Mind the Cast: FENa versus Microscopy in AKI

Melanie P. Hoenig and Samir M. Parikh

When the patient dies, the kidneys may go to the pathologist, but while he lives the urine is ours. It can provide us day by day, month by month, and year by year, with a serial story of the major events going on within the kidney.

Thomas Addis 1948

The simplified language used to describe AKI adopted along with clinical criteria does not alter the fact that this clinical syndrome can be instigated by a diverse range of insults and characterized by a variable clinical course. Barring an unequivocal resolution of oliguria after volume expansion, clinicians possess scant diagnostic tools to differentiate AKI syndromes and must rely on data gleaned from urine chemistry and urinalysis.

The fractional excretion of sodium (FENa), calculated with data from blood and a random urine specimen at the time of AKI, has been used to separate patients with prerenal azotemia from those with acute renal failure. The FENa has been criticized for the fact that it may not perform in the setting of CKD, glomerulonephritis, or obstruction; yet this observation is as it should be. The FENa is only informative if the patient is in a steady state, rather than AKI, as with a patient with CKD, the urine sodium and therefore the FENa may be low or high, depending on sodium intake or the use of diuretics. In glomerulonephritis, the FENa is expected to be low if the tubules encounter a reduction in delivered filtrate but could be high if the patient has tubulointerstitial involvement/inflammation or a more subacute decline in kidney function. Yet, despite these shortcomings, if the FENa is low, most believe that this implies conserved kidney tubular function and potentially a better kidney outcome.

In the accompanying report, Varghese et al. explore the concordance between the FENa and the findings of muddy brown granular casts in the urine sediment. The authors prospectively studied all patients with AKI stage ≥2 (Kidney Disease: Improving Global Outcomes) at their institution over a 2-year course seen in consultation when research staff were available. Unfortunately, in this report, the authors did not categorize patients on the basis of urine output. In their cohort of 270 patients who had concomitant sediment examination and FENa assessed, median serum creatinine at the time of consultation was 3.7 mg/dl and had increased from a median baseline of 1 mg/dl. Nearly two thirds of the patients had ATI from ischemic and/or toxic insult, and just 4% had prerenal azotemia on the basis of a history of volume depletion and resolution of AKI after fluid resuscitation. Yet, a third of patients had a FENa <1%. Thus, they found a disappointingly low negative predictive value for a low FENa when used to exclude ATI.

In contrast, about half of the patients had muddy brown granular casts on evaluation of the urine sediment, and they found a very high positive predictive value for muddy brown casts as a marker of ATI. Although the poor performance of the FENa here may be dictated by the case mix and may not represent the spectrum of patients who develop AKI in the hospital, it is likely that this case mix—with many patients who have ATI—does represent patients commonly seen on nephrology consultative services who have not readily improved with routine care and merit additional evaluation by a nephrologist. In addition, nearly 20% of patients had an “intermediate syndrome” with both a low FENa and significant muddy brown granular casts. Of this group, all had clinical courses consistent with delayed improvement or incomplete recovery, a natural history most consistent with clinical “acute tubular necrosis” rather than the more benign prerenal state.

This group of patients—low FENa but muddy brown casts—highlights a dilemma that has confronted clinicians and researchers for decades: despite the promise of recovery when the FENa is low, when patients also have muddy brown granular casts in the urine sediment, the clinical course appears to match the urine sediment rather than the low FENa. On the surface, these discordant data challenge our understanding of the factors at play in a stressed nephron, but perhaps only because of the simplistic framework when there are at least two additional considerations at play.
Over time, if ischemia persists, the majority of nephrons may become unable to conserve sodium maximally. As a result, the 

Figure 1. | Hypothetical depiction of the distribution of “single nephron” fractional excretion of sodium (FENa) for the whole kidney. In the setting of ischemia, initially, the majority of nephrons may conserve the ability to reabsorb sodium such that the “total” FENa is <1%. Over time, if ischemia persists, the majority of nephrons may become unable to conserve sodium maximally. As a result, the “total” FENa exceeds 1%. Ongoing damage leads to death and sloughing of renal tubular epithelial (RTE) cells, which may appear in the urine or later the setting of ischemia, initially, the majority of nephrons may conserve the ability to reabsorb sodium such that the 

