CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will use the fractional excretion of sodium and the fractional excretion of urea to find the cause of acute kidney injury

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Finding the cause of acute kidney injury: Which index of fractional excretion is better?

ABSTRACT

The fractional excretion of urea (FEU) is a useful index for differentiating the main categories of causes of acute kidney injury, ie, prerenal causes and intrinsic causes. It may be used in preference to the more widely used fractional excretion of sodium (FENa) in situations in which the validity of the latter is limited, such as in patients taking a diuretic.

KEY POINTS

Finding the cause of acute kidney injury is important, as management strategies differ.

Although cutoff values differ among studies, in a patient with acute kidney injury, an FENa lower than 1% suggests a prerenal cause, whereas a value higher than 3% suggests an intrinsic cause.

Similarly, an FEU less than 35% suggests a prerenal cause of acute kidney injury, whereas a value higher than 50% suggests an intrinsic one.

The FENa can be falsely high in patients taking a diuretic; it can be falsely low in a number of intrinsic renal conditions, such as contrast-induced nephropathy, rhabdomyolysis, and acute glomerulonephritis.

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An acute kidney injury can result from a myriad of causes and pathogenic pathways. Of these, the two main categories are prerenal causes (eg, heart failure, volume depletion) and causes that are intrinsic to the kidney (eg, acute tubular necrosis). Together, these categories account for more than 70% of all cases.[1–3]

While early intervention improves outcomes in both of these categories, the physician in the acute care setting must quickly distinguish between them, as their treatments differ. Similar clinical presentations along with confounding laboratory values make this distinction difficult. Furthermore, prolonged prerenal azotemia can eventually lead to acute tubular necrosis.

Therefore, several methods for distinguishing prerenal from intrinsic causes of acute kidney injury have been developed, including urinalysis, response to fluid challenge, the blood urea nitrogen-to-plasma creatinine ratio, levels of various urine electrolytes and biomarkers, and, the topics of our discussion here, the fractional excretion of sodium (FENa) and the fractional excretion of urea (FEU).[4] While each method offers a unique picture of renal function, the validity of each may be affected by specific clinical factors.

Of note, the FENa has been shown to be inaccurate in patients with myoglobinuria,[5] sepsis,[6] or contrast-induced nephropathy,[7] and in those taking a diuretic[8] (**TABLE 1**). The FEU, which is not affected by concomitant diuretic use, has been proposed as an alternative. However, its utility has been debated.

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TABLE 1

Causes of falsely low FENa in patients with an intrinsic cause of acute kidney injury

Cardiorenal disease, hepatorenal disease, congestive heart failure, or other chronic low-flow states
Renal artery stenosis (bilateral)
Acute glomerulonephritis
Acute interstitial nephritis
Selected causes of acute tubular necrosis
Radiocontrast dyes
Rhabdomyolysis
Myoglobinuria, hemoglobinuria
Nonoliguric acute tubular necrosis

In light of the frequent use of diuretics in inpatients and outpatients, a review of the utility of the FEU test is warranted. We will therefore present the theory behind the use of the FENa and the FEU for distinguishing intrinsic from prerenal causes of acute kidney injury, the relevant literature comparing the utility of these investigations, and our suggestions for clinical practice.

A euvolemic person with normal renal function and moderate salt intake has an FENa of about 1%

ACUTE KIDNEY INJURY DEFINED

Acute kidney injury (formerly called acute renal failure) describes an abrupt decline in renal function. Consensus definitions of it have been published and are gaining more widespread acceptance and use.[9,10] The current definition is[10]:

- An absolute increase in serum creatinine ≥ 0.3 mg/dL (26.4 µmol/L) in 48 hours, or
- A percentage increase in serum creatinine ≥ 50% in 48 hours, or
- Urine output < 0.5 mL/kg/hour for > 6 hours.

These clear criteria allow for earlier recognition and treatment of this condition.

Acute kidney injury is fairly common in hospitalized patients, with 172 to 620 cases per million patients per year.[11–14] Furthermore, hospitalized patients with acute kidney injury continue to have high rates of morbidity and death, especially those with more severe cases, in which the mortality rate remains as high as 40%.[15]

FRACTIONAL EXCRETION OF SODIUM

The FENa is a measure of the extraction of sodium and water from the glomerular filtrate. It is the ratio of the rate of sodium filtration (the urinary sodium concentration times the urinary flow rate, divided by the plasma sodium concentration) to the overall glomerular filtration rate, estimated by the renal filtration of creatinine. It can be calculated as the ratio of plasma creatinine to urine creatinine divided by the ratio of plasma sodium to urine sodium:

$$\frac{\textit{plasma creatinine} \times \textit{urinary sodium}}{\textit{plasma sodium} \times \textit{urinary creatinine}}$$

A euvolemic person with normal renal function and moderate salt intake in a steady state will have an FENa of approximately 1%.[16]

In 1976, Espinel[17] originally showed that the FENa could be used during the oliguric phase in patients in acute renal failure to differentiate between prerenal acute kidney injury and acute tubular necrosis. Given the kidney's ability to reabsorb more sodium during times of volume depletion, Espinel suggested that an FENa of less than 1% reflected normal sodium retention, indicating a prerenal cause, ie, diminished effective circulating volume. A value greater than 3% likely represented tubular damage, indicating that the nephrons were unable to properly reabsorb sodium.

