Recommendations on Acute Kidney Injury Biomarkers
From the Acute Disease Quality Initiative Consensus Conference
A Consensus Statement

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Abstract

IMPORTANCE In the last decade, new biomarkers for acute kidney injury (AKI) have been identified and studied in clinical trials. Guidance is needed regarding how best to incorporate them into clinical practice.

OBJECTIVE To develop recommendations on AKI biomarkers based on existing data and expert consensus for practicing clinicians and researchers.

EVIDENCE REVIEW At the 23rd Acute Disease Quality Initiative meeting, a meeting of 23 international experts in critical care, nephrology, and related specialties, the panel focused on 4 broad areas, as follows: (1) AKI risk assessment; (2) AKI prediction and prevention; (3) AKI diagnosis, etiology, and management; and (4) AKI progression and kidney recovery. A literature search revealed more than 65,000 articles published between 1965 and May 2019. In a modified Delphi process, recommendations and consensus statements were developed based on existing data, with 90% agreement among panel members required for final adoption. Recommendations were graded using the Grading of Recommendations, Assessment, Development and Evaluations system.

FINDINGS The panel developed 11 consensus statements for biomarker use and 14 research recommendations. The key suggestions were that a combination of damage and functional biomarkers, along with clinical information, be used to identify high-risk patient groups, improve the diagnostic accuracy of AKI, improve processes of care, and assist the management of AKI.

CONCLUSIONS AND RELEVANCE Current evidence from clinical studies supports the use of new biomarkers in prevention and management of AKI. Substantial gaps in knowledge remain, and more research is necessary.

Introduction

Acute kidney injury (AKI) is common in hospitalized adults and children and associated with serious complications and high health care costs. Traditionally, 2 functional biomarkers, serum creatinine (sCr) and urine output, are used to define AKI, but these markers are limited by delayed changes following kidney injury and have low sensitivity and specificity. Several novel biomarkers have been shown to detect AKI earlier and are more sensitive than sCr (Table). For any prevention strategies
Table. Description and Characteristics of Common Biomarkers of AKI

