A prospective evaluation of urine microscopy in septic and non-septic acute kidney injury

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Abstract

Background. Sepsis is the most common trigger for acute kidney injury (AKI) in critically ill patients. We sought to determine whether there are unique patterns to urine sediment in septic compared with non-septic AKI.

Methods. Prospective two center cohort study of adult critically ill patients with septic and non-septic AKI, defined by the RIFLE criteria. Eligible patients had clinical, physiologic and laboratory data extracted. Blood and urine were sampled for urine biochemistry, microscopy and neutrophil gelatinase-associated lipocalin (NGAL). A urine microscopy score (UMS) was derived based on the observed quantification of renal tubular cells and casts in the sediment. The UMS was compared between septic and non-septic AKI and correlated with NGAL, worsening AKI, renal replacement therapy (RRT) and hospital mortality.

Results. Eighty-three patients were enrolled. Mean (SD) age was 64.3 (16.6) years, 60.2% were male, Charlson comorbidity score was 3.3 (2.8) and Acute Physiology and Chronic Health Evaluation II score was 21.4 (7.6). Septic AKI was present in 43 patients (51.8%). RIFLE class at enrollment was not different between groups (P = 0.43). Septic AKI was associated with higher UMS compared with non-septic AKI (P = 0.001). There was no correlation between UMS and fractional excretion of sodium (FeNa) or fractional excretion of urea (FeU). Elevated urine NGAL (uNGAL) correlated with higher UMS (P = 0.0003), while correlation with plasma NGAL was modest (P = 0.05). Worsening AKI occurred in 22.9% with no difference between septic and non-septic groups. A UMS score ≥3 was associated with increased odds of worsening AKI [adjusted odds ratio 8.0; 95% confidence intervals (CI), 1.03–62.5, P = 0.046]. For a UMS ≥3, sensitivity and specificity were 0.67 (95% CI, 0.39–0.86) and 0.95 (0.84–0.99) and positive and negative predictive values were 0.80 (0.49–0.94) and 0.91 (0.78–0.96) for detecting worsening AKI, respectively. While there were no differences between septic and non-septic AKI, higher UMS correlated with need for RRT (15.7%, P = 0.02) and in-hospital death (30.1%, P = 0.01); however, this did not persist in multivariable analysis.

Conclusions. Septic AKI is associated with greater urine microscopy evidence of kidney injury compared with non-septic AKI, despite similar severity of AKI. A UMS ≥3 correlated with higher uNGAL and was predictive of worsening AKI. Urine microscopy may have a complementary role for discerning septic from non-septic AKI, discriminating severity and predicting worsening AKI in critically ill patients.

Keywords: acute kidney injury; fractional excretion of sodium; microscopy; neutrophil gelatinase-associated lipocalin; sepsis

Introduction

Acute kidney injury (AKI) is common in hospitalized and critically ill patients and has an important modifying effect on mortality, kidney recovery and health resource utilization [1–3].

Sepsis is recognized as the most important contributing factor for AKI [2]. These patients generally have a poorer prognosis when compared to AKI of non-septic origin [4–6]. Experimental data have suggested that there may be important pathophysiologic differences between septic and conventional ischemic/toxic-induced AKI [7–9]. Considering these differences, discriminating septic and non-septic AKI may have clinical relevance and prognostic importance.

The diagnosis of AKI is characteristically based on absolute or relative changes to conventional laboratory values (i.e. serum creatinine, urea) and/or urine output. These parameters, at selected thresholds, have been integrated into a recent consensus definition and classification scheme for AKI, forwarded by the Acute Dialysis Quality Initiative and later in modified form by the AKI Network (AKIN) [10, 11].

