Concomitant Identification of Muddy Brown Granular Casts and Low Fractional Excretion of Urinary Sodium in AKI

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Key Points
• There is discordance between presence of muddy brown granular casts and the value of fractional excretion of urinary sodium in the determination of acute tubular injury.
• Muddy brown granular casts represent acute tubular injury as confirmed by tissue biopsy diagnosis.
• Muddy brown granular casts have greater prognostic value than fractional excretion of urinary sodium.

Abstract
Background Fractional excretion of urinary sodium (FENa) is a widely utilized clinical test to evaluate acute kidney injury (AKI). A low FENa (<1%) is deemed consistent with prerenal azotemia and inconsistent with acute tubular injury (ATI). Muddy brown granular casts (MBGC) on microscopic examination of urinary sediment (MicrExUrSed) are highly suggestive of ATI. We hypothesized that there is poor concordance between the presence of MBGC and FENa in ATI.

Methods We conducted a prospective observational study in patients with AKI seen during inpatient consultation. We extracted patients who underwent assessment of percentage of low power fields (LPFs) with MBGC by MicrExUrSed and concomitant measurement of FENa. Diagnostic concordance between MBGC and FENa and their individual prognostic value were examined.

Results Our cohort included 270 patients, 111 (41%) of whom were women. Median age was 61 years (range 27–92 years), and median serum creatinine was 3.7 mg/dl (range 1.2–22.0 mg/dl). MBGC were found in 49% (133/270). FENa <1% (inconsistent with ATI) was found in 50/133 (38%), 38/115 (33%), and 16/45 (36%) of those with >0%, ≥10%, and ≥50% LPFs with MBGC, respectively. Concordance between FENa and MBGC for ATI diagnosis was deemed fair (estimated k-coefficient = 0.2), and poor (k = −0.11) within a subgroup of patients with preexisting chronic kidney disease (n = 139). In patients with biopsy-proven ATI (n = 49), MBGC had 100% specificity and 100% positive predictive value for ATI. MBGC were associated with greater risk for ≥50% increase in creatinine from baseline at discharge (acute kidney disease [AKD]).

Conclusions About two of five patients with MBGC identified by MicrExUrSed presented with FENa <1%. Presence of MBGC was consistent with ATI, as verified by biopsy, and were predictive of AKD. These data suggest that the sole reliance in low FENa to exclude ATI should be abandoned, and MicrExUrSed should be pursued for AKI diagnosis.

Introduction
Fractional excretion of urinary sodium (FENa) is a widely utilized diagnostic test in the evaluation of AKI. Seminal studies have described the diagnostic value of FENa in differentiating prerenal azotemia from acute tubular necrosis (1,2). Thereafter, a low FENa (<1%) has been considered consistent with prerenal azotemia and not due to acute tubular injury (ATI). However, these early studies excluded patients with chronic kidney disease (CKD), acute glomerular disease, urinary tract obstruction, or those who received diuretic therapy. In the presence of diuretics, FENa has been found to be less reliable (3). Furthermore, other studies have shown suboptimal performance of FENa to differentiate prerenal azotemia from ATI (4). Despite these pitfalls, FENa remains deeply embedded in medical education as a leading tool in differentiating the etiology of AKI.

Identification of muddy brown granular casts (MBGC) by microscopic examination of urinary
sediment (MicrExUrSed) constitutes a finding highly suggestive of ATI (5,6). Several studies have demonstrated the diagnostic and prognostic potential of urine microscopy scores on the basis of the presence and quantification of granular casts (7–9). In clinical practice, discrepancy between MicrExUrSed findings and FENa value is often encountered. Therefore, we hypothesized that there is a lack of concordance between FENa and the presence of MBGC, and that MBGC are a more reliable indicator of ATI, even in the presence of a low FENa.

Methods

This study was conducted with approval by the Institutional Board Review and in accordance with the Declaration of Helsinki. Urine specimens were collected from patients with AKI stage ≥2 (Kidney Disease: Improving Global Outcomes) (10) 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.