<table>
<thead>
<tr>
<th>AKI biomarker</th>
<th>Biological role</th>
<th>Source</th>
<th>Stress marker</th>
<th>Damage marker</th>
<th>Functional marker</th>
<th>Potential role in clinical practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine aminopeptidase; alkaline phosphatase; γ-glutamyl transpeptidase</td>
<td>Enzymes located on the brush border villi of the proximal tubular cells; released into urine after tubular damage</td>
<td>Coca et al., 2008</td>
<td>Urine</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Calprotectin</td>
<td>Cytosolic calcium-binding complex; derived from neutrophils and monocytes; detectable in urine in intrinsic AKI</td>
<td>Charlton et al., 2014; Heller et al., 2011</td>
<td>Urine</td>
<td>X</td>
<td></td>
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<tr>
<td>C-C motif chemokine ligand 14</td>
<td>Pro-inflammatory chemokine; released into urine following stress or damage of tubular cells</td>
<td>Hoste et al., 2020</td>
<td>Urine</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystatin C</td>
<td>13 kDa cysteine protease inhibitor produced by nucleated human cells; freely filtered</td>
<td>Coca et al., 2008; Ho et al., 2015; Ravn et al., 2019</td>
<td>Plasma</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Dickkopf-3</td>
<td>38 kDa stress-induced, kidney tubular epithelia-derived glycoprotein; secreted into urine under tubular stress conditions</td>
<td>Schunk et al., 2019</td>
<td>Urine</td>
<td>X</td>
<td>X</td>
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<tr>
<td>α glutathione S-transferase</td>
<td>Cytoplasmic enzyme in proximal tubule</td>
<td>Koyner et al., 2010</td>
<td>Urine</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β glutathione S-transferase</td>
<td>Cytoplasmic enzyme in distal tubules</td>
<td>Coca et al., 2008; Charlton et al., 2014</td>
<td>Urine</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocyte growth factor</td>
<td>Anti-fibrotic cytokine produced by mesenchymal cells and involved in tubular cell regeneration after AKI</td>
<td>Heller et al., 2011; Vaidya et al., 2008</td>
<td>Plasma</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Hepcidin</td>
<td>2.78 kDa peptide hormone predominantly produced in hepatocytes; freely filtered</td>
<td>Ho et al., 2015</td>
<td>Urine and plasma</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Tissue metalloproteinase-2; insulin-like growth factor binding protein-7</td>
<td>Metalloproteinases released during cell cycle arrest</td>
<td>Kashani et al., 2013; Ostermann et al., 2018; Joannidis et al., 2019</td>
<td>Urine</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Interleukin-18</td>
<td>18 kDa pro-inflammatory cytokine; released into urine following tubular damage</td>
<td>Coca et al., 2008; Ho et al., 2015</td>
<td>Urine</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Kidney injury molecule-1</td>
<td>Transmembrane glycoprotein produced by proximal tubular cell; released into urine after tubular damage</td>
<td>Coca et al., 2008; Ho et al., 2015; Koyner et al., 2010</td>
<td>Urine</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Liver-type fatty acid-binding protein</td>
<td>14 kDa intracellular lipid chaperone; freely filtered and reabsorbed in proximal tubule; urinary excretion after tubular cell damage</td>
<td>Ho et al., 2015</td>
<td>Urine and plasma</td>
<td>X</td>
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<tr>
<td>MicroRNA</td>
<td>Endogenous single-stranded non-coding nucleotides; &gt;50 individual microRNAs are expressed in AKI, especially in association with inflammation, apoptosis and fibrosis</td>
<td>Fan et al., 2019</td>
<td>Urine and plasma</td>
<td>X</td>
<td></td>
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<tr>
<td>Monocyte chemoattractant peptide-1</td>
<td>Peptide expressed in tubular epithelial cells, kidney mesangial cells and podocytes; released into urine</td>
<td>Moledina et al., 2017</td>
<td>Urine</td>
<td>X</td>
<td></td>
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<tr>
<td>N-acetyl-B-D-glucosaminidase</td>
<td>&gt;130 kDa lysosomal enzyme; released into urine after tubular damage</td>
<td>Charlton et al., 2014</td>
<td>Urine</td>
<td>X</td>
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<tr>
<td>Neutrophil gelatinase-associated lipocalin</td>
<td>At least 3 different types: (1) monomeric 25 kDa glycoprotein produced by neutrophils and epithelial tissues, including tubular cells; (2) homodimeric 45 kDa protein produced by neutrophils; (3) heterodimeric 135 kDa protein produced by tubular cells</td>
<td>Coca et al., 2008; Ho et al., 2015; Charlton et al., 2014</td>
<td>Urine and plasma</td>
<td>X</td>
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(continued)
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<tr>
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<th>Damage marker</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Netrin-1</td>
<td>50–75 kDa laminin-related molecule minimally expressed in proximal tubular cells of normal kidneys; released into urine after tubular cell damage</td>
<td>Ramesh et al, 2010</td>
<td>Urine</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Osteopontin</td>
<td>Glycoprotein expressed in tubular cells and interstitial infiltrating cells in areas of tubulointerstitial damage</td>
<td>Lorenzen et al, 2011</td>
<td>Plasma</td>
<td></td>
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<td>X X</td>
</tr>
<tr>
<td>Proenkephalin A</td>
<td>Endogenous polypeptide hormone in adrenal medulla, nervous system, immune system and renal tissue; freely filtered</td>
<td>Legrand et al, 2019</td>
<td>Plasma</td>
<td></td>
<td></td>
<td>X X X</td>
</tr>
<tr>
<td>Retinol binding protein</td>
<td>21 kDa glycoprotein; synthesized by liver; filtered by glomeruli and reabsorbed by proximal tubules; released into urine following tubular damage</td>
<td>Charlton et al, 2014</td>
<td>Plasma</td>
<td></td>
<td></td>
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<tr>
<td>Tumor necrosis factor</td>
<td>Pro-inflammatory cytokine; released after tubular damage</td>
<td>Ho et al, 2015</td>
<td>Plasma</td>
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<td>X</td>
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</tbody>
</table>

Abbreviation: AKI, acute kidney injury.

* Stress markers indicate cell stress; cell stress can resolve or progress to damage or alter kidney function.

* Damage markers indicate structural damage that may or may not be associated with reduced kidney function. These molecules include constitutive proteins released by the damaged kidney, molecules upregulated in response to injury, or nonkidney tissue products that are filtered, reabsorbed, or secreted by the kidney.

* Functional markers reflect changes in glomerular filtration.
to be effective, patients with high risk need to be identified before kidney insults result in kidney damage, and AKI needs to be diagnosed as early as possible.

In 2011, the 10th Acute Disease Quality Initiative (ADQI) meeting focused on AKI biomarkers and their application in clinical practice. The expert committee concluded that the evidence for AKI biomarkers was limited and insufficient for recommendations and that more research and strategies toward the adoption of biomarkers in clinical practice were needed. Subsequently, new AKI biomarkers have been discovered, clinical trials have been completed, and some biomarkers have gained official regulatory approval. In 2019, an ADQI meeting was called to review this new evidence and to develop recommendations regarding AKI risk assessment, prediction, prevention, diagnosis, management, and kidney recovery for practicing clinicians and researchers.