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Further to these parameters, an evaluation of the urine sediment is often viewed as a complementary measure for providing additional insight into the diagnosis and severity of AKI; however, it has not formally been integrated in consensus definitions [12]. There has been a paucity of data on the value of urine microscopy for the diagnosis, discrimination of etiology and/or prediction of worsening AKI in hospitalized patients, despite this being one of the oldest time-honored tests in nephrology. Moreover, no study has specifically evaluated urine microscopy in critical illness or sepsis. Two systematic reviews have suggested that there may be a limited role for urine microscopy in septic AKI [13, 14]. This has generated concern, for there may be a trend of omitting the routine assessment of urine microscopy in the evaluation of patients with AKI [15]. Recent data, however, have challenged this notion, showing urine microscopy has some diagnostic and prognostic value in hospitalized patients with AKI [15–18].

Neutrophil gelatinase-associated lipocalin (NGAL) has been identified as one of the most promising early kidney injury-specific biomarkers for AKI [19]. NGAL has been investigated across a range of clinical settings of AKI including cardiac surgery [20–22], sepsis [23, 24] and in patients presenting to the emergency department [25, 26]. To date, no study has investigated the relationship between kidney injury-specific biomarkers such as NGAL and urine sediment evidence of tubular cell injury in critically ill patients with AKI. We hypothesized that there would be differing patterns of renal tubular cells and/or casts in the urine sediment of septic compared with non-septic patients and that these would provide additional diagnostic and/or prognostic information. Accordingly, our objectives were to describe in a cohort of critically ill patients with septic and non-septic AKI:

1. the differences in the urine microscopy profile;
2. the association between urine microscopy and routine urine biochemistry and plasma NGAL (pNGAL)/urine NGAL (uNGAL);
3. the association between urine microscopy and worsening AKI;
4. the association between urine microscopy and need for renal replacement therapy (RRT) and hospital mortality.

Materials and methods

Study design

This was a prospective observational cohort study [24]. The reporting of this study follows the Strengthening the Reporting of Observational Studies in Epidemiology guideline [27]. The Human Research Ethics Committee at the Austin Hospital in Melbourne, Australia, approved this study.

Setting and participants

We studied critically ill patients with early AKI and an expected duration of stay in the intensive care unit (ICU) of ≥24 h. A total of 83 consecutive patients (43 with septic AKI and 40 with non-septic AKI) were recruited from two participating centers in Australia (1 academic tertiary—Austin Hospital; one private—Warringal Private Hospital). Eligible patients fulfilled all the following inclusion criteria:

1. adult (age ≥18 years);
2. evidence of early AKI, defined as fulfilling the RIFLE category—RISK or higher [10] and
3. evidence of sepsis (cases) [28] or no sepsis (controls).

Patients were excluded if they had one or more of the following:

1. prior kidney transplant;
2. end-stage kidney disease, defined as estimated glomerular filtration rate (eGFR) <15 mL/min/m² or chronic dialysis therapy;
3. prior RRT during index hospitalization;
4. confirmed and/or suspected acute glomerulonephritis, acute interstitial nephritis, renal vasculitis or postrenal etiology for AKI.

Study definitions

AKI was defined according to the RIFLE classification scheme [10]. Patients were diagnosed and severity classified based on changes from baseline serum creatinine and/or changes in urine output. Baseline serum creatinine was defined by the lowest outpatient serum creatinine in the 6-months preceding index hospitalization. Sepsis syndrome was defined according to consensus guidelines [28]. Illness severity was captured by the Acute Physiology and Chronic Health Evaluation (APACHE) II score [29]. Organ failure was assessed by the Sequential Organ Failure Assessment (SOFA) score [30]. Oliguria was defined as a urine output <<400 mL/24 h. RRT encompassed any form of intermittent hemodialysis or continuous RRT. Worsened AKI was defined as an increase in RIFE category (i.e. from RISK to INJURY or INJURY to FAILURE) or RRT initiation.