MicrExUrSed was performed as soon as possible and always within 1 hour of specimen collection. Once collected, specimens were kept at room temperature and transferred to the laboratory for processing (11). A 10-ml aliquot of urine was placed in a 15-ml high-clarity polypropylene conical tube and centrifuged at 800 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 onto a standard microscope slide, and a cover-slip was placed over it. This process was done with and without Sternheimer–Malbin stain (Kova, Garden Grove, CA). Then, each sample was examined by a trained operator using a Nikon Eclipse E200 microscope (Melville, NY) with ×10 and ×40 magnification objectives and a ×10 magnification eyepiece. The entirety of the slide was examined at both low-power field ([LPF]; ×100 magnification) and high-power field ([HPF]; ×400 magnification). Representative images of all sample slides were taken using an Apple iPhone 6s camera (Cupertino, CA) and LabCam microscopy adaptor (iDu Optics, New York, NY) on a Leica CME microscope (Buffalo Grove, IL). At least two operators independently assessed and scored each specimen; one operator was blinded to the clinical data, and one operator was unblinded. Operators included nephrologists, nephrology fellows, internal medicine residents, and medical students who were trained to quantify the percentage of LPFs with MBGC. A LPF was considered positive for MBGC if it contained at least one MBGC. A minimum of 36 LPFs per slide were assessed. Of note, several patients received up to three repeated MicrExUrSed on subsequent days (11).

A presumptive etiology of AKI was determined on the basis of available clinical information. Ischemic ATI was considered in cases when AKI occurred after hemodynamic instability (shock, hypotension, large fall in systolic blood pressure, tachyarrhythmia, bradycardia), volume depletion unresponsive to intravenous expansion, or exposure to vasomotor drugs (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcineurin inhibitors) that did not resolve upon 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). Presence of MBGC in MicrExUrSed was also taken into account for clinical diagnosis of ATI. Acute glomerulonephritis was considered when it was biopsy proven or when AKI included suggestive elements such as serological values, clinical context, and/or urinary acanthocytes. Hepatorenal syndrome was considered based on the established diagnostic criteria (12). 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. Obstructive uropathy was considered when AKI occurred with radiologic evidence of obstruction of the urinary outlet.

To assess the concordance of FENa and MBGC, the percentage of LPFs with MBGC in each sample with a recorded FENa was determined. FENa obtained within 24 hours of MicrExUrSed were eligible. A similar analysis was performed for fractional excretion of urea nitrogen (FEUN). A Cohen’s κ-coefficient was calculated to assess the degree of concordance or agreement between the tests in diagnosis ATI (presence of MBGC or FENa ≥1%). κ-Coefficient values range from −1, representing no agreement, to 1, representing perfect agreement. Additionally, a one-way ANOVA was performed to examine the relationship between MBGC abundance and variance of FENa between 0% and 1%, and between ≥1% and beyond. To assess the performance of MicrExUrSed or FENa for ATI diagnoses further, we examined a subgroup of patients with confirmed pathologic evidence of ATI from a kidney biopsy specimen. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were determined for both MBGC and FENa with respect to identifying biopsy-proven ATI. To assess and compare the prognostic value of MBGC, we computed two clinical outcomes: (1) ≥50% increase from baseline serum creatinine (sCr) at discharge (acute kidney disease or AKD); and (2) acute need for dialysis (AKI with need for renal replacement therapy [AKI-RRT]) during hospitalization. Odds ratios (OR) and positive likelihood ratios (+LR) were calculated to assess the ability of FENa ≥1%, ≥2%, and ≥5% compared with FENa <1%, respectively, and the presence of MBGC expressed as >0%, ≥10%, and ≥50% of LPFs compared with absence of MBGC, respectively, to predict AKD and AKI-RRT. Statistical analyses were performed using GraphPad Prism v7 (GraphPad Software, San Diego, CA). A P value <0.05 was deemed significant. A subanalysis was performed among patients without end stage liver disease (ESLD).

