Diagnostic Utility of Serial Microscopic Examination of the Urinary Sediment in Acute Kidney Injury

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Abstract

Background Microscopic examination of the urinary sediment (MicrExUrSed) is an established diagnostic tool for AKI. However, single inspection of a urine specimen during AKI is a mere snapshot affected by timing. We hypothesized that longitudinal MicrExUrSed provides information otherwise not identified in a single inspection.

Methods MicrExUrSed was undertaken in patients with AKI stage ≥2 and suspected intrinsic cause of AKI seen for nephrology consultation over a 2-year period. MicrExUrSed was performed on the day of consultation and repeated at a second (2–3 days later) and/or third (4–10 days later) interval. Cast scores were assigned to each specimen. Chawla scores (CS) 3–4 and Perazella scores (PS) 2–4 were categorized as consistent with acute tubular injury (ATI), whereas CS 1–2 and PS 0–1 were categorized as nondiagnostic for ATI (non-ATI). Nonrecovering AKI was defined as a rise in serum creatinine (sCr) ≥0.1 mg/dl between microscopy intervals.

Results At least two consecutive MicrExUrSed were performed in 121 patients (46% women, mean age 61±14, mean sCr at consult of 3.3±1.9 mg/dl). On day 1, a CS and PS consistent with non-ATI was assigned to 64 (53%) and 70 (58%) patients, respectively. After a subsequent MicrExUrSed, CS and PS changed to ATI in 14 (22%) and 16 (23%) patients. Thus, 20%–24% of patients only revealed evidence of ATI after serial MicrExUrSed was performed. Patients with nonrecovering AKI were more likely to change their PS to the ATI category (odds ratio, 5.8; 95% CI, 1.7 to 19.3; P=0.005 and positive likelihood ratio, 2.0; 95% CI, 1.3 to 2.9).

Conclusions Serial MicrExUrSed revealed diagnostic findings of ATI otherwise not identified in a single examination. A repeat MicrExUrSed may be warranted in patients AKI of unclear etiology that are not recovering.

Introduction

Microscopic examination of the urinary sediment (MicrExUrSed) is a well-established clinical tool of diagnostic and prognostic value in the evaluation of AKI (1–4). Specifically, the identification of renal tubular epithelial cells (RTECs) and granular casts (GCs) strongly suggest a diagnosis of acute tubular injury (ATI) (5,6), the most common cause of acquired AKI in the hospital setting (7). The abundance of “muddy” brown GCs is considered a pathognomonic finding for ATI. Over a decade ago, the first systematic approaches to grade findings from urinary sediment microscopy were developed. The Chawla score (CS) and Perazella score (PS) were created with the intention to standardize the identification of GCs, RTECs, and RTEC casts (RTECCs) (2,3). These scores demonstrated diagnostic and prognostic value in the evaluation of AKI due to ATI. The CS is determined by assessing the percentage of low-power fields (LPFs) with GCs and RTECCs, whereas the PS is determined by identifying the number of GCs in an LPF and the number of RTECs in a high-power field. However, these scores were designed on the basis of a single examination of the urinary sediment. Although casts provide valuable diagnostic clues, the natural history of cast formation remains unexplored. Thus, a single inspection of a urinary sediment specimen during AKI is a mere snapshot that depends on the day of inspection. Therefore, potential evidence of ATI can be missed. We hypothesized that longitudinal MicrExUrSed can provide additional diagnostic information otherwise not identified in a single inspection.

Materials and Methods

This study was conducted with approval from the Institutional Board Review and in accordance with the Declaration of Helsinki. Urine specimens were collected from patients with AKI stage ≥2 (measured by Kidney Disease: Improving Global Outcomes), who were seen on consultation in an inpatient nephrology service over a 2-year period at Ochsner Medical Center when an intrinsic etiology of AKI was suspected and members of the research staff were available (8).
Microscopic examination of the urinary sediment was performed as soon as possible, and always within 1 hour of sample collection. Once collected, specimens were kept at room temperature and transferred to the laboratory. A 10 ml aliquot of urine was placed in a 15 ml high-clarity polypropylene conical tube and centrifuged at 800 $\times$ g for 5 minutes. The supernatant was poured off, and the pellet was resuspended by manual agitation in the remaining 0.2 ml of supernatant. A plastic transfer pipette was used to place a single drop on a standard microscope slide, and a coverslip was placed over it. This process was done with and without Sternheimer-Malbin stain (Kova, Garden Grove, California) (9). Then each sample was examined by a trained operator using a Nikon Eclipse E200 microscope (Melville, New York) with 10$\times$ and 40$\times$ magnification objectives, and a 10$\times$ magnification eye-piece. The entirety of the slide was examined at both LPF (100$\times$ magnification) and high-power fields (400$\times$ magnification).