Study protocol and data sources

Patients were identified by daily surveillance of the two participating sites. Consecutive eligible patients underwent a medical record review and documentation of baseline clinical, physiologic and laboratory data. Data were extracted on standardized data forms. Clinical data extracted included demographics (i.e. age, sex, race); comorbid illness (i.e. Charlson comorbidity index [31]) and any exposure to diuretics and/or nephrotoxins (i.e. radiocontrast media, aminoglycosides, cardiopulmonary bypass, rhabdomyolysis, serum CK >1500 U/L; amphotericin). Data were further extracted on acute physiology and laboratory parameters (i.e. hemodynamics; use of mechanical ventilation; use of vasoactive drugs; illness severity score (APACHE II); organ failure scores (SOFA)) and premorbid and enrollment kidney function. All patients had indwelling urine catheters. Each patient had blood and urine samples collected at the time of enrollment.

Urine biochemistry preparation

Urine biochemistry included urinary sodium (UNa), potassium (UK), chloride (UCl), creatinine (UCr) and urea (UU). Calculated indices included fractional excretion of sodium (FeNa) and fractional excretion of urea (FeU). The FeNa was calculated as [(UNa/plasma Na)/(UCr/SCr) × 100]. The FeU was calculated as [(Uu/plasma urea)/(UCr/SCr) × 100].

Urine microscopy preparation

All samples were prepared in identical fashion and reviewed by a single trained investigator. Urine was captured from a fresh indwelling catheter specimen. The duration between time of collection and analysis was immediate whenever possible and generally <4 h. Urine sediment was evaluated with an Olympus BX41 phase contrast microscope with 10, 20 and 40 magnification objectives and a ×10 magnification eyepiece. Microscopic examination was performed on urine centrifuged (Heraeus Instruments, Biofuge Primo, Model # 7590) at 1500 r.p.m. (approximately 225 g) for 10 min and concentrated 10-fold by resuspending the deposit in one-tenth volume. Specimens were scanned under low power then intermediate whenever possible and generally <4 h. Urine sediment was evaluated with an Olympus BX41 phase contrast microscope with 10, 20 and 40 magnification objectives and a ×10 magnification eyepiece. Microscopic examination was performed on urine centrifuged (Heraeus Instruments, Biofuge Primo, Model # 7590) at 1500 r.p.m. (approximately 225 g) for 10 min and concentrated 10-fold by resuspending the deposit in one-tenth of the centrifuged volume. Specimens were scanned under low power then renal epithelial/tubular cells and granular casts were differentiated using representative high-power fields (×40 objective). Large clumps of debris were not evaluated. Cells and casts were counted and averaged. Each slide was graded using a novel urine microscopy score (UMS) outlined in Table 1.

Urine biochemistry preparation

Blood samples for pNGAL were collected in EDTA anticoagulated tubes, centrifuged at 5000 r.p.m. (approximately 2500 g) × 5 min and plasma stored at −70°C for batched analysis. We used the Triage NGAL Test (Biosite Inc., San Diego, CA), a point-of-care, fluorescence immunoassay for quantitative measurement of pNGAL, as previously described [24]. Urine samples for uNGAL testing were centrifuged at 1500 r.p.m. (approximately 225 g) × 10 min and supernatant stored at −70°C for batched analysis. uNGAL was measured by a chemiluminescent microparticle assay using the ARCHITECT platform (Abbott Diagnostics Inc., Abbott Park, IL), as previously described [24]. uNGAL was expressed as
nanogram per milligram creatinine, to standardize and correct for changes in urine concentration. All blood and urine samples were processed directly after collection. All samples were stored and transported frozen until immediately prior to pNGAL/uNGAL testing.

**Study outcomes**

The primary outcome was a comparison of the urine profile between septic and non-septic patients. Secondary outcomes evaluated the association of septic status and urine profile with: (i) urine biochemistry and pNGAL/uNGAL; (ii) worsening AKI and (iii) initiation of RRT and hospital mortality.