Results

From a primary cohort of 371 patients who underwent MicrExUrSed during the study period, 270 also had a FENa value obtained concomitantly, and these were included in the study. Women accounted for 111 (41%) patients. The median age was 61 years (range 27–92 years), and 40% were Black. The median sCr at the time of MicrExUrSed was 3.7 mg/dl (range 1.2–22.0 mg/dl). The etiology of AKI (pure de novo AKI 62%, AKI on CKD 38%) was ischemic ATI (47%), toxic ATI
was deemed fair (estimated LPFs with MBGC, respectively (Figure 1). Thus, the concordance between FEUN and MicrExUrSed for ATI diagnosis was deemed fair (estimated $\kappa$-coefficient=0.2; 95% confidence interval [95% CI], 0.08 to 0.3). When the data were subanalyzed on the basis of presence of preexisting CKD (i.e., AKI on CKD), FEUN was <1% in 20/52 (38%), 15/45 (33%), and 6/13 (46%) of those with >0%, ≥10%, and ≥50% LPFs with MBGC, respectively. The concordance between FEUN and MicrExUrSed for ATI diagnosis for those with AKI on CKD was deemed poor (estimated $\kappa$-coefficient=−0.09 [95% CI, −0.3 to 0.1]). To assess further whether the dichotomy of quantifying FENa as <1% or >1% masked a relationship between the abundance of MBGC and the value of FENa, we examined the distribution of FENa values between 0% and 1% with respect to the abundance of MBGC. An ANOVA for trend analysis revealed no significant relationship between the variance of FENa values between 0% and 1% and MBGC abundance (grouped as no MBGC, 0%–10%, 10%–50%, and ≥50%; $F=1.73$; $P=0.17$; Figure 2). Furthermore, we examined the distribution of FENa values ≥1% with respect to the abundance of MBGC. Similarly, an ANOVA for trend analysis revealed no significant relationship between the variance of FENa values ≥1% and MBGC abundance ($F=0.26$; $P=0.08$; Figure 2). In addition, on the basis of adjudicated clinical diagnoses, the sensitivity, specificity, PPV, and NPV of FENa ($n=158$) to distinguish ATI from prerenal azotemia were 54%, 67%, 94%, and 8%, respectively. When comparing patients with abundant MBGC and high FENa with those with abundant MBGC and low FENa, there was no difference in age, sex, race, or presence of preexisting CKD. However, there was a greater percentage with toxic ATN recorded before 28 biopsies, and FENa was 3.4 (1.2–22.0) and 3.7 (1.2–22.0) in 21 (75%) cases, and FENa was ≥1% (median time between FEUN and biopsy=5 days; range 1–15 days) in 21 (75%) cases, and FENa was <1% in seven cases (median time between FEUN and biopsy=5 days; range 1–11 days). All 28 (100%) cases with MBGC were found to have confirmatory evidence of ATI by histopathology. Among those without the presence of MBGC, eight (38%) were noted to have evidence of ATI by histopathology. Thus, the sensitivity, specificity, PPV, and NPV of MBGC to identify ATI as confirmed by kidney biopsy was 78%, 100%, 100%, and 62%, respectively. FENa was recorded before 28 biopsies, and FENa was ≥1% (median time between FEUN and biopsy=5 days; range 1–15 days) in 21 (75%) cases, and FENa was <1% in seven cases (median time between FEUN and biopsy=5 days; range 1–11 days). The sensitivity, specificity, PPV, and NPV of FENa ≥1% to identify ATI on kidney biopsy was 90%, 71%, 90%, and 71%, respectively. In addition, the sensitivity, specificity, PPV, and NPV of the combination of FENa ≥1% and the presence of MBGC to identify ATI on kidney biopsy were 94%, 100%, 100%, and 84%, respectively.