Methods

The 23rd ADQI consensus meeting followed established ADQI methods to provide statements based on existing evidence and professional judgement and to identify clinical research priorities. The consensus process incorporated a multistep modified Delphi method. In early 2019, the steering group identified 4 broad topics (eTable 1 in the Supplement) and invited a 23-expert panel, representing nephrology, critical care medicine, surgery, anesthesia, pediatrics, clinical biochemistry, and pharmacy. The project followed the ADQI methods as outlined in the this section. The article summarizes the conclusions of an international expert panel. The conclusions are based on the existing evidence in the literature. Therefore, institutional approval was not required. All panelists consented to their inclusion in this article. This report followed the Standards for Quality Improvement Reporting Excellence (SQUIRE) reporting guideline.

The working groups determined the key questions and identified relevant literature by searching PubMed, MEDLINE, Embase, the Cochrane Library, ClinicalTrials.gov, and Cochrane Controlled Trials Register, using the terms acute kidney injury or AKI and biomarker, combined with risk, diagnosis, etiology, prevention, management, prediction, or prognosis. Because of the volume of retrieved literature (>65,000 articles), representative publications were selected (eTable 2 in the Supplement). Articles were eligible if they were prospective or retrospective cohort studies, case-control studies, randomized clinical trials, or systematic reviews evaluating the role of serum or urinary biomarkers for AKI. Each working group drafted recommendations and consensus statements. Recommendations were graded based on the Grading of Recommendations Assessment, Development, and Evaluation system (eTable 3 in the Supplement). At a face-to-face meeting of all 23 panelists in Padova, Italy, from May 30 to June 2, 2019, each group presented their statements and recommendations. Panel members discussed the statements until agreement was reached regarding whether to retain, modify, or eliminate them. Only panelists who attended the face-to-face meeting participated in the discussion and final approval. Statements required 90% agreement from the panel to be included in the final document. The contributions of all groups were merged and reconciled by the steering group. The final document was approved by all panelists. Here, we report the conclusions.

Results

Biomarkers for AKI Risk Assessment

AKI is often already established when patients present with acute illness. Clearly, the implementation of primary prevention is not possible in these cases. However, situations in which elective clinical interventions or exposures place patients at risk of AKI provide opportunities to modify factors that contribute to AKI development and progression.
Consensus Statement 1
The decision to perform a Kidney Health Assessment (KHA) to gauge AKI susceptibility should integrate patient factors, including demographic characteristics, comorbidities, and previous AKI episodes with the expected intensity of a planned exposure that carries AKI risk. This recommendation received a grade of B, strong.

Predisposing factors, susceptibility, and intensity of precipitating factors determine the risk of AKI. The ADQI 22 working group developed a flow diagram outlining KHA of AKI susceptibility, which incorporates previous AKI history, blood pressure, chronic kidney disease (CKD) and drugs and/or dipstick (eFigure 1 in the Supplement). Two elective exposures that carry a particularly high AKI risk are major surgery and nephrotoxic medications.

Consensus Statement 2
The types of functional and/or damage biomarker evaluation to be performed should be driven by the results of the KHA for AKI susceptibility. This recommendation received a grade of B, strong.

The KHA for AKI susceptibility (eFigure 1 in the Supplement) includes the assessment of CKD/creatinine and dipstick (ie, proteinuria/albuminuria) both before and after a planned exposure associated with AKI risk. Traditional measures of kidney function include scCr, creatinine-based estimated glomerular filtration rate (eGFR) equations, serum cystatin C, cystatin plus creatinine-based eGFR equations, and selective techniques to measure GFR in high-risk patients. Kidney damage can be assessed by estimating or measuring urinary protein excretion.

New biomarkers and techniques are emerging that may allow better prediction of AKI risk. A study of 733 patients who underwent cardiac surgery demonstrated that the preoperative urinary concentration of dickkopf-3, a urinary cytokine and tubular stress biomarker, predicted the development of postoperative AKI and kidney function loss with an area under the receiver operating characteristic curve (AUROC) of 0.78.

Consensus Statement 3
We suggest that biomarkers of acute damage are not interpretable prior to a kidney insult and should not be used for AKI risk assessment. This recommendation received a grade of A, strong.

It is unlikely that patients scheduled to undergo nephrotoxic exposures or elective surgery in stable conditions will meet the criteria for kidney stress or acute damage to be predictive of subsequent AKI. However, future AKI biomarkers in patients with specific clinical risk stratification may help to detect those at risk of kidney complications after exposure. It is also plausible that markers of kidney fitness may be discovered, including in patients with normal GFR.

Biomarkers for AKI Prediction and Prevention
AKI affects approximately 15% of hospital admissions. Management is mainly focused on prevention and supportive care. In certain clinical settings, 20% to 30% of AKI cases are considered preventable.

Consensus Statement 4
We recommend using validated biomarkers to identify patient populations for whom preventive interventions have been shown to improve outcomes. This recommendation received a grade of A, strong.