**Statistical analysis**

All statistical analysis was performed with STATA version 11.0 (StataCorp., College Station, TX). Normally or near normally distributed variables are reported as means with SD and compared using the Student’s t-test or one-way repeated measures analysis of variance where appropriate. Non-normally distributed continuous data are reported as medians with either interquartile or total range and compared using the Mann–Whitney U-test, Kruskal–Wallis test or Friedman’s test where appropriate. Categorical data are reported as proportions and compared using chi-square or Fisher’s exact test. Spearman’s correlation was used to assess the relationship between UMS and urine biochemistry and NGAL. Multivariable linear regression was used to adjust for sepsis, APACHE II score and baseline kidney function. The association of UMS and worsening AKI was assessed by univariate and multivariable logistic regression. Covariates initially considered for this analysis included age, baseline kidney function and RIFLE category. Model fit was assessed by the goodness of fit test and discrimination was assessed by the area under the receiver operator characteristic curve. Data are presented as odds ratios (OR) with 95% confidence intervals (CI). A P-value of <0.05 was considered significant.

**Results**

In total, 83 consecutive patients were enrolled. The mean (SD) age was 64.3 (16.6) years, 60.2% were male and premorbid Charlson comorbidity score was 3.3 (2.8) points. The mean (SD) APACHE II scores were 21.4 (7.6), 71.1% were mechanically ventilated, 71.8% required vasoactive support and 56.6% were in shock.

**Clinical characteristics**

Septic AKI occurred in 43 patients (51.8%). The enrollment clinical characteristics of patients stratified by septic and non-septic AKI are presented in Table 2. Septic AKI patients were older, had greater comorbid illness, higher illness severity scores and were less likely to receive mechanical ventilation compared to non-septic controls. The most common sources of sepsis were thoracic and intra-abdominal (Table 3). Follow-up was complete to hospital discharge for all patients.

**Baseline kidney function**

Premorbid serum creatinine, urea and eGFR were not significantly different between septic and non-septic AKI (Table 4). At enrollment, serum creatinine, urea, urine output and RIFLE category were not significantly different between septic and non-septic AKI. Exposure to nephrotoxins and diuretics was also similar between groups.

**Clinical outcomes**

Worsened AKI occurred in 22.9% (n = 19). There was no difference between septic and non-septic AKI patients (Table 4). However, septic patients had higher burden of comorbid illness [4.5 (3.3) versus 3.0 (2.8), P = 0.03]; greater APACHE II scores [26.9 (6.9) versus 19.7 (7.1), P = 0.0002] and lower baseline eGFR [73.5 (28.9) versus 95.1 (29.6), P = 0.006]. RRT was initiated in 15.7% (n = 13) with no difference between septic and non-septic AKI patients. Hospital mortality was higher in septic compared with non-septic AKI patients (44.2 versus 15.0%, P = 0.004).

**Urinary markers**

Urine microscopy at enrollment was available for 78 patients (94%). Five patients had insufficient urine available for analysis. Septic AKI was associated with significantly worse UMS compared with non-septic controls, despite no difference in RIFLE class (Table 5). There was no difference in urine sodium or derived biochemical indices.
Urine microscopy in septic AKI

(i.e. FeNa, FeU) by UMS. UMS score showed modest linear correlation with pNGAL (correlation coefficient 0.31, P = 0.043); however, this became nonsignificant after adjustment for sepsis, APACHE II score and baseline kidney function (P = 0.49). uNGAL showed stronger univariate correlation with UMS (correlation coefficient 0.41, P = 0.0002) (Figures 1 and 2) that persisted after adjustment in multivariate analysis (P = 0.012). An increasing UMS was associated with higher adjusted OR for worsening AKI (Table 6). For a UMS/C21 ≥ 3, sensitivity and specificity were 0.67 (95% CI, 0.39–0.86) and 0.95 (0.84–0.99), respectively, and positive and negative predictive values were 0.80 (0.49–0.94) and 0.91 (0.78–0.96) for detecting worsening AKI. While a higher UMS was associated with greater likelihood of receiving RRT and crude hospital death; these observations did not persist in multivariable adjustment.

Discussion

We conducted a prospective cohort study comparing the urine microscopy profile in critically ill patients with septic and non-septic AKI and its association with kidney injury-specific biomarkers, worsening AKI, need for RRT initiation and hospital mortality.