With respect to prognosis, there was a significant number of events. Among those with MicrExUrSed assessed ($n=371$), 68% had AKD, and 37% had AKI-RRT (Table 4). The presence of MBGC was associated with greater probability for AKD at discharge, whereas FENa ≥1% was not associated with the outcome. However, neither presence of MBGC nor FENa ≥1% was associated with AKI-RRT (Figure 3). Omitting patients with ESLD, the OR and +LR

| Table 1. Baseline characteristics of the patients included in the cohort |
|--------------------|------------------|------------------|
| **Characteristic** | **Entire Cohort** | **Cohort with MicrExUrSed and FENA** |
| **Age, median (range)** | 61 (20–92) | 61 (27–92) |
| **Sex** | | |
| Women | 38% (140) | 41% (111) |
| Men | 62% (231) | 59% (159) |
| **Race** | | |
| White | 59% (219) | 54% (147) |
| Black | 33% (124) | 40% (109) |
| Hispanic | 3% (12) | 3% (7) |
| Asian | 1% (4) | <1% (1) |
| Native American | <1% (1) | <1% (1) |
| Unknown | 3% (11) | 2% (5) |
| **Etiology of AKI** | | |
| Ischemic ATI | 50% (184) | 47% (126) |
| Toxic ATI | 10% (36) | 9% (23) |
| Ischemic/toxic ATI | 10% (37) | 14% (37) |
| Hepatorenal syndrome | 10% (38) | 9% (24) |
| Acute | 9% (33) | 11% (29) |
| glomerulonephritis | | |
| Prerenal azotemia | 5% (19) | 4% (11) |
| Interstitial nephritis | 2% (6) | 1% (4) |
| Cardiorenal syndrome | 3% (10) | 2% (5) |
| Obstructive nephropathy | <1% (3) | 1% (4) |
| Other | 1% (5) | 3% (7) |
| CKD | 37% (139) | 38% (102) |
| Baseline serum creatinine, mg/dl, median (range) | 1.4 (0.8–4.2) | 1.0 (0.6–4.2) |
| Serum creatinine at first urine microscopy, mg/dl, median (range) | 3.4 (1.2–22.0) | 3.7 (1.2–22.0) |

Data are expressed as % (n) unless otherwise indicated. MicrExUrSed, microscopic examination of the urinary sediment; FENA, fractional excretion of urinary sodium; ATI, acute tubular injury.
of AKD at discharge further increased among those patients with MBGC identified by MicrExUrSed, whereas the OR and +LR of FENa ≥1\% for AKD remained nonsignificant in this subgroup (Figure 3). With respect to AKI-RRT, although the OR and +LR were numerically higher compared with those for the overall cohort, presence of MBGC was not associated with greater probability of AKI-RRT in the non-ESLD subgroup. Similarly, FENa ≥1\% was not associated with AKI-RRT in this subgroup (Figure 3). The prognostic value of the combination of FENa ≥5\% and MBGC ≥50\% LPFs compared with that of either FENa or MBGC alone was similarly nonsignificant for AKI-RRT but inferior to MBGC alone for AKD (Supplemental Figure 1).

**Discussion**

FENa remains a heavily utilized test in current clinical practice as a “go-to” test to differentiate prerenal azotemia from ATI (13). The diagnostic and prognostic value of urinary cast scores obtained by MicrExUrSed that incorporate the identification of MBGC as markers of ATI has been previously demonstrated and validated by others (7–9,14).

Our study aimed to assess the concordance between these tests. Based on clinical observations, we hypothesized that there is discordance between the FENa and MicrExUrSed findings. We showed that coexistence of the presence of MBGC (abundant in many instances) and a FENa >1\% was a frequent phenomenon that was captured in 37\% of patients in our AKI cohort who underwent MicrExUrSed and had a FENa obtained within 24 hours of the MicrExUrSed. In agreement with our findings, a previous study reported that FENa was <1\% in around 50\% of those with high urinary cast scores consistent with ATI (9). Although abundant MBGC denote ATI, a low FENa theoretically denotes a prerenal state. Thus, this discordance challenges the established notion of low FENa as means to exclude ATI as
AKI etiology. Notably, the discordance between FENa and MBGC was even more pronounced in the context of AKI superimposed on CKD. Similarly, a FEUN of 35% is considered consistent with prerenal azotemia (3). Carvounis et al. identified 89% of patients with prerenal azotemia and diuretic use with FEUN <35% (15). However, we found even greater discordance between FEUN and MBGC.