The performance of current prediction models to identify patients at risk of AKI is variable. The negative predictive value is generally good, but the positive predictive value of most models is moderate to low. In susceptible patients exposed to injurious events, validated biomarkers can predict the development or progression of AKI and may provide opportunities for intervention. Trials have demonstrated that timely initiation of preventive strategies in patients with positive stress biomarkers after a kidney insult, ie, tissue inhibitor of metalloproteinases 2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) were
effective at preventing AKI. The patients in the Prevention of AKI trial were randomized based on patients who had an urinary concentration of TIMP-2 × IGFBP7 of at least 0.3 (ng/mL)³/1000 after cardiac surgery to protocolized vs standard care. At 72 hours, there was a 17% reduction in AKI. A similar approach was followed in the Biomarker-Guided Intervention to Prevent Acute Kidney Injury After Major Surgery study. Patients undergoing major abdominal surgery were randomized to intervention vs standard care. There was a 13% reduction in AKI stages 2 and 3. Similarly, the implementation of a nephrology rapid response team that used TIMP-2 × IGFBP7 monitoring to identify at-risk patients for preventative Kidney Disease Improving Global Outcomes (KDIGO) strategies reduced the need for kidney replacement therapy (KRT).

The use of functional biomarkers may also optimize drug dosing. For decades, sCr has been used for this purpose. However, the use of sCr or any sCr-based estimate requires kidney function to be at a steady state. Cystatin C is less reliant on muscle mass and dietary intake and offers an alternative approach to estimate GFR. Reports indicate that in a steady state, eGFR estimated by creatinine–cystatin C is more precise and accurate at determining a measured GFR than eGFR estimated by creatinine or cystatin C alone. The use of CKD Epidemiology Collaboration (CKD-EPI) eGFR including creatinine and cystatin C in a vancomycin dosing algorithm improved the achievement of target vancomycin trough concentrations by 22% compared with historical controls using CKD-EPI eGFR estimated with creatinine alone. For life-saving drugs with potential nephrotoxic effects, the concomitant use of functional and damage biomarkers has the potential to provide important information to gauge dosing and duration of treatment and to prevent AKI.

Consensus Statement 5
We suggest combining clinical assessment and validated biomarkers to triage patients and optimize the timing and type of interventions designed to improve processes of care and patient outcomes. This recommendation received a grade of C, strong.

Combining the clinical assessment and traditional tests with new AKI biomarkers provides information that may change processes of care and guide therapy. Negative results can be valuable, too. For instance, critically ill patients with oliguria and urinary TIMP-2 × IGFBP7 of less than 0.3 (ng/mL)³/1000 do not have an increased risk of progressing to more severe AKI. Repeated biomarker testing may be relevant, too, depending on the change in patient risk profile.

Biomarkers for AKI Diagnosis, Etiology, and Management
There is a persistent unmet need for an earlier identification of patients with AKI. Furthermore, diagnostic tools that identify the location, mechanism, etiology, severity, and prognosis of AKI are necessary.

Consensus Statement 6
We suggest that a combination of damage and functional biomarkers, along with clinical information, be used to improve the diagnostic accuracy of AKI, to recognize the different pathophysiological processes, to discriminate AKI etiology, and to assess AKI severity. This recommendation received a grade of B, conditional.

The discovery of specific biomarkers of kidney injury has enabled a more precise delineation of the pathophysiology, site, mechanisms, and severity of injury (Table). Some patients with positive damage biomarkers do not fulfill traditional AKI criteria yet have worse outcomes. We propose that clinical information enriched by damage and functional biomarkers could lead to more sensitive AKI definitions. We therefore suggest a modification of KDIGO stage 1 AKI to reflect 3 substages (ie, 1S, 1A, and 1B) and to subcategorize stages 2 and 3 AKI by presence of biomarkers (Figure 1 and Figure 2). Stage 1S identifies an early stage when there is evidence of kidney injury that is not detected by creatinine and urine output criteria. For example, in 345 children undergoing cardiopulmonary bypass, the combination of functional (cystatin C) and damage (neutrophil gelatinase-associated lipocalin [NGAL]) biomarkers was superior to sCr in predicting the severity and
Recent studies have shown that increased urine NGAL (uNGAL) concentrations without increased sCr levels have a four-fold increased risk of all-stage AKI on day 3 compared with those without an uNGAL and sCr increase (uNGAL negative and sCr negative). Similarly, compared with patients who had no increase in uNGAL concentrations but...
an increase in sCr levels, patients who had uNGAL and sCr increases had a 12-fold increased risk of AKI stage 2 or 3 on day 3.