First, the very architecture of the kidney promotes heterogeneous responses across nephrons, thus making it possible that some nephrons are sodium avid whereas others are sloughing dead cells to form muddy brown casts. Under normal conditions, there are significant differences in oxygen delivery and consumption in different regions of the kidney (5). Moreover, the populus cortical nephrons encounter different challenges from their scattered juxtaglomerular counterparts. For both nephron types, filtered blood is the source of oxygen as the efferent arterioles transition to the peritubular capillaries and then the vasa recta. In the cortex where the partial pressure of oxygen is high, proximal tubules consume roughly 50% of the nephrons’ required oxygen, with a rich array of mitochondria on the basolateral surfaces needed to generate the energy to reabsorb sodium against a large unfavorable gradient. The partial pressure of oxygen falls in the medulla where the metabolically active cells of the thick ascending limb extract much of this supply. Despite dynamic changes in the complex intrarenal microcirculation to preserve renal oxygenation, the distal portion of the proximal tubule—the S3 segment in the outer medulla—and the thick ascending limb of the loop of Henle are highly vulnerable to injury (6,7).

In defiance of this apparent architectural destiny, injury is often surprisingly limited when human AKI kidney biopsies have been studied. Subtle abnormalities have been noted such as vacuolization of tubular cells; when more obvious changes are present such as flattened epithelium or loss of brush border, these tend to be focal rather than global (8). Even in experimental animal models of AKI when the insult is controlled and the histology appears more uniform, heterogeneity of response is unequivocally apparent from single-cell RNA profiling studies (9,10).

In addition to factors related to the architecture of the kidney, the clinical scenarios that result in persistent AKI are typically complex. Combinations of etiological factors may contribute to the mixed scenario of low FENa but muddy brown casts. For example, patients exposed to a nephrotoxin who have underlying cardiac or hepatic dysfunction may have a low FENa related to reduction in kidney perfusion or an increase in venous congestion but muddy brown casts from the toxic insult. This heterogeneity of clinical factors often superimposed on CKD and a myriad of pharmacologic agents are likely to make the FENa less relevant.

Although many have hoped that a low FENa might represent evidence of preserved kidney function and a better clinical outcome, the authors have shown that this is not the case if the patient also has an abnormal urine sediment with many muddy brown casts. It should be no surprise that a single random urine cannot represent the sum of a complex process of filtration, secretion, and reabsorption by all nephrons (Figure 1). Instead, this report provides evidence for the primacy of the urine sediment over urine chemistries when the data are discordant. This finding is timely because there has been a resurgence of interest in provider performed microscopy, in part fueled by social media and Free Open Access Medical Education (11). Just as a strong diuretic response to a furosemide stress test promises hope (12), the presence of muddy brown casts portends a rocky clinical course.

**Disclosures**

M.P. Hoenig reports honoraria from the Primed conference. S.M. Parikh reports consultancy for Aerpio, Alkermes, Astellas, Boehringer Ingelheim, Cytokinetics, Flagship Pioneering, Janssen, Leerink Swann, Merck, Mission Therapeutics, Mitobridge, Novo-Meta, and Pfizer; research funding from Baxter; patents or royalties from UpToDate; and an advisory or leadership role for the Journal of the American Society of Nephrology and Kidney360.

**Funding**

None.

**Acknowledgments**

The content of this article reflects the personal experience and views of the authors and should not be considered medical advice or recommendations. The content does not reflect the views or opinions of the American Society of Nephrology (ASN) or Kidney360. Responsibility for the information and views expressed herein lies entirely with the authors.
Author Contributions
M.P. Hoenig was responsible for conceptualization and wrote the original draft of the manuscript. S.M. Parikh was responsible for visualization and reviewed and edited the manuscript.

References
1. Addis T: Glomerular Nephritis, Diagnosis and Treatment, New York, Macmillan, 1948

Received: February 14, 2022 Accepted: February 17, 2022

See related article, “Concomitant Identification of Muddy Brown Granular Casts and Low FENa in AKI,” on pages 627–635.