Representative images of all sample slides were taken using an Apple iPhone 6S camera (Cupertino, California) and LabCam microscopy adaptor (iDu Optics, New York, New York) on a Leica CME microscope (Buffalo Grove, Illinois). At least two operators independently assessed and scored each specimen, one operator was blinded to the clinical data and one was unblinded. Operators included nephrologists, nephrology fellows, internal medicine residents, and medical students who were trained to determine both PS and CS.

Microscopic examination of the urinary sediment was first performed on the day of consult (day 1). Then, a subsequent serial MicrExUrSed was attempted to be performed at a second time interval defined as days 2–3 from the day of the consult, and/or at a third time interval defined as day 4–10 from the day of the consult. A second and third serial microscopy was not uniformly completed for all of the patients in the cohort. Microscopic examination of the urinary sediment was not repeated if the patient was anuric, discharged, deceased, commenced hemodialysis, or there was an inability to collect urine due to staffing or logistics.

Urinary cast scores (CS and PS) for ATI were determined at each serial microscopy interval (Supplemental Tables 1 and 2) (5,6). A CS of 3–4 and a PS of 2–4 was categorized as consistent with ATI, whereas a CS of 1–2 and PS of 0–1 was categorized as nondiagnostic for ATI (Figures 1 and 2).

To evaluate for factors influencing the probability of conversion of the urine cast score from the non-ATI category to the ATI category, we examined the course and timing of AKI. Thus, we defined nonrecovering AKI as a rise in serum creatinine $\geq$0.1 mg/dl at the time of either the second or third serial microscopy compared with the serum creatinine on the day of the first microscopy. When the serum creatinine trends down even by 0.1 mg/dl, most clinicians interpret it as a positive trajectory and the initial diagnostic suspicion is typically not challenged. However, when serum creatinine does not decrease, the practicing clinician might be interested in reassessing the tentative diagnosis. In addition, we arbitrarily defined early period of AKI as the first 6 days after the onset of AKI and late period of AKI as $\geq$7 days since the onset of AKI.

A presumptive etiology of AKI was determined on the basis of available clinical information as previously reported (10): ischemic ATI was considered in patients when AKI occurred after hemodynamic instability (shock, hypotension, large fall in systolic BP, tachyarrhythmia, bradyarrhythmia), volume depletion unresponsive to intravenous expansion or exposure to vasomotor drugs (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcineurin inhibitors) that did not resolve on drug...
discontinuation; toxic ATI was considered when AKI occurred after exposure to an exogenous toxin (e.g., iodinated radiocontrast, vancomycin) or endogenous toxin (e.g., myoglobin, light chains); acute GN was considered when it was biopsy proven or when AKI included suggestive elements such as serologic values, clinical context, and/or urinary acanthocytes; hepatorenal syndrome was considered on the basis of the established diagnostic criteria (11); prerenal azotemia was considered when AKI occurred after a history of volume depletion, and the AKI resolved after some form of fluid resuscitation; cardiorenal syndrome was considered when AKI occurred in the context of acute decompensated heart failure; and obstructive uropathy was considered when AKI occurred with radiologic evidence of obstruction of the urinary outlet.