TIMP-2 and IGFBP7 have also been shown to improve risk stratification in critically ill patients with AKI stage 1.14 Evaluation of longer-term outcomes demonstrated that the associated risks of TIMP-2 × IGFBP7 of greater than 2.0 (ng/mL)^2/1000 were equivalent to AKI progression even in instances in which no progression from AKI stage 1 was seen based on sCr and urine output. The ability to recognize the various pathophysiological processes mediating AKI will likely be critical in developing targeted therapies and designing pharmacological trials.38,66

Consensus Statement 7

We suggest that a combination of biomarkers may assist the planning of therapy and management of AKI. This recommendation received a grade of C, conditional.

Uncertainty regarding when kidney injury actually occurred is common. Biomarkers may be able to provide guidance in determining the onset and presence of kidney damage so that potential therapies can be initiated before the injury becomes irreversible67 (eFigure 2 in the Supplement). Multiple biomarkers have the potential to shed light on the pathophysiology and provide an early detection system superior to creatinine.36,68

Biomarker-guided algorithms and goal-directed management protocols appear to provide benefit in preventing and/or mitigating AKI.21,22,56,69,70 For instance, if biomarkers indicate kidney stress before permanent damage occurs, there is the possibility of reversing AKI21,22 (eFigure 2 in the Supplement). Consequently, embedding biomarkers within goal-directed management protocols has the potential to affect AKI recovery.70

Consensus Statement 8

Inclusion of biomarker data with clinical assessments can be used to identify patients who will need KRT and facilitate optimal timing of KRT initiation. The recommendation received a grade of C, conditional.

Currently, the decision to start KRT is based on clinical judgement and conventional criteria. Several studies have evaluated different biomarkers in predicting the need for KRT with variable results.34 In a meta-analysis of more than 15 000 patients,34 the pooled AUROCs for urine and blood NGAL for prediction of KRT were 0.72 (95% CI, 0.64-0.80) and 0.76 (95% CI, 0.71-0.80), respectively, while sCr and cystatin C had pooled AUROCs of 0.76 (95% CI, 0.73-0.80) and 0.77 (95% CI, 0.73-0.81), respectively. Urine biomarkers interleukin-18, cystatin C, and TIMP-2 × IGFBP7 showed pooled AUROCs of 0.67 (95% CI, 0.61-0.73), 0.72 (95% CI, 0.58-0.87), and 0.86 (95% CI, 0.79-0.93), respectively.34 Some limitations for biomarker-based predictions are the variable cutoffs, the reliance on single measurements, and confounding by underlying comorbidities and clinical conditions.

The furosemide stress test (FST) has been proposed as a means to predict the need for KRT after kidney transplantation and in patients with AKI.71,72 Clinical risk scores predicting KRT are available for specific situations, i.e., after cardiac surgery, but biomarkers of kidney damage have not been incorporated. In patients receiving mechanical ventilation, sCr combined with normalized urine NGAL (nuNGAL) and serum cystatin C combined with either nuNGAL or uNGAL were found to be the best predictors for KRT initiation (AUROC = 0.80).40 Among patients without AKI on intensive care unit admission, the combination of serum cystatin C and Acute Physiology and Chronic Health Evaluation score performed best (AUROC = 0.78). In 2 randomized clinical trials, plasma NGAL failed to enrich the prediction for early KRT initiation.46,73 Future studies should incorporate sequential assessments of both functional and damage biomarkers in patients identified as having high risk for needing KRT based on clinical risk scores.

Most studies evaluating the role of biomarkers to guide KRT discontinuation have relied on urine output, urinary Cr, or urea clearance.74 The FST has also been shown to predict discontinuation of KRT (AUROC = 0.84).75 An observational study33 explored the role of serum cystatin C and NGAL in
110 patients at the time of cessation of continuous renal replacement therapy (CRRT). Patients who successfully discontinued CRRT had lower serum cystatin C levels and higher urine output at CRRT cessation than those who had to restart KRT. However, sCr and NGAL levels were not significantly lower in the group that recovered compared with patients in whom CRRT was restarted. Another study of 110 critically ill patients on CRRT showed that serum NGAL was predictive of successful discontinuation of CRRT in patients with AKI but no sepsis whereas urine output was a significant predictor in patients with AKI with sepsis. Collective data suggest that there is currently limited evidence to support the use of any individual biomarker for predicting successful KRT cessation.

**Biomarkers to Assess AKI Progression and Kidney Recovery**

Studies have found that complete and sustained reversal of AKI episodes within 48 to 72 hours of onset was associated with better outcomes than persistent AKI; however, different definitions for persistent AKI were applied. Thus the ADQI 16 working group proposed defining persistent AKI as AKI that lasts more than 48 hours and recommended the use of biomarkers to risk stratify patients for whom additional workup and evaluation might be warranted.

**Consensus Statement 9**

We suggest that novel biomarkers can be used for prediction of duration and recovery of AKI. This recommendation received a grade of C, weak.

