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Fractional Excretion of Sodium and Urea are Useful Tools in the Evaluation of AKI: CON

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"Only a Sith deals in absolutes."
- Obi-Wan Kenobi

Distinguishing pre-renal AKI (p-AKI) from acute tubular necrosis (ATN) is often challenging, but making this distinction early and accurately has therapeutic and prognostic value. Prompt fluid administration and other maneuvers to improve renal perfusion can be undertaken to reverse p-AKI, whereas these interventions may be futile or even injurious if parenchymal damage has already accrued, as in ATN. Calculating the fractional excretions of sodium (FENa) and urea (FEUrea) were proposed to address this clinical dilemma.[1, 2] While both tests are widely taught and frequently used, they are flawed and should not routinely be employed in the workup of AKI. Instead, more reliable and broadly applicable tests such as urine sediment microscopy can provide more insight, particularly when combined with thorough clinical history and physical examination.

Physiological and conceptual limitations of FENa and FEUrea

Given their perceived simplicity and utility, FENa and FEUrea are taught early in medical education as a means to distinguish p-AKI from ATN. These indices are fundamentally measures of tubular reabsorptive activity whose interpretation hinges upon the kidney's expected response to reduced effective arterial blood volume (EABV). Fractional excretion (FE) accounts for the relationship between solute excreted in the urine and the amount filtered at the glomerulus, providing an indication of how the tubule is handling solute at any given moment. When faced with declining EABV, as in p-AKI, we assume that the kidney increases sodium and urea reabsorption, which decreases their FE. Conversely, ATN would be associated with higher FE because damaged tubules cannot effectively reclaim these solutes. Likewise, FENa <1% and FEUrea <35% are used as cutoffs for p-AKI. Early reports of FENa and FEUrea proposed

cutoffs of FENa >3% and FEUrea >40% for attributing AKI to intrinsic renal disease but these upper limits are less often used in practice.[1-4] However, these assumptions have numerous caveats that severely limit the reliability of FENa and FEUrea to distinguish p-AKI from ATN.

In order for fractional excretion of a given solute to serve as a proxy for renal perfusion, (1) that solute should be avidly reabsorbed in states of volume depletion, (2) reabsorption should be impaired in ATN, and (3) reabsorption should be unaffected by drugs and conditions that do not cause tubular injury.[5] All variables required for the calculation of FENa and FEUrea can be altered by disease states, medications, or even variations in normal physiology (**Table 1**).[5-7] For example, bicarbonaturia associated with vomiting leads to an obligate increase in urinary sodium excretion to maintain luminal electroneutrality, which can in turn increase FENa even in p-AKI. Maximal sodium reabsorption may no longer be possible in CKD due to tubular atrophy, persistently inflating FENa. In hospital settings where FE is most commonly applied, intravenous fluids are frequently administered before urine chemistries can be obtained, confounding the interpretation of FENa and FEUrea. Moreover, this maneuver itself may reverse p-AKI, obviating the need for laboratory studies and calculation of FE.

As noted by Seethapathy and Fenves, FENa and FEUrea are solely markers of tubular response to perfusion—not diagnostic tests for AKI etiology.[8] At best, FENa and FEUrea provide circumstantial evidence for a diagnosis and still require clinicians to assess all available information. Cardiorenal syndrome, hepatorenal syndrome, and hypovolemic p-AKI are all associated with low FENa but have divergent treatments.

Inconsistent real-world performance

Knowing that FENa could be influenced by a myriad of clinical scenarios, Espinel crafted the inclusion criteria of his seminal report accordingly, studying only 17 oliguric patients without diuretic exposure, CKD, acute glomerulonephritis, or urinary tract obstruction.[1] Subsequent studies applying FENa to more diverse populations have yielded mixed results, as demonstrated by the wide variation in performance characteristics of FENa.[3] Studies demonstrating the best performance of FENa and FEUrea for distinguishing p-AKI from ATN tended to be those with the most highly-selected populations. However, in populations including persons with CKD or those receiving diuretics, FENa was less reliable for identification of p-AKI.[3, 9] These inconsistencies point to a fundamental problem: the patients for whom FENa is most valid represent only a narrow slice of those with AKI.[6, 7]

