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

Corey Cavanaugh

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Introduction

“Where is the knowledge we have lost in information?” – T.S. Elliot

The urine sediment analysis is one of the oldest diagnostic tests we perform in nephrology. It long preceded BP measurement, lung auscultation by stethoscope, and serum chemistry measurement. However, it is clear that, within the last 10 years, a great leap forward has been taken in using novel urine biomarkers to diagnose and prognosticate AKI. Yet I will argue that manual urine microscopy remains the single most powerful diagnostic test for AKI. AKI is the consequence of a diverse list of nephrotoxins, both exogenous and endogenous, in virtually any compartment of the kidney, including vascular, tubular, and glomerular compartments, and the interstitium. Urine microscopy provides valuable diagnostic information in regards to type and severity of the injury. It is important to note that automated urine microscopy has replaced manual microscopy in many institutions. However, automated urinalysis lacks the sensitivity and specificity to identify pathologic casts, crystals, and dysmorphic red blood cells when compared with manual microscopy performed by a nephrologist (1). Therefore, manual urine microscopy by a trained nephrologist as a diagnostic tool in AKI will be discussed.

Urine Microscopy for Acute Tubular Injury versus Prerenal AKI

Acute tubular injury (ATI) remains the most common cause of AKI in the hospitalized patient. Although causes of ATI are often reduced to ischemic or toxic tubular injury, the ability to confirm tubular injury remains a common clinical challenge. The predominant methods for diagnosis of AKI are still based on an elevation of serum creatinine and/or urine output measurement. However, these tests cannot reliably differentiate the etiology of AKI (e.g., prerenal azotemia versus ATI) without extensive knowledge of clinical history, volume assessment, and/or kidney imaging. Often, a trial-and-error method of intravenous fluids or diuretics to further elucidate the cause is attempted. It is here that urine microscopy offers high diagnostic accuracy in ATI, while enhancing the ability to explore the differential diagnosis for AKI. In 2008, a cross-sectional study of 276 patients with AKI (defined by 50% increase in creatinine from baseline), in which nephrology was consulted for AKI, a urine sediment scoring system based on the number of granular casts and renal tubular epithelial cell casts (RTECs) was used (2). A seen in Table 1, this scoring system was able to predict the final diagnosis of acute tubular necrosis (ATN) with high certainty. The odds ratio (OR) for ATN incrementally increased with an increase in severity of the scoring system (all compared with score 0; score 1, OR, 9.7; 95% confidence interval [95% CI], 5.3 to 18.6; score ≥2, OR, 74.0; 95% CI, 16.6 to 329.1). Moreover, in patients with a high pretest probability of ATN, a urine sediment score of two or more resulted in a positive predictive value of 100%. Whereas in patients with an initial diagnosis of prerenal AKI, a score of zero to one yielded a negative predictive value of 91% for ATN. Thus, in patients where the diagnosis of prerenal AKI rise is called into question, the finding of granular casts or RTECs can be a valuable marker of clinically significant tubular injury.

Unfortunately, there are few studies comparing manual microscopy with novel urine biomarkers. This is likely, in part, due to the difficulty in obtaining, standardizing, and quantifying the urine sediment. However, in a study of 249 patients with AKI, urine biomarkers kidney injury molecule-1, neutrophil gelatinase-associated lipocalin, and IL-18 performed comparably with the urine sediment analysis using the Perazella scoring system when evaluating outcomes of worsened AKI stage from enrollment to peak serum creatinine or in-hospital death (4). This was further supported in a prospective observational study by Bagshaw et al. (5). In their study, using a similar urine scoring system to the Perazella score, septic AKI was associated with greater microscopic evidence of AKI compared with nonseptic AKI. Importantly, urine neutrophil gelatinase-associated lipocalin showed a modest correlation (0.41, P=0.002) when compared with the urine microscopy score for...
AKI, while also predicting worsening AKI in patients who were critically ill (5). Although it is not clear if one urine sediment scoring system is superior to another, emphasis is placed on the overall value of grading sediment, which has significant diagnostic value in AKI.