Among patients with community-acquired pneumonia enrolled in the Genetic and Inflammatory Markers of Sepsis cohort, the predictive value of plasma NGAL concentrations on day 1 on kidney recovery was investigated in 181 patients with severe AKI. Recovery was defined as being alive and not requiring KRT at hospital discharge. Plasma NGAL alone predicted nonrecovery of kidney function (AUROC = 0.74). However, when compared with a clinical model, plasma NGAL did not augment risk prediction.

The performance of plasma proenkephalin-A was evaluated in 956 patients with sepsis who were enrolled in the multicenter Albumin Italian Outcome Sepsis trial. Among the subgroup of 255 patients with a sCr level of 2.0mg/dL (to convert to millimoles per liter, multiply by 88.4) on the first day, 31% had an improvement in kidney function within 48 hours. Median (interquartile range) sCr level on day 1 was significantly lower in patients who recovered kidney function within 48 hours compared with those who did not recover (2.9 [2.5-3.3] mg/dL vs 3.2 [2.6-4.2] mg/dL; P = .006). Their median (interquartile range) day 1 plasma proenkephalin-A concentration was also significantly lower (137 [89-188] pmol/L) compared with patients without kidney recovery (226 [145-352] pmol/L). A study in patients with septic AKI showed significantly higher proenkephalin-A concentrations in patients with major adverse kidney events, patients with persistent AKI, and those who had worsening of kidney function. The increase in proenkephalin-A concentrations preceded elevation of sCr levels in patients with worsening kidney function. A 2020 study of 331 critically ill patients with AKI stage 2 or 3 demonstrated that urinary C-C motif chemokine ligand 14 was predictive of persistent AKI. Finally, in 733 patients undergoing cardiac surgery, preoperative ratio of urinary dickkopf-3 to creatinine concentrations greater than 471 pg/mg was associated with a significantly higher risk of persistent kidney dysfunction (odds ratio, 6.67; 95% CI, 1.67-26.61; P = .007) and dialysis dependency (odds ratio, 13.57; 95% CI, 1.50-122.77; P = .02) after 90 days compared with a ratio of 471 pg/mg or less.

**Consensus Statement 10**

Currently there is insufficient evidence to recommend the routine use of novel biomarkers to refine acute kidney disease (AKD) staging. This recommendation received a grade of C, strong.

AKD describes acute or subacute damage and/or loss of kidney function for a duration as long as 90 days (Figure 3). To date, no study has evaluated the predictive value of novel biomarkers for AKD staging and subsequent outcomes.
Consensus Statement 11

We recommend that biomarkers predictive of CKD staging and progression be incorporated into a comprehensive post-AKI/AKD care bundle and KHA. This recommendation received a grade of C, strong.

Studies have evaluated the long-term prognostic value of biomarkers for predicting KRT dependence and death among critically ill patients with AKI. Serum creatinine has a very limited role as a biomarker for kidney function in patients receiving KRT. A study using the Biological Markers of Recovery for the kidney cohort found increased concentrations of plasma interleukin (IL)-8 and IL-18 and tumor necrosis factor receptor type 1 (TNFR-I) on day 1 were independently associated with slower kidney recovery by day 60 among critically ill patients treated with KRT. In an analysis of multiple markers simultaneously, increased IL-8 and TNFR-I in combination were associated with slower recovery and increased IL-8, migration inhibitory factor, and TNFR-I concentrations were associated with mortality. Using the same cohort, higher day 8 concentrations of plasma IL-6, IL-8, IL-18, IL-10, TNFR-I, and TNFR-II were associated with lower kidney recovery, and plasma concentrations of IL-6, IL-8, IL-10, IL-18, migration inhibitory factor, TNFR-I, and death receptor 5 were associated with mortality among patients receiving KRT.

Another study evaluated serum osteopontin, IL-6, and cystatin C for kidney recovery among 102 patients with AKI requiring KRT. Lower levels of osteopontin and IL-6 were associated with greater odds of 60-day survival with AUROC of 0.81 and 0.74, respectively. The AUROC value for predicting survival reached its highest level when all biomarkers were combined with urine output and urinary and serum sCr upon discontinuation of KRT (AUROC = 0.88).