The clinical utility of this index was apparent, as the management of prerenal azotemia and acute tubular necrosis differ.[18] While both require fluid repletion, the risk of volume overload in acute tubular necrosis is high. Furthermore, acute tubular necrosis secondary to nephrotoxins could require hemodialysis to facilitate clearance of the offending agent.

The FENa test was subsequently validated in a number of studies in different populations and is still widely used.[19–21]

Limitations to the use of the FENa have been noted in various clinical settings. Notably, it can be falsely depressed in a number of intrinsic renal conditions, such as contrast-induced nephropathy, rhabdomyolysis, and acute glomerulonephritis. Conversely, pa-

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tients with prerenal acute kidney injury who take diuretics can have a falsely elevated value due to the pharmacologically induced renal excretion of sodium independent of volume status. This is commonly seen in patients on diuretic therapy with baseline low effective circulating volumes, such those with congestive heart failure and hepatic cirrhosis.

FRACTIONAL EXCRETION OF UREA

Urea is continuously produced in the liver as the end product of protein metabolism. It is a small, water-soluble molecule that freely passes across cell membranes and is therefore continuously filtered and excreted by the kidneys. Not merely a waste product, urea is also important in water balance and constitutes approximately half of the normal solute content of urine.[22]

Urea's excretion mechanisms are well characterized.[22,23] It is absorbed in the proximal tubule, the medullary loop of Henle, and the medullary collecting ducts via facilitated diffusion through specific urea transporters.[24] After being absorbed in the loop of Henle, urea is resecreted, a process that creates an osmotic gradient along the medulla that ultimately regulates urea excretion and reabsorption in the medullary collecting duct. Low-volume states are associated with decreased urea excretion due to a physiologic increase in antidiuretic hormone secretion, and the reverse is true for high-volume states.

The FEU has been recognized as a clinically useful tool. The correlation between serum and urine urea concentrations was investigated as early as 1904.[25] However, most studies during the ensuing century focused on the serum urea concentration or the creatinine-to-urea ratio as a measure of glomerular failure.[26–28] In 1992, Kaplan and Kohn[29] proposed that the FEU could be a useful measure for assessing renal dysfunction in acute kidney injury. Conceptually similar to the FENa, the FEU is calculated as:

$$\frac{\textit{serum creatinine} \times \textit{urinary urea}}{\textit{serum urea} \times \textit{urinary creatinine}}$$

An FEU less than 35% suggests a prerenal cause of acute kidney injury, while a value greater than 50% suggests an intrinsic one.

FRACTIONAL EXCRETION OF UREA VS FRACTIONAL EXCRETION OF SODIUM

Kaplan and Kohn (1992)

Kaplan and Kohn,[29] in their 1992 study, retrospectively analyzed 87 urine samples from 40 patients with renal dysfunction (not specifically acute kidney injury) thought to be secondary to volume depletion in which the FENa was discordant with the FEU.

Findings. Thirty-nine of the 40 patients treated with diuretics had a high FENa value. However, the FEU was low in all of these patients, leading the authors to conclude that the latter may be the more useful of the two indices in evaluating patients receiving diuretics who present with symptoms that suggest prerenal azotemia.

Limitations of the study. On closer inspection, these findings were not generalizable, for several reasons. First, the time that elapsed between administration of diuretics and evaluation of urinary electrolytes varied widely. Additionally, the study was a retrospective analysis of isolated urine specimens without clear correlation to a clinical patient or context. For these reasons, prospective analyses to investigate the utility of the fractional excretion of urea needed to be conducted.

FENa and FEU are increased in older people, making the standard cutoff values less reliable

Carvounis et al (2002)

Carvounis et al[30] prospectively evaluated the FENa and the FEU in 102 consecutive intensive care patients with acute kidney injury (defined as a serum creatinine concentration > 1.5 mg/dL or an increase of more than 0.5 mg/dL in less than 48 hours). Oliguria was not an inclusion criterion for the study, but patients with acute glomerulonephritis and obstructive nephropathy were excluded. The study grouped subjects into those with prerenal azotemia, prerenal azotemia plus diuretic use, or acute tubular necrosis on the basis of the clinical diagnosis of the attending nephrologist.