As outcome measures, we assessed the odds ratio (OR) and positive likelihood ratio (1 LR) and 95% confidence interval (95% CI) of conversion of urine cast score from a non-ATI category to an ATI category by either the CS or the PS, on the basis of two exposure variables: nonrecovering AKI and late period of AKI. Additionally, we assessed the effect of serial MicrExUrSed on the predictive value of urine cast scores, PS or CS, in determining the likelihood of a poor renal outcome defined as a combined endpoint of ≥50% increase in serum creatinine at discharge (acute kidney disease, AKD) or need for RRT during AKI (AKI-RRT). Because hepatorenal syndrome type 1 is a functional form of AKI known to carry a high risk for poor renal outcomes without overt findings of ATI by MicrExUrSed (11), we established a prespecified subgroup of AKI in patients without end-stage liver disease (non-ESLD) for both analyses. Statistical analyses were performed using GraphPad Prism 7 software package (San Diego, California). A P value <0.05 was deemed significant.

Results
A total of 497 microscopic examinations of the urinary sediment were performed during the study period. Of these,
Figure 3. Flow chart illustrating the patient selection and study methods. *Patients did not receive serial microscopy due to anuria, discharge, death, commencement of hemodialysis, or inability to collect urine due to staffing or logistics.

Table 1. Baseline characteristics of patients included in the cohort (n=121)

| Characteristic                              | Result                              |
|--------------------------------------------|-------------------------------------|
| Age, yr, median (xxx)                      | 61 (25–88)                          |
| Gender, % (n)                              |                                     |
| Female                                     | 36 (44)                             |
| Male                                       | 64 (77)                             |
| Race, % (n)                                |                                     |
| White                                      | 62 (75)                             |
| Black                                      | 31 (37)                             |
| Hispanic                                   | 4 (5)                               |
| Unknown                                    | 3 (4)                               |
| Primary etiology of AKI, % (n)             |                                     |
| Ischemic ATI                               | 59 (71)                             |
| Toxic ATI                                  | 6 (7)                               |
| Ischemic/toxic ATI                         | 9 (11)                              |
| Hepatorenal syndrome                       | 13 (16)                             |
| Acute GN                                   | 5 (6)                               |
| Prerenal azotemia                          | 3 (4)                               |
| Interstitial nephritis                     | 2 (2)                               |
| Cardiorenal syndrome                       | <1 (1)                              |
| Obstructive nephropathy                    | <1 (1)                              |
| Other                                      | 2 (2)                               |
| Secondary etiology of AKI, % (n)           |                                     |
| Ischemic ATI                               | 8 (1)                               |
| Toxic ATI                                  | 8 (1)                               |
| Hepatorenal syndrome                       | 54 (7)                              |
| Obstructive nephropathy                    | 23 (3)                              |
| Other                                      | 8 (1)                               |
| Preexisting CKD stages 3A to 5*, % (n)     | 35 (45)                             |
| Baseline serum creatinine, mg/dl, median (range) |                     |
| AKI on CKD                                 | 1.5 (0.9–4.3)                       |
| de novo AKI (no preexisting CKD)           | 0.9 (0.6–1.7)                       |
| Serum creatinine at first urine microscopy (mg/dl) | 3.3 (0.8–12.0)                  |
| AKI KDIGO stage at first urine microscopy (%) |                                     |
| Stage 2                                    | 20                                  |
| Stage 3                                    | 80                                  |

AKI, acute kidney injury; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes.

*CKD status was determined by baseline eGFR before AKI. Patients without baseline eGFR data were considered de novo AKI.
Serial inspection was not performed in 222 patients and those were excluded. At least two serial microscopic examinations of the urinary sediment were performed in 121 patients with AKI that composed the cohort (Figure 3). Among them, 105 had a subsequent microscopic examination performed on the second time interval (days 2 or 3 after consultation), and 49 had subsequent microscopic examination performed on the third time interval (days 4–10 after consultation). Three serial examinations were performed on 33 (27%) patients. The patients who entered the cohort had a median age of 61 (25–88) years, 36% of them (n=44) were female, and were primarily White (62%) or Black (31%) race. The mean serum creatinine at the time of the initial urine microscopy was 3.3±1.9 mg/dl, with 80% of the patients diagnosed with stage 3 AKI, and 20% with stage 2 AKI. Preexisting CKD stages 3A to 5 was present in 35%. The presumptive etiology of AKI on the basis of clinical grounds with consideration of MicrExUrSed findings was primarily ischemic ATI, which accounted for 59% (n=71) of patients (Table 1). Dialysis was required in 46 (38%) patients during their course of AKI.