The degree of discordance between MBGC and FENa may be perceived as surprising, given the expectation that there would be preserved sodium reabsorption in a prerenal state and decreased reabsorption of those molecules in intrinsic tubular injury. We speculate that this disagreement is likely related to the heterogeneity of renal injury in ATI (16). However, it remains to be fully elucidated what is unique about the subgroup of patients with abundant MBGC and low (<1%) FENa compared with those with abundant MBGC and high (≥1%) FENa. One explanation could be that the greater severity of tubular damage, the greater the FENa. However, no difference was observed in clinical outcomes (AKI-RRT, AKD) between the groups (Table 2). Certain factors may theoretically lead to coexistence of low FENa and abundant MBGC, such as degree of damage to the early (S1) and distal segments (S3) of the proximal tubule (which may affect the integrity of sodium and organic transporters) or to the medullary thick ascending loop of Henle (which may affect urinary concentration mechanisms)—factors that ultimately influence the value of FENa (17–24) (Figure 4). Overlap or relative dominance of toxic versus ischemic tubular insult may also play a role. In fact, more patients with toxic ATI exhibited a low FENa, as described by others (25,26). Moreover, fewer patients with concomitant glomerular pathology presented with low FENa—a finding that challenges previous reports. Thus, the multifactorial aspect of many cases of ATI and its associated heterogeneity in tubular injury may lead to the observed variability in FENa. Because uromodulin, the matrix of MBGC, is synthesized in the mTALH, MBGC may tacitly indicate injury to the mTALH (27). However, the formation of casts also depends on electrolyte composition of the filtrate, which can be affected by the integrity of the proximal tubule. Ultimately, MBGC provide tangible evidence of ATI (Figure 4).
Early studies suggested that FENa could be an optimal test for AKI diagnosis. Espinel et al. reported a statistically different value of FENa in prerenal azotemia compared with ATI (P<0.001) and noted 88% of patients with prerenal azotemia had FENa values <1% (2). Similarly, Miller et al. reported that 90% of patients with prerenal azotemia were found to have FENa values <1% (1). Notably, those studies excluded patients with preexisting CKD, acute glomerular disease, urinary tract obstruction, or those who had received diuretic therapy. Therefore, generalizability of their findings to in-hospital AKI is limited. Later, work by others questioned the diagnostic utility of FENa in AKI diagnosis. Forms of toxic ATI such as rhabdomyolysis and contrast-induced AKI have been reported to present with FENa <1% (25,26). Similarly, FENa <1% performs poorly as a threshold to eliminate ATI in patients with AKI in the context of cirrhosis (28). A meta-analysis found urinary indices to be deceptive in states of sodium avidity and obstruction, and in situations with altered intrarenal hemodynamics, documenting 84 patients with low FENa in cases of intrinsic renal failure (29).

Our primary objective was not to reassess the diagnostic utility of MicrExUrSed for distinguishing ATI from prerenal states. Perazella et al. reported a PPV of 100% to diagnose ATI if the pretest probability was high (8). We concur with their conclusions and have incorporated this notion into our clinical practice. On the other hand, in our study, FENa values were not considered for adjudication of AKI etiology. As a result, we were able to assess the diagnostic performance of FENa. The PPV of FENa ≥1% to diagnose ATI was optimal at 94%. However, FENa <1% had a NPV of only 8% to exclude ATI. Therefore, a FENa ≥1% performs well as an indicator of ATI, and a FENa <1% performed poorly as indicator of prerenal azotemia. Notably, the high prevalence of ATI in our cohort may have driven the large discrepancy between the PPV and the NPV of FENa.