Findings. The FEU was more sensitive than the FENa in detecting prerenal azotemia, especially in those with prerenal azotemia who were receiving diuretics. Overall, the FEU had higher sensitivity and specificity for prerenal azotemia regardless of diuretic usage, and more importantly, the best overall positive and negative predictive value for detect-

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ing it (99% and 75% respectively).

These results indicate that, in patients given diuretics, the FENa fails to discriminate between prerenal azotemia and acute tubular necrosis. Conversely, the FEU was excellent in discriminating between all cases of prerenal azotemia and acute tubular necrosis irrespective of the use of diuretics. This has significant practical application, given the frequency of diuretic use in the hospital, particularly in intensive care patients.

Limitations of the study. While the findings supported the utility of the FEU, the study population was limited to intensive care patients. Furthermore, the authors did not report the statistical significance of their findings.[30]

Pépin et al (2007)

Pépin et al[8] performed a similar study, investigating the diagnostic utility of the FENa and the FEU in patients with acute kidney injury, with or without diuretic therapy.

The authors prospectively studied 99 consecutive patients confirmed by an independent nephrologist to have acute kidney injury (defined as an increase in serum creatinine of more than 30% over baseline values within less than 1 week) due to either volume depletion or ischemia. They excluded patients with less common causes of acute kidney injury, such as rhabdomyolysis, obstructive nephropathy, adrenal insufficiency, acute glomerulonephritis, and nephrotoxic acute kidney injury, as well as patients with chronic kidney disease.

Diuretics are widely used in acute kidney injury and can elevate the FENa

Patients were grouped into those with transient acute kidney injury (from decreased kidney perfusion) and persistent acute kidney injury (attributed to acute tubular necrosis), with or without diuretic therapy, according to predefined clinical criteria. They were considered to have diuretic exposure if they had received furosemide (Lasix) within 24 hours or a thiazide within 48 hours of sampling.

Findings. The FENa proved superior to the FEU in patients not taking diuretics and, contrary to the findings of Carvounis et al,[30] exhibited diagnostic utility in patients taking diuretics as well. Neither index discriminated between the different etiologies exceptionally well, however.

Of note, the study population was more inclusive than in previous studies, with only 63 intensive care patients, thus making the results more generalizable to all cases of inpatient acute kidney injury. Furthermore, the study included patients with and without oliguria, and the sensitivity and specificity of both the FENa and the FEU were higher in the nonoliguric group (n = 25).

Limitations of the study. The authors admit that a long time may have elapsed between diuretic administration and urine measurements, thereby mitigating the diuretic's natriuretic effect independent of the patient's volume status. While this variable may account for the better performance of the FENa than in the other studies, it does not account for the poor performance of the FEU.

Additionally, few of the findings reached statistical significance.

Lastly, a high percentage (30%) of patients had sepsis. The FEU is less effective in patients with infection, as cytokines interfere with the urea transporters in the kidney and colon.[31]

Lim et al (2009)

Lim et al[32] conducted a study similar in design to that of Pépin et al.[8]

Findings. The FEU was as clinically useful as the FENa at distinguishing transient from persistent acute kidney injury in patients on diuretics. Using a cutoff FEU of less than 30% and a cutoff FENa of less than 1.5% for transient acute kidney injury (based on calculated receiver operating characteristic curves), FENa was more sensitive and specific than FEU in the nondiuretic groups. In patients exposed to diuretics, FEU was more sensitive but less specific than FENa.

FRACTIONAL EXCRETION OF UREA IN OLIGURIA

Diskin et al (2010)

In 2010, Diskin et al[33] published a prospective, observational study of 100 consecutive patients with oliguric azotemia referred to a nephrology service. They defined acute kidney injury as serum creatinine concentration greater than 1.9 mg/dL and urine output less than 100 mL in 24 hours. They used a higher FEU cutoff for prerenal azotemia of less than 40% to reflect the known urea secretion rate in oliguric patients (600 mL/24 hours). They

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used an FENa of less than 1% and greater than 3% to distinguish prerenal azotemia from acute tubular necrosis.

Findings. The FEU was more accurate than the FENa, giving the right diagnosis in 95% vs 54% of cases ($P < .0001$). The difference was exclusively due to the FEU's greater utility in the 67 patients who had received diuretics (98% vs 49%, $P < .0001$). Both the FEU and the FENa accurately detected acute tubular necrosis. As expected, the FENa outperformed FEU in the setting of infection, in which cytokine stimulation interferes with urea excretion.

Limitations of the study. Approximately 80% of the patients had prerenal azotemia, potentially biasing the results toward a test geared toward detecting this condition. However, since prerenal causes are more common than intrinsic causes, the authors argued that their cohort more accurately reflected the population encountered in clinical practice.