On day 1, a CS and PS consistent with non-ATI was assigned to 64 (53%) and 70 (58%) patients, respectively. Among those 64 and 70 patients, CS and PS changed from the non-ATI category to ATI in 16 (23%) and 14 (22%) (Figure 4). Thus, 14 of 71 (20%) (by CS) and 16 of 67 (24%) (by PS) patients only revealed evidence of ATI after serial urinary sediment microscopy was performed. In contrast, in 23 out of 51 (45%) patients (by PS) and 20 out of 57 (35%) patients (by CS), the initial urine sediment inspection classified the specimen under the ATI category, but it regressed to non-ATI on subsequent serial inspection. Of note, 11 out of 23 (55%) per PS and 11 out of 20 (48%) per CS had nonrecovering AKI.

When the findings by microscopic examination of the urinary sediment were assessed over time, we observed that specimens categorized as ATI were identified throughout the temporal spectrum of AKI (Figure 5). Although the highest number of patients with ATI was found within the 4–6 day AKI interval, patients with AKI were found at all time intervals.

Patients with nonrecovering AKI were more likely to change their PS from non-ATI to ATI, compared with those with stable or improved AKI (OR, 5.8; 95% CI, 1.7 to 19.3, $P=0.005$ and + LR, 2.0; 95% CI, 1.4 to 2.9). On the basis of
CS, the OR was 1.1 (95% CI, 0.6 to 3.2), not statistically significant ($P=0.09$) and the + LR was 1.2 (95% CI, 0.6 to 2.2). Among the non-ESLD subgroup ($n=63$), on the basis of PS, OR was 12.4 (95% CI, 2.4 to 65.1), $P=0.003$ and + LR was 2.5 (95% CI, 1.5 to 4.2). On the basis of CS, the OR was 1.3 (95% CI, 0.3 to 6.8), $P=0.73$ and + LR was 1.2 (95% CI, 0.5 to 2.7) (Figure 6).

In terms of the influence of timing of the microscopic examination of the urinary sediment, there was no significant difference in the rate of change in ATI category when the serial microscopy was performed at a late stage of AKI ($\geq 7$ days) compared with early AKI (<7 days). On the basis of PS, the OR was 1.0 (95% CI, 0.4 to 2.8), $P=1.0$ and + LR was 1.0 (95% CI, 0.7 to 1.5). On the basis of CS, the OR was 0.8 (95% CI, 0.6 to 2.3), $P=0.7$ and + LR was 0.9 (95% CI, 0.6 to 1.4) (Figure 6).

Additionally, we assessed whether serial urinary sediment microscopy improved the prognostic value of a single inspection. With findings obtained on initial microscopy alone, urine cast scores did not predict AKD or AKI-RRT. On the basis of PS, the OR was 1.8 (95% CI, 0.7 to 4.2), $P=0.2$ and + LR was 1.4 (95% CI, 0.8 to 2.5). On the basis of CS, the OR was 1.3 (95% CI, 0.6 to 3.0), $P=0.5$ and + LR was 1.2 (95% CI, 0.7 to 1.9). With the addition of serial microscopy, both the OR and + LR numerically decreased on the basis of PS (OR, 1.5; 95% CI, 0.6 to 3.3, $P=0.37$ and + LR, 1.2; 95% CI, 0.8 to 1.8) and numerically increased on the basis of CS (OR, 1.8; 95% CI, 0.8 to 4.0, $P=0.18$ and + LR, 1.3; 95% CI, 0.9 to 1.9) but remained equally nonsignificant (Figure 7). However, when the analyses were restricted to the non-ESLD subgroup ($n=63$), serial microscopy partially altered the prognostic value of ATI cast scores. On the basis of PS, at initial microscopy alone, the OR was 3.1 (95% CI, 1.1 to 9.3), $P=0.04$ and + LR was 1.9 (95% CI, 1.0 to 3.8), whereas after serial microscopy, the OR was 2.6 (95% CI, 0.9 to 7.4), $P=0.09$ and + LR was 1.4 (95% CI, 0.9 to 2.2). On the basis of CS, at initial microscopy the OR was 2.3 (95% CI, 0.8 to 6.4, $P=0.13$ and + LR was 1.4 (95% CI, 0.9 to 2.2), whereas after serial microscopy, the OR was strengthened to 3.3 (95% CI, 1.0 to 10.3), $P=0.04$ and + LR remained 1.4 (95% CI, 1.0 to 2.0).

