladhar SM, Puntmann VO, Soni M et al. Rapid detection of acute kidney injury by plasma and urinary neutrophil gelatinase-associated lipocalin after cardiopulmonary bypass. J Cardiovasc Pharmacol 2009; 53: 261–266
45. Perry TE, Muellechegel JD, Liu KY et al. Plasma neutrophil gelatinase-associated lipocalin and acute postoperative kidney injury in adult cardiac surgical patients. Anesth Analg 2010; 110: 1541–1547
46. Wagener G, Gubitosi G, Wang S et al. Urinary neutrophil gelatinase-associated lipocalin and acute kidney injury after cardiac surgery. Am J Kidney Dis 2008; 52: 425–433
47. Liangos O, Tighiouart H, Perianayagam MC et al. Comparative analysis of urinary biomarkers for early detection of acute
kidney injury following cardiopulmonary bypass. Biomarkers 2009; 14: 423–431

48. Endre ZH, Pickering JW, Walker RJ et al. Improved performance of urinary biomarkers of acute kidney injury in the critically ill by stratification for injury duration and baseline renal function. Kidney Int 2011; 79: 1119–1130

49. Hoase M, Bellomo R, Devarajan P et al. Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis 2009; 54: 1012–1024

50. Ichimura T, Asseldonk EJ, Humphreys BD et al. Kidney injury molecule-1 is a phosphatidylserine receptor that confers a phagocytic phenotype on epithelial cells. J Clin Invest 2008; 118: 1657–1668

51. Bailly V, Zhang Z, Meier W et al. Shedding of kidney injury molecule-1, a putative adhesion protein involved in renal regeneration. J Biol Chem 2002; 277: 39739–39748

52. Bonventre JV. Kidney injury molecule-1 (KIM-1): a urinary biomarker and much more. Nephrol Dial Transplant 2009; 24: 3265–3268

53. Waanders F, Vaidya VS, van Goor H et al. Effect of renin-angiotensin-aldosterone system inhibition, dietary sodium restriction, and/or diuretics on urinary kidney injury molecule-1 excretion in non-diabetic proteinuric kidney disease: a post hoc analysis of a randomized controlled trial. Am J Kidney Dis 2009; 53: 16–25

54. Waanders F, van Timmeren MM, Stegeman CA et al. Kidney injury molecule-1 in renal disease. J Pathol 2010; 220: 7–16

55. Han WK, Waikar SS, Johnson A et al. Urinary biomarkers in the early diagnosis of acute kidney injury. Kidney Int 2008; 73: 863–869

56. Vaidya VS, Waiker SS, Ferguson MA et al. Urinary biomarkers for sensitive and specific detection of acute kidney injury in humans. Clin Transl Sci 2008; 1: 200–208

57. Liang XL, Liu SX, Chen YH et al. Combination of urinary kidney injury molecule-1 and interleukin-18 as early biomarker for the diagnosis and progressive assessment of acute kidney injury following cardiopulmonary bypass surgery: a prospective nested case-control study. Biomarkers 2010; 15: 332–339

58. Ferguson MA, Vaidya VS, Waiker SS et al. Urinary liver-type fatty acid-binding protein predicts adverse outcomes in acute kidney injury. Kidney Int 2010; 77: 708–714

59. Oyama Y, Takeda T, Hama H et al. Evidence for megalin-mediated proximal tubular uptake of L-FABP, a carrier of potentially nephrotoxic molecules. Lab Invest 2005; 85: 522–531

60. Yamamoto T, Noiri E, Ono Y et al. Renal L-type fatty acid-binding protein in acute ischemic injury. J Am Soc Nephrol 2007; 18: 2894–2902

61. Matsui K, Kamijo-Ikemori A, Hara M et al. Clinical significance of tubular and podocyte biomarkers in acute kidney injury. Clin Exp Nephrol 2011; 15: 220–225

62. Siew ED, Ikizler TA, Gebretsadik T et al. Elevated urinary IL-18 levels at the time of ICU admission predict adverse clinical outcomes. Clin J Am Soc Nephrol 2010; 5: 1497–1505

63. Parikh CR, Abraham E, Ancukiewicz M et al. Urine IL-18 is an early diagnostic marker for acute kidney injury and predicts mortality in the intensive care unit. J Am Soc Nephrol 2005; 16: 3046–3052

64. Herget-Rosenthal S, van Wijk JA, Brocker-Preuss M et al. Increased urinary cystatin C reflects structural and functional renal tubular impairment independent of glomerular filtration rate. Clin Biochem 2007; 40: 946–951

65. Nejat M, Hill JV, Pickering JW et al. Albuminuria increases cystatin C excretion: implications for urinary biomarkers. Nephrol Dial Transplant 2011; doi: 10.1093/ndt/gfr222

66. Nejat M, Pickering JW, Walker RJ et al. Urinary cystatin C is diagnostic of acute kidney injury and sepsis, and predicts mortality in the intensive care unit. Crit Care 2010; 14: R85

67. Harrison DJ, Kharbanda R, Cunningham DS et al. Distribution of glutathione S-transferase isoenzymes in human kidney: basis for possible markers of renal injury. J Clin Pathol 1989; 42: 624–628

68. Westhuyzen J, Endre ZH, Reece G et al. Measurement of tubular enzymuria facilitates early detection of acute renal impairment in the intensive care unit. Nephrol Dial Transplant 2003; 18: 543–551

69. Walshe CM, Odejayi F, Ng S et al. Urinary glutathione S-transferase as an early marker for renal dysfunction in patients admitted to intensive care with sepsis. Crit Care Resusc 2009; 11: 204–209

70. Lameire NH, Vanholder RC, Van Biesen WA. How to use biomarkers efficiently in acute kidney injury. Kidney Int 2011; 79: 1047–1050

71. De Geus H, Le Noble J, Zijlstra F et al. Early predictive value of neutrophil gelatinase-associated lipocalin in adult ICU patients with acute kidney injury. Crit Care Med 2009; P255. Abstract

72. Endre ZH, Walker RJ, Pickering JW et al. Early intervention with erythropoietin does not affect the outcome of acute kidney injury (the EARLYARF trial). Kidney Int 2010; 77: 1020–1030

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