How Can Urine Microscopy Influence the Differential Diagnosis of AKI?

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cute kidney injury (AKI), which is associated with increased morbidity and mortality, is a relatively common complication in hospitalized patients (1–3). The most common cause of AKI in hospitalized patients is acute tubular necrosis (ATN) followed by prerenal azotemia (4). Because therapies and prognoses for prerenal azotemia and ATN differ substantially, early clinical differentiation is desirable to assist the clinician in patient treatment. For example, an early diagnosis of prerenal azotemia would facilitate early treatment to correct volume status and potentially prevent ATN. Also, in the setting of AKI from ATN, it would avoid worsening of the clinical course with incorrect therapies such as excessive volume resuscitation leading to pulmonary edema and other untoward end organ effects.

Presently, the diagnosis of AKI is primarily based on changes in serum creatinine concentration, blood urea nitrogen, and urine output. These biomarkers are very helpful in diagnosis of AKI but rarely help in discriminating between ATN and prerenal azotemia. Urine biochemistry measures, such as fractional excretion of sodium and urea, also provide important information in the differentiation of AKI into traditional categories of prerenal azotemia and ATN (5–9) when the patient is not on diuretics or does not have underlying chronic kidney disease. Urinalysis and urine microscopy are also commonly used to differentiate these two causes of AKI and are generally accepted as critical for the evaluation of patients with kidney disease. Urine microscopy is the best surrogate for the histologic state of the kidney and is not affected by underlying chronic kidney disease or presence of medications. As a result, urine sediment analysis is considered an integral part of the clinical workup of kidney disease in hospitalized patients with AKI.

Urinary microscopy in patients with ATN classically is described as containing renal tubular epithelial cells, renal tubular epithelial cell casts, granular casts, and muddy brown or mixed cellular casts, whereas sediment in patients with prerenal azotemia usually demonstrates occasional hyaline casts (10–14). Because urine microscopy is readily available, rapid, and inexpensive, valuable information that will improve the differential diagnosis of AKI might be quickly obtained from this test. We recently published a cross-sectional study that supports the utility of urine microscopy in differentiating prerenal azotemia from ATN (15).

In that article, we examined the utility of the number of granular casts and urine scoring system for the diagnosis of ATN. We found merit in these urinary parameters in confirming the preurine microscopy diagnosis (prerenal azotemia versus ATN) as well as changing the diagnosis from one to the other in a significant number of patients. We presented sensitivity, specificity, and likelihood ratios (LR) of various urine sediment findings as they relate to final diagnosis of ATN or prerenal azotemia. What has generated the most interest is the utility of the LR based on the urine sediment for postmicroscopy diagnosis of ATN or prerenal azotemia. LR are used to assess the accuracy of a diagnostic test and to help in selecting an appropriate diagnostic test or sequence of tests. When clinicians order a diagnostic test, they want to know which test will best rule in or rule out disease in the patient. In the language of clinical epidemiology, initial assessment of the likelihood of disease (pretest probability) is estimated, a test is performed to shift suspicion one way or the other, and then a final assessment of disease likelihood is determine (posttest probability). LR estimate how much we should shift clinical suspicion for a particular test result. Because tests can be positive or negative, there are at least two LR for each test. The positive LR (LR+) estimates the increase in disease probability if the test is positive, whereas the negative LR (LR−) estimates the decrease in disease probability if the test is negative. LR have advantages over sensitivity and specificity because they are less likely to change with the prevalence of the disorder, they can be calculated for several levels of the symptom/sign or test, they can combine the results of multiple diagnostic tests, and they can be used to calculate posttest probability for a target disorder. Thus, they help clinicians navigate these large zones of clinical uncertainty (16).

The LR for various sediment findings are demonstrated in Table 1. The clinician can use the LR from the appropriate urine sediment score to estimate the posttest probability of their diagnosis (ATN versus prerenal azotemia) on the basis of their pretest probability. We provide two scenarios to illustrate the concept.

The first scenario is as follows. The clinician has evaluated a patient with AKI and is not entirely certain of the cause but
believes that the patient has prerenal azotemia with a pretest probability of 60% \([\text{pretest odds} = 1.50; \ (\text{pretest probability} / \ 1 - \text{pretest probability})]\). Upon examination of the urine sediment, 1 to 5 granular casts are noted, which gives an LR of 0.34 for prerenal azotemia. Using the clinician's pretest odds of 1.50, the posttest odds of prerenal azotemia are 0.51 \([1.50 / 0.34 = 0.51; (\text{pretest odds} \times \text{LR})]\) and posttest probability is 33%.