When a subgroup analysis of patients with nonrecovering AKI ($n=66$) were assessed for prediction of AKD or AKI-RRT, we found that on initial microscopy, on the basis of PS,
the OR was 1.3 (95% CI, 0.4 to 4.9), \( P = 0.66 \) and + LR 1.2 (95% CI, 0.6 to 2.3), whereas on the basis of CS, the OR was 1.9 (95% CI, 0.5 to 7.2), \( P = 0.67 \) and + LR was 1.4 (95% CI, 0.7 to 2.7). On subsequent microscopy, the OR and + LR were once again numerically decreased on the basis of PS (OR, 1.1; 95% CI, 0.3 to 4.2, \( P = 0.91 \) and + LR, 1.0; 95% CI, 0.6 to 1.7) but numerically increased on the basis of CS (OR: 2.2; 95% CI, 0.5 to 9.5, \( P = 0.28 \) and + LR, 1.3; 95% CI, 0.7 to 2.4) (Figure 8).

**Discussion**

Microscopic examination of the urinary sediment is an established technique to aid in the diagnosis of AKI (12). Many practitioners use this tool in clinical practice. When an initial urinary inspection reveals a bland sediment without relevant findings, treatment providers may occasionally perform a second inspection later in the course of AKI, particularly in scenarios where clinical suspicion for an intrinsic cause of AKI is high. Although this approach of repeating urinary sediment inspection may be customary for a subset of nephrology providers, it lacked supporting evidence of its benefit. Thus, our report provides a rationale for the performance of serial urinary sediment examination when clinically indicated.

Our study evaluated the utility of serial urinary sediment microscopy and demonstrated that it is valuable diagnostically. By repeating urinary sediment microscopy, we were able to uncover an additional approximately 20%–25% of patients with ATI that were not identified on the initial microscopy. This accounts for approximately 20%–25% of total patients with ATI (Figure 4). Thus, many patients with overt ATI could be missed with a single inspection. Furthermore, we observed that patients with nonrecovering AKI were more likely to convert from non-ATI to ATI category as per PS. This observation is clinically meaningful in that practitioners often encounter patients with AKI without a clear-cut etiology. In those patients, if the kidney function improves, determining the etiology may be seen as clinically irrelevant. However, when patients exhibit a stagnant or worsening clinical course, it may be important for the practitioner to reassess the etiology of AKI due to potential implications in management. Our results indicate that serial urinary sediment microscopy may offer additional diagnostic clues to ascertain the etiology of AKI.

The natural history of cast formation is not fully understood (13). When microscopic examination of the urinary sediment is performed, it has remained unclear whether the timing of the test may affect the ability of the operator to catch relevant findings. Thus, we assessed the relationship between the temporal spectrum of AKI and the findings on urine microscopy. We observed a wide distribution of patients with ATI along the duration of AKI (Figure 5). In other words, patients with ATI were identified when the inspection of a urine specimen was performed either early or late in the course of AKI. This observation is reassuring in that the duration of AKI should not discourage against performing or repeating the test. Interestingly, evidence
of ATI appears to be clustered around days 4–6 from the onset of AKI, but that observation may only reflect the higher number of examinations performed within that time period, likely due to the average timing of the inpatient nephrology consultations. Furthermore, another aspect related to timing was the observation of a small subset of patients found to have ATI on initial microscopy but not on serial microscopy. This finding suggests that a bland sediment in a single inspection late in the course of AKI could correspond to a case of ATI should the inspection had occurred earlier. Thus, clinical suspicion remains critical when interpreting findings on urine microscopy.