Additionally, only patients with oliguria and more advanced kidney injury (serum creatinine > 1.9 mg/dL) were included in the study, potentially limiting the applicability of these results in patients with preserved urine output in the early stages of renal failure.

The authors concluded that the FEU should be used in patients with suspected prerenal azotemia on diuretic therapy and should not be used in patients with sepsis.

TABLE 2 summarizes the findings of the studies discussed above.[8,15,30,32,33]

TABLE 2

The FENa and the FEU in clinical studies

PERFORMANCE MEASURE	FENa	FEU
Sensitivity		
For prerenal azotemia	78%[8] – 96%[32]	48%[8] – 92%[32]
For prerenal azotemia, on diuretic	29%[33] – 63%[32]	79%[8] – 100%[32]
For intrinsic causes	56%[30] – 75%[15]	68%[30] – 75%[8]
Specificity		
For prerenal azotemia	67%[33] – 96%[30]	75%[8] – 100%[33]
For prerenal azotemia, on diuretic	81%[8] – 82%[33]	33%[8] – 91%[33]
For intrinsic causes	78%[15] – 100%[30,33]	48%[8] – 98%[30]
Positive predictive value		
For prerenal azotemia	86%[8,15] – 98%[30]	79%[8] – 100%[33]
For prerenal azotemia, on diuretic	86%[8] – 89%[33]	71%[8] – 98%[33]
For intrinsic causes	64%[8] – 100%[30]	43%[8] – 94%[30]
Negative predictive value		
For prerenal azotemia	60%[33] – 86%[30]	43%[8] – 83%[30]
For prerenal azotemia, on diuretic	18%[33] – 49%[8]	44%[8] – 83%[33]
For intrinsic causes	82%[30] – 86%[8]	79%[8] – 86%[30]

Data from Pépin et al,[8] Carvounis et al,[30] Lim et al[32], and Diskin et al.[33] Not all measures of validity were included or could be calculated from each study. Definitions of acute kidney injury and cutoff values for FENa and FEU differed among the studies; see text for details.

FENa = fractional excretion of sodium; FEU = fractional excretion of urea

FRACTIONAL EXCRETION OF UREA IN CHILDREN AND THE ELDERLY

The FEU has also been validated in populations at the extremes of age.

In children, Fahimi et al[34] performed a cross-sectional study in 43 patients referred to a nephrology service because of acute kidney injury.

An FEU less than 35% had greater sensitivity and specificity than an FENa less than 1% for differentiating prerenal from intrinsic causes in pediatric populations. An FEU of less than 30% had an even greater power of distinguishing between the two. Interestingly, 15 of the 26 patients in the group with prerenal azotemia had an FENa greater than 1%, 8 of whom had an obvious cause (diuretic therapy in 5, salt-losing congenital adrenal hyperplasia in 2, and metabolic alkalosis in 1).

In elderly people, urinary indices are less reliable because of reduced sodium and urea reabsorption and urinary concentrating capability. Thus, the FENa and FEU are increased, making the standard cutoff values unreliable and unpredictable for distinguishing prerenal from intrinsic causes of acute kidney injury.[35]

WHICH TEST SHOULD BE USED?

Both the FENa and the FEU have been validated in prospective trials as useful clinical indices in identifying prerenal azotemia. Results of these studies vary as to which index is superior and when. This may be attributable to the various definitions of acute kidney injury and diagnostic criteria used in the studies as well as the heterogeneity of patients in each study.

However, the preponderance of evidence indicates that the FEU is more useful than the FENa in patients on diuretics. Since diuretics

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are widely used, particularly in acute care settings in which acute kidney injury is prevalent, the FEU is a useful clinical tool and should be utilized in this context accordingly. Specifically, when there is a history of recent diuretic use, the evidence supports ordering the FEU alone, or at least in conjunction with the FENa. If the two indices yield disparate results, the physician should look for circumstances that would alter each one of them, such as sepsis or an unrecognized dose of diuretic.

In managing acute kidney injury, distinguishing prerenal from intrinsic causes is a difficult task, particularly because prolonged prerenal azotemia can develop into acute tubular necrosis. Therefore, a single index, calculated at a specific time, often is insufficient to properly characterize the pathogenesis of acute kidney injury, and a combination of both of these indices may increase diagnostic sensitivity and specificity.[36] Moreover, urine samples collected after acute changes in volume or osmolarity, such as blood loss, administration of intravenous fluids or parenteral nutrition, or dialysis may compromise their diagnostic utility, and care must be taken to interpret the results in the appropriate clinical context.

The clinician must be aware of both the respective applications and limitations of these indices when using them to guide management and navigate the differential diagnosis in the appropriate clinical settings.

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