Key findings

Firstly, critically ill septic patients had notably higher UMS when compared with non-septic patients. While the septic patients were generally sicker, the microscopy scores were higher, despite no difference in the severity of AKI when assessed by routine measures such as RIFLE category, creatinine, urea or oliguria. Secondly, urine biochemical indices (i.e. FeNa, FeU) generally correlated poorly with UMS. While there was no apparent difference by sepsis; ~50% of patients with a UMS/C21 ≥ 3 had a FeNa < 1%.

Table 4. Details of kidney function and outcomes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Septic (n = 43)</th>
<th>Control (n = 40)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline kidney function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (µmol/L) [median (IQR)]</td>
<td>75 (65–85)</td>
<td>76 (68–90)</td>
<td>0.73</td>
</tr>
<tr>
<td>Serum urea (mmol/L) [mean (SD)]</td>
<td>5.8 (2.3)</td>
<td>5.8 (2.3)</td>
<td>0.75</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²) [mean (SD)]</td>
<td>87.9 (27.0)</td>
<td>92.5 (34.4)</td>
<td>0.50</td>
</tr>
<tr>
<td>eGFR &lt; 60 mL/min/1.73m² (n, %)</td>
<td>3 (7.0)</td>
<td>6 (15.0)</td>
<td>0.30</td>
</tr>
<tr>
<td>Enrollment kidney function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (µmol/L) [mean (SD)]</td>
<td>155 (94)</td>
<td>146 (146)</td>
<td>0.71</td>
</tr>
<tr>
<td>Serum urea (mmol/L) [mean (SD)]</td>
<td>12.2 (7.1)</td>
<td>10.1 (8.5)</td>
<td>0.25</td>
</tr>
<tr>
<td>RIFLE category at enrollment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk (n, %)</td>
<td>26 (60.5)</td>
<td>30 (75.0)</td>
<td>0.43</td>
</tr>
<tr>
<td>Injury (n, %)</td>
<td>10 (23.3)</td>
<td>6 (15.0)</td>
<td>0.74</td>
</tr>
<tr>
<td>Failure (n, %)</td>
<td>7 (16.3)</td>
<td>4 (10.0)</td>
<td>0.53</td>
</tr>
<tr>
<td>Urine output (mL/h) [median (IQR)]</td>
<td>63 (46–132)</td>
<td>69 (44–145)</td>
<td>0.74</td>
</tr>
<tr>
<td>Oliguria (n, %)</td>
<td>5 (12.2)</td>
<td>7 (19.4)</td>
<td>0.17</td>
</tr>
<tr>
<td>Nephrotoxin (n, %)</td>
<td>24 (55.8)</td>
<td>29 (72.5)</td>
<td>0.17</td>
</tr>
<tr>
<td>Urine [sodium] (mmol/L) [median (IQR)]</td>
<td>50.9 (38.6)</td>
<td>72.2 (51.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>FeNa (%) [median (IQR)]</td>
<td>0.93 (0.13–2.20)</td>
<td>0.72 (0.28–2.89)</td>
<td>0.85</td>
</tr>
<tr>
<td>FeU (%) [median (IQR)]</td>
<td>38.7 (27.2–49.3)</td>
<td>42.0 (31.1–51.3)</td>
<td>0.44</td>
</tr>
<tr>
<td>Loop diuretics (n, %)</td>
<td>29 (67.4)</td>
<td>21 (52.5)</td>
<td>0.19</td>
</tr>
<tr>
<td>Worsened AKI (n, %)</td>
<td>10 (23.6)</td>
<td>9 (22.5)</td>
<td>1.0</td>
</tr>
<tr>
<td>RRT (n, %)</td>
<td>5 (12.5)</td>
<td>8 (18.6)</td>
<td>0.55</td>
</tr>
<tr>
<td>Hospital death (n, %)</td>
<td>19 (44.2)</td>
<td>6 (15.0)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*Nephrotoxin exposure included: radiocontrast media; aminoglycosides, cardiopulmonary bypass, rhabdomyolysis (serum CK >1500 U/L); amphotericin.