Figure 3. Transition From Acute Kidney Injury (AKI) to Recovery, Acute Kidney Disease (AKD), or Chronic Kidney Disease (CKD)

Biomarkers of kidney damage and function can refine the prediction of rapid recovery (ie, transient AKI) or persistent AKI. AKD is assessed between 7 and 90 days after an acute event. Prior to day 7, AKI criteria may still be reached, and after 90 days, CKD criteria are applicable. Scarc e data suggest that new biomarkers of kidney damage and function can refine the prediction of poor outcomes (ie, death, chronic kidney disease) at intensive care unit discharge compared to serum creatinine. Reprinted from Acute Disease Quality Initiative 23 used with permission. ESKD indicates end-stage kidney disease.
In patients receiving KRT, a higher cystatin C value at discontinuation of KRT was independently predictive of chronic dialysis.45 Urinary concentrations of TIMP-2 × IGFBP7 of greater than 0.3 (ng/mL)^2/1000, compared with 0.3 (ng/mL)^2/1000, have also been shown to be associated with death or KRT in patients with AKI (hazard ratio, 2.16; 95% CI, 1.32-3.53).37 More recently, the FROG-ICU study evaluated the prognostic utility of different AKI biomarkers obtained at intensive care unit discharge on 1-year outcome in 1207 intensive care unit survivors.19 Of 460 patients with AKI, 58 patients (12.6%) were identified as having AKI at intensive care unit discharge. Most patients with AKI in the intensive care unit had elevated biomarkers of kidney damage at discharge even with apparent recovery based on scCr level. However, the predictive value for 1-year mortality was only modest (AUROC range, 0.61-0.70).

Discussion

We have provided recommendations for the use of AKI biomarkers in routine clinical practice. However, there are still a substantial number of knowledge gaps that need to be covered in future studies (Box).

**Box. Research Recommendations**

1. Studies need to be performed to determine whether novel AKI biomarkers offer additional benefit in assessment of AKI risk prior to a planned nephrotoxic exposure.
2. Appropriate performance of candidate biomarkers should be evaluated for optimal results of preventive measures guided by biomarkers, in particular:
   a. the role of damage biomarkers to prevent AKI after specific exposures (ie, drugs) needs further investigation;
   b. the cost-effectiveness of using biomarkers to predict and prevent AKI needs further evaluation; and
   c. the time course, cutoffs, and interactions between functional and damage biomarkers of AKI should be further assessed.
3. Studies should investigate the role of single vs serial measurements of biomarkers in the prediction of AKI and the impact of preventive measures.
4. Research is necessary to investigate the role of nonkidney biomarkers (eg, procalcitonin, natriuretic peptide, troponin) to identify patient populations at risk for AKI.
5. We suggest further research on whether a combination of validated biomarkers can help improve the detection of etiology and the management of AKI.
6. We suggest further research on how the inherent characteristics of biomarkers (including temporal patterns) affect the understanding of the process leading to AKI, its complications, and recovery.
7. Investigations should focus on determining whether a change in serum creatinine/oliguria without change of damage biomarker is associated with worse kidney and patient outcomes.
8. Investigations should focus on determining whether elevation in biomarkers without any changes in serum creatinine/oliguria is associated with worse kidney and patient outcomes.
9. The role of serial biomarker testing should be compared with real-time glomerular filtration rate measurement.
10. Future studies are needed to evaluate the combination of damage and functional biomarkers with clinical assessments to determine the risk profiles of patients who may need kidney replacement therapy.
11. Research is needed to evaluate the utility of dynamic assessment of functional and structural markers correlated with clinical data to define the optimal timing for initiating and stopping kidney replacement therapy.
12. Studies have identified a number of candidate biomarkers and diagnostics for persistent AKI and kidney recovery. We recommend prospective validation of these novel biomarkers for prediction of persistent AKI and kidney recovery. These biomarkers should also be evaluated for their ability to improve patient management alone or in combination.
13. We recommend prospective validation of candidate biomarkers for acute kidney disease staging and prognosis and to predict successful kidney replacement therapy discontinuation.
14. We recommend prospective validation of candidate biomarkers, in combination with clinical assessment tools for the prediction of chronic kidney disease staging and longer-term outcomes after AKI or acute kidney disease.

Abbreviation: AKI, acute kidney injury.
Limitations
This study has limitations. Our recommendations are based on existing evidence and consensus but we did not perform a systematic review of all individual studies. We also acknowledge that further biomarker studies are in progress or have been completed since the ADQI meeting was held and that it is possible that the results would affect our recommendations.

Conclusions
Considerable progress has been made in the field of AKI biomarkers, which has resulted in a better understanding of the pathophysiology of AKI and improved outcomes with biomarker-guided management. Our consensus recommendations based on existing data aim to assist clinicians at the bedside. We acknowledge that the current literature contains some bias and limitations, and further research is needed. However, the prospect of clearer identification of high-risk patients and different AKI subphenotypes and the integration of appropriately selected biomarkers in routine clinical practice hold the key to further improvement in AKI care.
Author Contributions: Drs Ostermann and Zarbock had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Ostermann and Zarbock are co-first authors. Drs Kellum and Ronco are co-senior authors.

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Obtained funding: Zarbock, Mehta, Kellum.

Administrative, technical, or material support: Ostermann, Zarbock, Macedo, Bell, Forni, Guzzi, Murray, Rimmelé, Rosner, Shaw, Kellum.