Studies in AKI assessing the diagnostic utility of various clinical tests are hindered by the fact that the gold standard for diagnosis of ATI by which the tests in question are measured against are usually based on retrospective chart review and/or clinical judgment. Ideally, tissue diagnosis constitutes definite proof of ATI. A previous study reported correlation of MicrExUrSed with tissue diagnosis and found a sensitivity of 75% in identifying ATI on biopsy using supravital staining techniques (30), whereas others noted a poor correlation between FENa values and tubular injury on histopathology (R=0.267) (31). In our cohort, MBGC had a 100% specificity and 100% PPV for prediction of ATI based on biopsy. FENa ≥1% also performed well as a predictor of ATI with a PPV of 90%. On the other hand, FENa <1% had a NPV of 71%. However, only seven patients who underwent kidney biopsy had a FENa <1%.

Therefore, it is not possible to draw clear conclusions about the NPV of FENa <1%. More importantly, these histologically based data from a subset of patients within the cohort validate the established notion that MBGC are a definite indicator of ATI and strongly suggest that in cases of discordance between FENa and MicrExUrSed, identification of MBGC by MicrExUrSed should override a low FENa. However, a FENa ≥1% had greater sensitivity and NPV than MBGC in identifying ATI on biopsy. Our analysis of FENa ≥5% and presence of MBGC found the combined diagnostic value of these two measures to be superior to one in isolation when in agreement. Additionally, it should be noted that ATI can often coexist with other glomerular pathologies on biopsy (Table 3).

Our cohort included 50% of patients receiving diuretics. Diuretics can promote natriuresis and increase the value of FENa, thereby impairing its diagnostic power. However, our main observation relates to misleading values of FENa <1% coexisting with MBGC rather than misleading values of FENa ≥1%. In fact, diuretics might have masked an even greater percentage of patients with FENa <1% and concomitant MBGC. Nevertheless, we assessed the performance of FEUN as an alternative to FENa on the basis of previous reports suggesting that it is a better test in cases of AKI in patients exposed to diuretics (3,15). Interestingly, we found an even greater discordance between MBGC and FEUN.

Although our primary objective was centered on diagnosis, we examined the performance of MicrExUrSed as a

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**Table 3. Histopathological findings of a subgroup of patients who underwent kidney biopsy**

| Diagnosis                                      | (N=49) |
|-----------------------------------------------|--------|
| ATI (isolated finding)                        | 8 (16%)|
| ATI with other concomitant pathology          | 28 (57%)|
| ATI+glomerulonephritis                        | 14 (29%)|
| ATI+podocytopathy                             | 7 (14%)|
| ATI+diabetic nephropathy                      | 4 (8%)|
| ATI+interstitial nephritis                    | 6 (12%)|
| ATI+miscellaneous pathology                   | 6 (12%)|
| Glomerulonephritis                            | 6 (12%)|
| Podocytopathy                                 | 1 (2%)|
| Diabetic nephropathy                          | 3 (6%)|
| Interstitial nephritis                        | 3 (6%)|
| Miscellaneous pathology                       | 3 (6%)|

The percentages overall do not add to 100% because of two or three overlapping diagnoses within the same specimen and because of rounding. ATI, acute tubular injury.

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**Table 4. Proportion of patients reaching clinical end points (increase in serum creatinine ≥50% from baseline at discharge [AKD] or need for renal replacement therapy [AKI-RRT])**

| Outcome          | FENa measured and MicrExUrSed assessed | MicrExUrSed assessed |
|------------------|----------------------------------------|----------------------|
| AKD              | N=200                                  | N=282                |
|                  | 130 (65%)                              | 193 (68%)            |
| AKI-RRT          | N=270                                  | N=371                |
|                  | 103 (38%)                              | 139 (37%)            |