There are several limitations to our study. Firstly, our study was relatively small and observational in nature, making it prone to bias. Secondly, our study had relatively limited statistical power. This did not allow for more comprehensive multivariable adjustment of potential confounding variables in the regression analysis of UMS and serum biochemistry, serum/urine NGAL, worsening AKI and RRT initiation or mortality. Thirdly, also due to the sample size and relatively low overall event rate, our findings may be prone to a type II error. Fourthly, for this study, only one nonblinded clinician scored all urine microscopy. Despite these limitations, our study is the first prospective study performed in critically ill patients to correlate urine microscopy findings and kidney injury-specific biomarkers such as NGAL and identifies several novel associations which are logical and biologically plausible. However, we recognize our findings are preliminary and require additional confirmatory investigation.

Comparison with prior literature

There is a relative paucity of clinical studies that have assessed the value of urine microscopy in the diagnostic
evaluated AKI and none have focused on critically ill populations [12, 15–18, 32]. Marcussen et al. [17]
described the urine cytodiagnostic profile in a small cohort of 51 non-critically ill hospitalized patients with AKI. Similar to our data, this study showed a higher total number of observed renal tubular cells and casts in patients with more severe AKI, including those that required RRT. Chawla et al. [16]

Table 5. UMS stratified by sepsis and AKI parameters

<table>
<thead>
<tr>
<th>Urine sediment score</th>
<th>Total* (n, %)</th>
<th>Septic</th>
<th>Control</th>
<th>Risk</th>
<th>Injury</th>
<th>Failure</th>
<th>FeNa [median (IQR)]</th>
<th>FeNa &lt;1% (n, %)</th>
<th>FeU [median (IQR)]</th>
<th>pNGAL (ng/mL) [median (IQR)]</th>
<th>uNGAL (ng/mg) [median (IQR)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>27 (34.6)</td>
<td>6 (15)</td>
<td>21 (55.3)</td>
<td>21 (38.9)</td>
<td>5 (35.7)</td>
<td>1 (10.0)</td>
<td>0.94 (0.26–2.91)</td>
<td>14 (51.9)</td>
<td>39.6 (33.9–61.6)</td>
<td>173 (98–252)</td>
<td>27 (9–97)</td>
</tr>
<tr>
<td>1–2</td>
<td>25 (32.1)</td>
<td>15 (37.5)</td>
<td>10 (26.2)</td>
<td>18 (33.3)</td>
<td>4 (28.6)</td>
<td>3 (30.0)</td>
<td>0.55 (0.10–0.94)</td>
<td>19 (76.0)</td>
<td>40.4 (34.5–48.8)</td>
<td>161 (108–262)</td>
<td>84 (36–249)</td>
</tr>
<tr>
<td>≥3</td>
<td>26 (33.3)</td>
<td>19 (47.5)</td>
<td>7 (18.4)</td>
<td>15 (27.8)</td>
<td>5 (35.7)</td>
<td>6 (60.0)</td>
<td>0.93 (0.32–2.20)</td>
<td>13 (50.0)</td>
<td>30.9 (14.7–46.8)</td>
<td>426 (250–509)</td>
<td>550 (32–1948)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.001</td>
<td></td>
<td></td>
<td>0.32</td>
<td></td>
<td></td>
<td>0.17</td>
<td>0.11</td>
<td>0.41</td>
<td>0.07</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Urine in five patients was unsuitable for evaluation.

Table 6. UMS stratified by worsened AKI, RRT and hospital death

<table>
<thead>
<tr>
<th>Urine Microscopy Score</th>
<th>Groups (n, %)</th>
<th>RIFLE category (n, %)</th>
<th>Urine biochemistry</th>
<th>Biomarkers</th>
</tr>
</thead>
</table>

Fig. 1. Boxplot of uNGAL stratified by UMS.