**Diagnostic Scope of Urine Microscopy**

Although urine scoring systems in AKI may offer insight to the degree of tubular injury, an etiology is not necessarily identified simply because a few granular casts or RTECs were seen. Yet, with the exclusion of IL-9 and TNF-α showing high specificity for acute interstitial nephritis (AIN), the novel biomarkers have not been shown to differentiate AKI mediated by drugs, infection, or crystals causing tubular injury (6). This is a critical shortcoming because it cannot guide the clinician to targeted treatment (e.g., stopping the culprit drug). AKI due to drug-induced crystal formation can be rapidly diagnosed when characteristic crystals of methotrexate, acyclovir, sulfadiazine, ciprofloxacin, and amoxicillin, to name a few, are observed in the urine sediment of a patient with AKI (7). Recognizing the drug-specific crystalline morphology within casts in AKI is diagnostic for crystal-induced kidney injury, and, in some cases, can spare more advanced testing, such as kidney biopsy. Rarely, pathognomonic crystals of tyrosine and cysteine can provide the clinician with valuable diagnostic clues to these rare metabolic disorders. Traditionally, AIN is a diagnosis that can only be confirmed with biopsy, although, as previously mentioned, the biomarkers IL-9 and TNF-α are an intriguing discovery that appear specific for AIN. The observation of white blood cell casts, although rare, is also supportive of a diagnosis of AIN in the appropriate clinical setting.

A major challenge in the diagnostic power of urine microscopy lies in the interobserver reliability of nephrologists examining urine sediment. In a recent study of 14 nephrologists, interobserver reliability varied significantly, with modest agreement with regards to casts at 59% (95% CI, 50% to 69%) and κ of 0.52 (95% CI, 0.42 to 0.62) (8). However, all 14 nephrologists agreed that manual microscopy provided more clinical information than could be obtained by the urine microscopy report from their hospitals’ laboratories. Further, in this study, agreement for dysmorphic red blood cells was high at 91% and a κ of 0.83 (95% CI, 0.80 to 0.86). This high agreement is critical, because the nephrologists’ evaluation of hematuria has long required a urine sediment analysis. The search for dysmorphic red blood cells (acanthocytes), the classic hallmark of glomerular bleeding, can prove to be an extremely valuable diagnostic discovery, because a threshold of ≥5% carries a specificity for glomerular disease of 98% (9). Urine microscopy was shown to have powerful diagnostic ability in a recent retrospective study of biopsy sample–proven lupus nephritis with low grade proteinuria. In 222 patients who underwent kidney biopsy for suspected lupus nephritis, 46 of the 222 patients had <0.5 g/d proteinuria, below the traditional threshold to warrant kidney biopsy. Remarkably, all patients had histologic evidence of lupus nephritis, and all had dysmorphic red blood cells (10). Lastly, it is worth mentioning that urine microscopy has diagnostic value for identifying bacteria, protozoa, fungi in urinary tract infection, and even fecal material in cases of enterovesical stenosis—although this, admittedly, can be hard to identify to the untrained eye. Commonly, urine microscopy can offer diagnostic clues that carry high specificity to an etiology that, short of kidney biopsy, cannot otherwise be inferred in a rapid manner.

**Conclusion**

Although the accuracy of urine microscopy is hampered by interobserver reliability, extensive training, time, equipment, and certification, it remains a powerful diagnostic test for AKI. Clearly, nephrology is headed for an era of precision medicine and novel biomarkers are at the forefront of this movement. Biomarkers offer not only diagnostic but also powerful prognostic data, beyond what is understood by creatinine. However, urine microscopy will not be replaced by novel biomarkers, but will serve to enhance their targeted application. Although it is easy to get lost in the abundance of information that may be coming regarding the use of urine biomarkers, we microscopists can rest assured that the urine sediment analysis still provides valuable, irreplaceable diagnostic information.

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Author Contributions

C. Cavanaugh wrote the original draft.

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See related debate, “Urine Sediment Exam Provides More Diagnostic Information in AKI than Novel Urinary Biomarkers: CON,” and commentary, “Urine Sediment Exam Provides More Diagnostic Information in AKI than Novel Urinary Biomarkers: COMMENTARY,” on pages 600–603 and 604–607, respectively.