Aside from diagnostic capacity, CS and PS have been previously shown to be prognostic biomarkers (2,3). Urinary sediment findings have been found to correlate well with biomarkers of AKI and were associated with higher odds of poor renal outcomes (AKI-RRT) (4,14). Contrary to previous reports, in our study, ATI score was not associated with AKD or AKI-RRT, neither on the basis of initial or serial urinary sediment microscopy (Figure 7). However, our cohort was enriched with more patients with ATI by study design compared with previous studies (4,14). Furthermore, patients with ESLD with hepatorenal syndrome type 1 were overrepresented in our cohort compared with previous reports. There are two considerations to take into account in patients with ESLD. Firstly, hepatorenal syndrome type 1 is a functional form of AKI that often progresses to anuria and need for dialysis without evidence of ATI by urine microscopy (11,15). Therefore, ATI scores are expected to be less predictive of poor renal outcomes in this population. Secondly, in patients with pronounced hyperbilirubinemia, RTEC, and RTECC can be found even in the absence of AKI (16). Therefore, misleading ATI scores can be found in that subgroup. Consequently, we reanalyzed the data, restricting them to patients without ESLD, and observed a significant improvement in the prognostic value of ATI score (Figure 7). Despite the enhanced prognostic strength of ATI score for AKD or AKI-RRT in the non-ESLD subgroup, the magnitude of the OR was less than that observed in previous reports (4,14). A plausible explanation for the difference is that our cohort was enriched for patients with more severe AKI.

Our study is not without limitations. First, we rely on the interpretation of trained operators to score each specimen. Although each operator was thoroughly trained to assess and score each sample, variability is plausible. However, interobserver agreement has been reported to be acceptable among nephrologists and/or nephrology providers (2). There is possibility of observer bias as one operator was unblinded. In addition, we found heterogeneity in the

Figure 7. | AKI prognosis assessed by single and serial urine microscopy. OR assessed on the basis of urine sediment score (ATI or non-ATI) at (A) initial microscopy among the entire cohort, (B) serial microscopy among the entire cohort, (C) initial microscopy among non-end stage liver disease (non-ESLD) subgroup, and (D) serial microscopy among non-ESLD subgroup. ATI, acute tubular injury; AKD, acute kidney disease.
results depending on the urine cast score used, namely PS versus CS. Although PS and CS have similarities, they rely on different elements. In particular, PS uses RTECs and CS uses RTECCs. Moreover, CS uses a wide range of percentage of LPFs with casts to assign a score of 3 (10%–90%), and it is often difficult to display uniformity of a sample across all LPFs. Within that range of percentage of LPFs with casts, specimens can fall into a non-ATI or ATI score on the basis of PS that uses the number of GC per LPF instead of the percentage of LPFs with findings. As a result, PS and CS may be seen as complementary, with PS somewhat more robust diagnostically and CS somewhat more robust prognostically. However, a larger sample size may be needed to corroborate these observations. Additionally, our study population is enriched with intrinsic causes of AKI, such as ATI, as it was made up of patients for whom nephrology was consulted and the team suspected an intrinsic cause of AKI. We caution generalizations in other populations that are predominantly prerenal in etiology. In addition, we did not adjust for confounding factors, such as urine output, but we accounted for serum creatinine level and duration of AKI.

In summary, our study adds to the existing literature that indicates microscopic examination of the urinary sediment is a useful clinical tool. Our findings expand its value by demonstrating that serial inspection may provide additional information with potential clinical relevance. We suggest considering the performance of serial urinary sediment microscopy in patients with AKI with suboptimal clinical or nonrecovering course and of uncertain etiology.

Disclosures

J. Velez has participated in advisory board meetings for Mallinckrodt Pharmaceuticals and Retrophin and in a speaker bureau for Otsuka Pharmaceuticals. None of the products related to those engagements are discussed in this manuscript. All remaining authors have nothing to disclose.

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Author Contributions

A.A. Alalwan, A.M. Alghamdi, E. Gonzalez, and M.S. Rivera were responsible for data curation and investigation; J.C.Q. Velez was responsible for conceptualization, investigation, supervision, wrote the original draft, and reviewed and edited the manuscript; and V. Varghese was responsible for data curation, investigation, wrote the original draft, and reviewed and edited the manuscript.
Supplemental Material
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Supplemental Table 1. Criteria matrix for Chawla Score
Supplemental Table 2. Criteria matrix for Perazella Score

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