Supervision: Ostermann, Zarbock, Goldstein, Murugan, Bell, Mehta, Murray, Rosner, Shaw, Ronco.

Conflict of Interest Disclosures: Dr Ostermann reported receiving grants from BioMerieux, Baxter, and BioPorto and speaker honoraria from BioMerieux outside the submitted work. Dr Zarbock reported receiving grants and personal fees from Baxter, Astute Medical, and Fresenius; grants from Astellas, Deutsche Forschungsgesellschaft, Bundesministerium fuer Bildung und Forschung, and Else Kriener-Fresenius-Stiftung; and personal fees from Amomed, Ratiopharm, BioMerieux, AM Pharma, Springer, and Anaesthesia and Analgesia during the conduct of the study as well as receiving grants from Deutsche Forschungsgesellschaft, Else Kriener-Fresenius-Stiftung, and Astellas; and personal fees from Baxter, Fresenius, and Astute Medical; and personal fees from AM Pharma, BioMerieux, Amomed, Springer, and Anaesthesia and Analgesia outside the submitted work. Dr Goldstein reported receiving personal fees from MediBeacon and grants and personal fees from BioPorto outside the submitted work. Dr Kashani reported receiving grants from Astute Medical during the conduct of the study. Dr Bell reported having an investigator-initiated research grant from Baxter. Dr Forni reported receiving personal fees from Astute Medical and BioMerieux; receiving research funding from Baxter and Ortho-Clinical-Diagnostics; and receiving speaker or consultant honoraria from Fresenius, Exthera, Baxter, and Astute Medical. Dr Guzzi reported being a speaker for BioMerieux outside the submitted work. Dr Joannidis reported receiving grants from Baxter; grants and personal fees from Fresenius Kabi; and speaking and/or consulting honoraria from Sphingotec, CLS-Behring, Fresenius and Astute Medical outside the submitted work. Dr Legrand reported receiving research support from Sphingotec during the conduct of the study as well as consulting fees from Novaritis and speaking fees from Fresenius and Baxter outside the submitted work. Dr Mehta reported serving on the advisory boards of BioMerieux, Baxter, and Sphingotec; serving on the steering committee of AM Pharma; receiving research funding from Fresenius Medical and Fresenius Kabi; and consulting for Baxter, AM Pharma, Intercept, BioMerieux, Sanofi, GE Healthcare, Indalo, Sphingotec, and Mallinckrodt outside the submitted work. Dr Murray reported receiving personal fees from FAST Biomedical, AM Pharma, Renibus Therapeutics, and Sphingotec outside the submitted work. Dr Murugan reported receiving grants from the National Institute of Diabetes and Digestive and Renal Diseases outside the submitted work. Dr Pickkers reported receiving travel and consultation honoraria from AM Pharma, Sphingotec, Adrenomed, Exponential Biotherapies, and Baxter outside the submitted work. Dr Prowle reported receiving personal fees from Nikkiso Europe, Baxter, Fresenius, MediBeacon, Quark Pharma, and BioMerieux; receiving funding from BioMerieux; and serving as a consultant with MediBeacon, Quark Pharma, GE Healthcare, and Nikkiso Europe outside the submitted work. Dr Rimmelé reported receiving personal fees from BioMerieux during the conduct of the study as well as grants and personal fees from Baxter, personal fees from Fresenius, and personal fees from Braun outside the submitted work. Dr Shaw reported receiving personal fees from Edwards Lifesciences, FAST Biomedical, Astellas, and Renibus Therapeutics outside the submitted work. Dr Kellum reported receiving grants and personal fees from Astute Medical and BioMerieux during the conduct of the study and grants and personal fees from Fresenius, Potrero, and RenalSense outside the submitted work. Dr Ronco reported serving on the advisory board of Baxter, writing papers for GE, receiving speaking fees from Cytosorbents and Jafros, consulting with Medtronic and Asahi Kasei Medical Co, belonging to the speakers bureau for Ortho-Clinical-Diagnostics, and serving on the advisory board of BioMerieux outside the submitted work. No other disclosures were reported.

Funding/Support: The face-to-face meeting was supported by educational grants from Baxter, Nxstage, Astute Medical, Sphingotec, Cytosorbents, and BioPorto.

Role of the Funder/Sponsor: The funders had no involvement in the selection of the panelists, design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or
approval of the manuscript; and decision to submit the manuscript for publication. Representatives were present at the face-to-face meeting but did not participate in the panel discussions, voting, or final decisions.

Additional Information: Panelists received travel reimbursement but no honoraria.

REFERENCES


SUPPLEMENT.

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eTable 2. Selected Articles that Served as Evidence for the Recommendations

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eFigure 1. Kidney Health Assessment

eFigure 2. Use of AKI Biomarkers During Course of AKI