FEUrea has been proposed as an alternative index of tubular integrity that is valid in patients receiving diuretics.[2] In contrast to sodium, the proximal reabsorption of urea was thought to be unaffected by more distally-acting diuretics, but we now know that urea transporters are located throughout the nephron.[10] Diuretics have been shown to alter FEUrea in hospitalized patients with hypervolemia and acute decompensated heart failure.[4] Furthermore, urea transporter expression may be influenced by volume-independent variables such as sepsis.[11]

Even when used precisely in the intended populations, FENa and FEUrea only represent the renal handling of solute at a single timepoint and do not account for the dynamic nature of renal injury; serial measurements throughout the course of renal injury have been demonstrated to change substantially.[4] Furthermore, FENa and FEUrea comprise an average over the whole kidney, overshadowing variation in tubular injury. In this way, a low FENa or FEUrea could obscure tubular injury where only a subset of nephrons are affected while others remain functional.[12]

Better alternatives

The presence of granular or muddy brown casts and renal tubular epithelial cells (RTEC) on urine microscopy has consistently demonstrated good diagnostic and prognostic performance. The number of casts and RTEC correlate strongly with renal recovery and dialysis need.[6, 13] Importantly, urine microscopy has outperformed FENa and FEUrea for diagnosing ATN among inpatients with AKI receiving nephrology consult.[13] Urine microscopy findings are also associated with sustained creatinine elevation after discharge, whereas FENa and FEUrea are not clearly useful for prognostication.[13]

Like urine microscopy, novel biomarkers of renal tubular injury are increasingly appreciated for their potential as sensitive indicators of renal tubular cell injury and compare favorably FENa in AKI prognosis.[14] Kidney Injury Molecule-1 (KIM-1) is a tubule injury biomarker that can be measured in blood and urine and is qualified by the FDA for detection of kidney injury in pre-clinical drug development.[15] Liver-type fatty acid binding protein (L-FABP) and insulin-like growth factor-binding protein-7 (IGFBP-7) have been leveraged for the NephroCheck platform (Astute Medical, Inc.) to detect high-risk AKI in critically-ill patients.[16] We are hopeful that ongoing research investments will bring even more advances in the application of tubule injury biomarkers for better diagnosis, prognosis, and treatment of AKI subtypes.

Conclusions

The widespread use of FENa and FEUrea to determine the etiology of AKI is well-meaning but misguided. These tests add little useful information beyond a good history and

physical examination and carry the risk of misleading clinicians to incorrect diagnoses and treatments. Even if FENa and FEUrea are useful in limited clinical contexts, the long list of exceptions and confounders undermine their validity in a modern patient cohort. In cases where there is concern for tubule injury, urine microscopy appears to offer more value than either FENa or FEUrea. Developments in investigational biomarkers of tubule injury may soon deliver even more sensitive and specific ways to characterize kidney injury. Ultimately, FENa and FEUrea are nice models for renal physiology, but they perform better in the classroom than the clinic. First, we should do no harm and eschew tests that so often fail to provide reliable and useful information that advances care for our patients.

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Table 1. Circumstances affecting variables used in the calculation of FENa/FEUrea.

Low urine sodium not due to p-AKI	**High urine sodium not due to ATN**
Normal kidney function with low or moderate salt intake	Normal kidney function with high salt intake
Acute glomerulonephritis	Normal kidney function after administration of sodium-containing IV fluid
Acute urinary obstruction	Resolving urinary obstruction
	Bicarbonaturia and other anions (e.g. toluene)
	Glucosuria (including SGLT2 inhibitor use)
Low urine sodium despite ATN	**High urine sodium despite p-AKI**
AKI with liver failure or CHF	Administration of sodium-containing IV fluid
Recent iodinated radiocontrast exposure	Diuretics
Early sepsis-associated AKI	CKD
Pigment nephropathy from myoglobinuria or hemoglobinuria	Glucosuria
	Bicarbonaturia and other anions (e.g. toluene)
	Salt-wasting nephropathies (e.g. Bartter or Gitelman syndrome)

AIN = acute interstitial nephritis; ATN = acute tubular necrosis; CHF = congestive heart failure; CKD = chronic kidney disease; NSAID = nonsteroidal anti-inflammatory drug; p-AKI = pre-renal acute kidney injury; SGLT2 = sodium-glucose cotransporter-2. Adapted with permission from: Perazella MA, Coca SG. Traditional urinary biomarkers in the assessment of hospital-acquired AKI. *Clin J Am Soc Nephrol,* 7**:** 167-174, 2012 10.2215/cjn.09490911.