Fig. 2. Correlation of uNGAL and UMS.
developed and validated a urine sediment cast scoring index, based on the detection of granular and renal tubular cell casts, and prospectively evaluated its performance for prediction of worsening AKI or need for RRT in 18 hospitalized non-ICU patients with AKI. Those patients with worsening AKI had a significantly higher cast scoring index compared to those who had early kidney recovery. This study found that a standardized scoring method for urine microscopy can be applied and have utility for predicting the clinical course for hospitalized patients with AKI. More recently, Perazella et al. [15, 18] have reported two larger prospective observational studies evaluating the diagnostic value of a urine sediment score in non-ICU hospitalized patients with AKI to predicting a composite of ‘worsened AKI’, defined as an increase in AKIN stage, need for RRT and/or hospital death. Of the 197 patients included in the primary analysis, 40% (n = 79) experienced worsened AKI. A higher urine sediment score was associated with an increased adjusted risk for worsening AKI. Our data would reinforce these findings, suggesting a higher UMS at the time of evaluation was more predictive of worse clinical outcome when compared to patients with benign urine sediment.

However, none of these studies specifically examined the urine sediment in critically ill septic patients. Graber et al. [32] examined the urine microscopy findings in 65 non-ICU septic AKI patients and described abundant ‘bubble cells’, renal tubular cells and casts in those with more established AKI. However, in a systematic review, we found few studies describing the urine microscopy in septic AKI, and in those that did, the majority reported normal urine sediment [13]. Contrary to such reports, our data would now suggest that, in critically ill patients characterized by a higher illness severity, the urine microscopy in septic AKI shows greater evidence of tubular injury when compared to non-septic patients with similar severity of AKI.

**Interpretation and clinical relevance**

Our data would support the premise that a standardized method of urine microscopy evaluation can help discriminate patient subsets with AKI. These observations support prior experimental data suggesting septic AKI may show important differences in pathophysiology and be characterized by a relatively higher burden of acute tubular injury when compared to non-septic AKI [7–9]. This novel finding is further corroborated by the correlation between increasing UMS and increasing uNGAL, both measures of tubular injury. This would support the notion that, in the absence of kidney biopsy data, uNGAL may be a superior biomarker of histological renal tubular injury compared with pNGAL. Interestingly, however, the association between increasing tubular injury and tubular function would appear more complex and somewhat dissociated. A significant proportion of those patients with high UMS had relatively preserved tubular function when expressed as capacity to generate a FeNa <1%. This would suggest a significant proportion of patients may be diagnosed with ‘prerenal azotemia’ yet have microscopic evidence of tubular injury. These findings may relate to the heterogeneous nature of tubular injury associated with AKI in critical illness or the use of vasopressors and/or diuretics [33–35]. An alternative hypothesis may relate to sepsis-induced reductions in creatinine production, as shown by Doi et al, which may explain the UMS finding [36]. For example, it is possible that the septic AKI patients developed more severe AKI as reflected by the UMS findings, but the serum creatinine did not rise, as it would have in non-septic AKI due to the effect of sepsis on creatinine production.

Overall, our observations would further assert the complementary value of inclusion of routine urine microscopy in the diagnostic evaluation of AKI and utility for predicting worsening AKI in critically ill patients [15, 16, 18].

**Conclusion**

Septic AKI is associated with greater urine microscopic evidence of kidney tubular injury compared with non-septic AKI, despite similar severity in AKI. Moreover, a higher UMS correlates with elevations in kidney injury-specific biomarkers; however, not with conventional urine biochemical indices. An increase in the UMS was also associated with higher adjusted likelihood of worsening AKI and correlated with RRT initiation and mortality. These observations would imply that urine microscopy may be of more clinical utility that appreciated in the evaluation of critically ill patients with AKI. Furthermore, these findings question the diagnostic and prognostic value and interpretability of conventional measures of AKI such as the FeNa. Further investigation is needed to better understand whether an assessment of urine microscopy has complementary role for improved discrimination of AKI severity and prediction of the clinical course for critically ill patients with AKI.

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