When one looks at it the other way, a pretest probability for ATN of 40% will have the following posttest probability based on the following number of granular casts: 0 casts, posttest probability is 13%; 1 to 5 casts, posttest probability is 66%; and 6 to 10 casts, posttest probability is 86%. Thus, the presence or absence of casts importantly influences the posttest probabilities when the pretest probabilities are in a middle/uncertain range (30 to 70% certainty) for the clinician. Importantly, the marked difference of the LR is evident when one looks at the difference between 1 to 5 granular casts (LR 2.97) and 6 to 10 granular casts (LR 9.68) in the setting of ATN. The skewed nature of LR is evident by the fact that 6–10 granular casts are required to have a meaningful LR. Figure 1 demonstrates these principles and gives posttest probabilities for various combinations of pretest probabilities and urine sediment findings (17).

The second scenario is as follows. The clinician has evaluated a patient with AKI and is fairly certain that the patient has ATN with a pretest probability of 90% \([\text{pretest odds} = 9]\). Upon examination of the urine sediment, only a few hyaline casts are noted, which gives an LR of 0.23 for ATN. Using the clinician’s pretest probability of 90% and plotting on Figure 2A, the posttest probability of ATN is 68%. Alternatively, 1 to 5 granular

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**Table 1. LR for diagnoses of ATN and prerenal azotemia on the basis of number of granular casts present in the urinary sediment**

<table>
<thead>
<tr>
<th>Granular Casts</th>
<th>LR (ATN)</th>
<th>LR (Prerenal Azotemia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.23</td>
<td>4.35</td>
</tr>
<tr>
<td>1 to 5</td>
<td>2.97</td>
<td>0.34</td>
</tr>
<tr>
<td>6 to 10</td>
<td>9.68</td>
<td>0.10</td>
</tr>
</tbody>
</table>

*Adapted from reference (15). ATN, acute tubular necrosis; LR, likelihood ratio.*

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Figure 1. (A) Conditional probabilities for the various granular cast numbers in the setting of prerenal azotemia. The pretest probability and the number of granular casts in the urine sediment allow the clinician to calculate the posttest probability of prerenal azotemia. For example, the vertical line at the pretest probability of 60% demonstrates three different posttest probabilities on the basis of findings in urine sediment. (B) Conditional probabilities for the various granular cast numbers in the setting of acute tubular necrosis (ATN). The pretest probability and the number of granular casts in the urine sediment allow the clinician to calculate the posttest probability of ATN. For example, the vertical line at pretest probability of 40% demonstrates three different posttest probabilities on the basis of findings in urine sediment.

Figure 2. (A) Conditional probabilities for the various granular cast numbers in the setting of ATN. Note that a high pretest probability of ATN (>70%) is influenced very little by the urine sediment examination. (B) Conditional probabilities for the various granular cast numbers in the setting of prerenal azotemia. Note that a low pretest probability of prerenal azotemia (<30%) is influenced very little by the urine sediment examination.
casts and 6 to 10 granular casts will have an LR of 2.97 and 9.68 for ATN, respectively, and the posttest probabilities will be 96 and 98%, respectively (Figure 2B). When one looks at it the other way, a pretest probability for prerenal azotemia of 10% will have the following posttest probabilities based on the following number of granular casts when plotted on Figure 2B: 0 casts, posttest probability is 32%; 1 to 5 casts, posttest probability is 4%; and 6 to 10 casts, posttest probability is 1%. It is obvious from the examples that the urine microscopy findings will have little effect on the posttest probability when the pretest probability is at the extremes (high or low) and will provide little help in ruling in or ruling out the clinical disorder. Once again, Figure 2 illustrates the points.

In conclusion, urine microscopy and examination of the sediment is advantageous because of its widespread availability, technique simplicity with conventional equipment, and low cost. Our cross-sectional study of urine microscopy in the setting of hospital-acquired AKI suggests that ATN can be confidently differentiated from prerenal azotemia by determining the presence of granular casts and using a scoring system that is based on the number of casts. LR for both prerenal azotemia and ATN were calculated for the various categories of granular cast number in the urine sediment. The LR will allow clinicians to calculate posttest probability of either ATN or prerenal azotemia once they have estimated the pretest probability of either cause of AKI. As demonstrated, using these urinary data will be most useful when the pretest probability ranges between 30 to 70% and with 6 to 10 granular casts. In very high or low pretest probabilities, the urinary sediment findings are less useful.

Disclosures
None.

References