Kidney360

Urine Sediment Exam Provides More Diagnostic Information in AKI than Novel Urinary Biomarkers: CON

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Introduction

AKI is a common hospital-based complication defined by changes in serum creatinine (SCr) and urine output. Owing to the limitations of these two biomarkers, there has been intense investigation into urinary methods to detect AKI earlier and more accurately, including renewed interest in microscopic urinalysis and several investigations into novel urinary biomarkers of kidney dysfunction. Although both avenues have led to some progress, novel biomarkers of AKI have outpaced urinalysis in terms of their clinical utility and ability to improve the care of patients with AKI.

Urine Sediment Analysis Falls Short in Predicting Outcomes

For over a century, physicians have been analyzing urine sediment under microscopy as a method of further characterizing AKI. Given the longevity of this method, it is concerning that standardization and investigation into its clinical significance and prognostic abilities were largely ignored for decades. More recently, several AKI-urinalysis risk scores have been created to prognosticate kidney and patient-centered outcomes (Table 1) (1–3). These scores use the presence of renal tubular epithelial cells (RTEs) and granular casts to suggest the impending severity of AKI. Although they have not been widely validated, these scores do show that those with more RTEs and granular casts in their urine are destined for more severe AKI (1–3).

One limitation is that urine sediment analysis is typically performed after AKI is already established, clearly reducing its utility in early identification and prevention of AKI. Additionally, there are extremely limited data on validation of the scores outlined in the table. One of the only studies to independently assess these scores demonstrated that 20% and 25% of patients with established Stage 2 AKI did not have evidence of acute tubular injury by Chawla and Perazella scores, respectively, in their urine sediment until several days into their disease course (4). This means that a bland urine sediment from a patient with early AKI is not always reassuring, and speaks to the lackluster performance of these tests when rigorously investigated. This same study by Varghese *et al.* (4) also failed to demonstrate the association between initial urine sediment findings and the future receipt of dialysis (a proxy for the most severe forms of AKI). Perhaps multiple urine sediments over several days would provide better insight into a patient's AKI, but this is not practical nor current standard practice. Additionally, ability to obtain a freshly voided sample, oliguria/anuria, and time are all significant barriers to performing daily urine sediment analyses on every patient with AKI.

In addition to its limited prognostic ability, the interobserver variability of sediments hinders its diagnostic value. In one study, 14 experienced nephrologists were asked to identify casts, RTEs, and other common findings from standardized urine sediment photos. Importantly, their responses were highly variable when identifying RTEs or cellular casts (5). In looking at five distinct photos of RTEs, mean agreement was 56% with a κ of 0.29 (95% CI, 0.26 to 0.33). RTEs are used in all three of the aforementioned risk scores (1–3); if sediment examination is to be a useful clinical tool, the components of these scores must first be reliably identified by nephrologists (and other providers), regardless of their clinical experience. Although agreement of granular/muddy brown casts was slightly better (79% with a κ of 0.74; 95% CI, 0.71 to 0.78), this falls remarkably short of global agreement. This lack of agreement perhaps speaks to the general imperfections of identifying these cellular elements and the larger issue of their sensitivity and specificity to AKI itself. Schinstock *et al.* (6) looked at urine from 363 patients in the emergency room who were eventually admitted to the hospital and demonstrated that the presence of any RTEs was only 15% sensitive for the future development of any stage AKI. They also showed that the presence of any granular casts was only 9% sensitive and the combination of RTEs or granular casts were only 22% sensitive, with a positive predictive value of 41% (6).

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Table 1. Summary of published urinalysis AKI risk scores and their limitations

Study	Study Characteristics and Data	Scoring System	Limitations
Chawla *et al.* (2)	Score created on the basis of 30 single-center patients and a panel of three blinded nephrologists and validated in another 18 patients. Interobserver agreement was 99.8%. AUC for nonrecovery was 0.79.	Grade 1: No casts or RTE Grade 2: At least one cast or RTE but <10% of LPF Grade 3: Many casts or RTEs (between 10%–90% of LPF) Grade 4: Sheet of muddy brown casts and RTEs in >90% of LPF	• Small sample size even with the validation cohort • Exceedingly high interobserver agreement compared with the literature • Only in those with established AKI
Perazella *et al.* (3)	Validated in 197 single-center patients with acute tubular necrosis or prerenal AKI. Score ≥3 (compared with 0) was associated with 7.3 relative risk of AKI progression. AUC of 0.75 for AKI progression.	0 points: No casts or RTE seen 1 point each: 1–5 casts per LPF or 1–5 RTEs per HPF 2 points each: ≥6 casts per LPF or ≥6 RTEs per HPF	• Interobserver agreement fairly low (κ of 0.47) for RTEs • Urine microscopy performed at time of renal consultation rather than on day 1 of AKI • Not blinded to patient's clinical status • Single-center data
Bagshaw *et al.* (1)	83 patients with and without sepsis-associated AKI across two centers. Scores ≥3 had a PPV of 80% (49%–94%) and NPV of 91% (78%–96%) for AKI progression.	0 points: No casts or RTE seen 1 point each: 1 cast or 1 RTE per HPF 2 points each: 2–4 casts or RTEs per HPF 3 points each: ≥5 casts or ≥5 RTEs per HPF	• Only one person scored all urine sediments • Despite being two centers, small sample size • May be specific to patients who are critically ill

AUC, area under the curve; RTE, renal tubule epithelial cells; LPF, low power field; HPF, high power field; PPV, positive predictive value; NPV, negative predictive value.

Most importantly, to our knowledge, there have been no studies that demonstrated improved patient outcomes on the basis of urine sediment–informed clinical care. Unfortunately, automated urine analyzers do not yet identify many of the particles needed to diagnose AKI, leaving the urine sediment exam as an imperfect, user-dependent, and minimally useful tool in the workup of AKI.