FENa, fractional excretion of urinary sodium; MicrExUrSed, microscopic examination of the urinary sediment.
prognostic indicator of AKI and contrasted it against that of FENa. For this task, we performed separate analyses for a subset of patients without ESLD because of the pre-established notion that patients with ESLD can acquire AKI due to hepatorenal syndrome type 1, a severe form of AKI characterized by minimal to no presence of MBGC by virtue of its pathogenesis and that is often known to progress to ominous outcomes (including AKD and AKI-RRT) (12). Presence of MBGC predicted AKD but not AKI-RRT, whereas FENa performed poorly on both prognostic end points. Additionally, although combining both FENa and MBGC improved the identification of ATI, MBGC in isolation were superior in predicting AKD. Unlike this study, MicrExUrSed-based cast scores have previously shown strong prognostic value to predict AKI-RRT. However, by virtue of study design, our cohort was heavily enriched with patients with ATI. Only 5% of patients had prerenal azotemia compared with 40% in the study completed by Perazella et al. (8). Thus, our study was not optimally suited to assess prognosis. In addition, MicrExUrSed-based cast scores incorporate not only MBGC but also renal epithelial cells (RTEC) or RTEC casts. Therefore, inclusion of RTEC-based elements might have improved the prognostic estimates in our study.

There are several limitations associated with our study. First, we rely on the interpretation of trained operators to score the MicrExUrSed of 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 (7). Notably, the highest interobserver reliability was seen among granular and MBGC (32). Additionally, observation bias is possible because one observer was unblinded. The selection of our cohort could also limit generalization. Our study cohort is enriched with intrinsic causes of AKI because it was based on patients for whom nephrology was consulted. We caution generalization to other populations where intrinsic renal injury is not the predominant etiology of AKI. Also, the timing between MicrExUrSed and kidney biopsies may have introduced a confounder, given the fact that degree of histologic injury can evolve over time. Nonetheless, most biopsies were performed within a few days of the MicrExUrSed or determination of FENa. Additionally, we have reported predictive values of both FENa and MBGC in determining ATI. These values are highly influenced by prevalence and can be considered an additional limitation. Finally, we were unable to extract accurate urine output data. Because the diagnostic value of FENa is greater in oliguric states, our results may have been affected by the relative number of nonoliguric AKI cases.

In conclusion, our findings suggest that the isolated use of FENa <1% as means to exclude as etiology of AKI should be discouraged. To the contrary, identification of MBGC by MicrExUrSed in patients with AKI should be pursued as a reliable test for diagnosis of ATI.
Figure 4. Schematic illustrating a theoretical model to explain the spectrum of FENa values in patients with AKI due to acute tubular injury (ATI) with urinary sediment containing abundant MBGC. (A) Sodium (Na) avidity due to decreased effective arterial blood volume (EABV) in intact proximal tubuli (PT) promote Na reabsorption and reduce urinary Na (uNa) concentration, thereby reducing the numerator in the FENa equation. Conversely, damaged PT, back-leak of filtrate, and replenished EABV increase uNa and FENa. As the GFR declines and the serum creatinine (Cr) increases in AKI, the relative contribution of tubular secretion of Cr to the total urinary excretion of Cr increases, that is, influencing urinary Cr (uCr) concentration. Intact organic cationic transporters (OCTs) and organic anion transporters (OATs) permit Cr secretion, whereas plasma sulfates (SO₄²⁻) compete with Cr to occupy the OATs. Viable Na⁺K⁺2Cl⁻ cotransporter in the medullary thick ascending loop of Henle (mTALH) maintain interstitial tonicity and allow for water reabsorption and urine concentration. All of these parameters influence urinary Cr (uCr) concentration: affect the uCr and thus the value of FENa. Differences in absolute and relative dysfunction/injury to the early (S1) or distal segment (S3) of the PT or to the mTALH are expected in ischemic/toxic ATI and may influence the FENa. On the other hand, MBGC formation depends on synthesis of the cast matrix uromodulin, degree of cellular injury, and resulting protein and solute composition of the urine. (B) Heterogeneity in ischemic or toxic tubular insults may lead to variable compromise of cortical (C) and juxtamedullary (JM) nephrons, which may further influence the FENa via the mechanisms outlined above.
Supplemental Figure 1. Assessment of combined prognostication of fractional excretion of sodium ≥5% and muddy brown granular casts ≥30% per low-power field in the entire cohort and subanalyzed by the presence of end stage liver disease.

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