Novel Urine Biomarkers: The Future of AKI Care Is Here

Unlike microscopic urinalysis, many novel urinary biomarkers have been shown to identify patients before the presence of clinical AKI, but, perhaps more importantly, they have been consistently linked with adverse patient outcomes and have been shown to help improve outcomes when acted on (7–10). For example, in the Schinstock *et al.* (6) emergency room study, a urine neutrophil gelatinase associated lipocalin (uNGAL) value of ≥42.7 ng/ml provided a higher sensitivity (65%) and a positive predictive value on par with that of RTEs and granular casts. Improved sensitivity for detecting AKI allows clinicians to implement renal-protective measures before the development of advanced renal damage and can prevent severe AKI and its complications. Recently, Goldstein *et al.* (8) prospectively enrolled hospitalized children at high risk for nephrotoxin-associated AKI, and they demonstrated that uNGAL thresholds of 150 and 300 ng/ml can effectively rule out the future development of Stage 2 or higher AKI, and can potentially be used as a surrogate to replace daily blood draws.

uNGAL is not the only biomarker that has been shown to be elevated earlier than SCr and demonstrated the ability to affect/improve AKI care. There have been several studies that randomized patients at risk for AKI to receive kidney-focused care bundles using urinary tissue inhibitor of metalloprotease-2 and IGF binding protein 7 levels of ≥0.3 as part of the enrollment criteria (7,9,10). Those who received these Kidney Disease Improving Global Outcomes guideline–based care bundles—which include management of hemodynamic status (intravenous fluids, inotropes, and/or vasopressors), glycemic control, avoidance of nephrotoxins, and potentially nephrology consultation—had lower rates of moderate-severe AKI and shorter stays in the intensive care unit and hospital (7,9). These biomarkers may be helpful for the identification of the highest-risk patients who are likely to benefit from intense, costly, and time-consuming supportive care that may be difficult and impractical to deliver to all patients.

In addition to predicting AKI before it is clinically apparent, several biomarkers have shown diagnostic promise in the presence of established AKI. In a cohort of patients with newly diagnosed Stage 1 or 2 AKI after adult cardiac surgery, increased levels of urinary IL-18 and uNGAL have both been associated with progression to more severe stages of AKI when measured on the day of SCr increase (11). Beyond predicting which patients will experience AKI progression, novel biomarkers can help identify which patients will develop persistent AKI and need long-term dialysis. In a multicenter international study of 331 mixed patients in the intensive care unit who had established Stage 2 or 3 AKI, elevated urinary C-C motif chemokine ligand-14 was shown to predict when Stage 3 AKI would last beyond 72 hours (12). These findings were recently validated in a separate cohort of patients with severe AKI after cardiac surgery (13). Novel biomarkers can provide

Table 2. The diagnostic capabilities of urinary biomarkers of AKI

AKI Time Point	Biomarker	Findings
Before SCr/UOP-defined AKI	TIMP2*IGFBP7	An elevated urinary TIMP2*IGFBP7 >0.3 identifies patients at risk for severe AKI and, when coupled with a guideline-based, renal-protective care bundle, there are lower rates of severe (Stage 2/3) AKI and improved patient outcomes (shorter length of stay and lower cost of care) (7,9,10).
	uNGAL	Higher urinary NGAL (>42/7 ng/ml) on admission was associated with higher AKIN stages of AKI, with sensitivity of 64.5% (95% CI, 53.5% to 74.3%) and specificity of 64.5% (95% CI, 58.8% to 69.8%) (6).
Clinical AKI diagnosis	uNGAL	Elevated urine NGAL (>141 ng/ml) measured at the time of AKI diagnosis (SCr increase) was associated with 2.32 increased odds of progressive/worsening AKI compared with those with values <20.1 ng/ml (11).
	IL-18	Elevated urinary IL-18 (>185 pg/ml) measured at the time of AKI diagnosis was associated with 3.6 increased odds of progressive AKI compared with those with values <29.6 pg/ml (11).
Established AKI	CCL-14	Urinary CCL-14 levels >2.21 ng/ml in patients with stage 2 or 3 AKI after cardiac surgery provided a sensitivity of 78% and specificity of 95% for the development of Stage 2 or 3 AKI that lasted 72 hours of more. CCL-14 values provided an AUC of 0.91 for the receipt of RRT in the next 7 days (13).

SCr, serum creatinine; UOP, urine output; TIMP2*IGFBP7, tissue inhibitor of metalloproteinase-2*IGF binding protein 7; uNGAL, urine neutrophil gelatinase associated lipocalin; AKIN, Acute Kidney Injury Network; CCL-14, C-C motif chemokine ligand-14; AUC, area under the curve.

valuable data in prognosticating which patients will progress from an AKI perspective, allowing for the identification of those destined for a rapid kidney recovery versus those who may benefit from measures to prevent progression to acute and CKD.

In summary, the reliability of urine sediment analysis in diagnosing AKI is extremely limited by interpreter variability, lack of diagnostic findings until later in disease course, and lack of large-scale validation. Novel urinary biomarkers have demonstrated the ability to identify and risk stratify patients before and after there are changes in SCr or urine output. They provide clinically relevant information earlier or at the same time as urine sediment and can be used in several AKI time points (Table 2). These biomarkers can be paired with other tools like electronic risk scores, the furosemide stress test, or clinical variables to improve patient outcomes and should continue to become an essential part of clinical care for the nephrologist and critical care community.

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Author Contributions

J.L. Koyner reviewed and edited the manuscript; J.L. Koyner and A. La conceptualized the study; and A. La wrote the original draft.

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