CHAPTER 55

Assessment of Urine Biochemistry

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OBJECTIVES

This chapter will:

1. Discuss the evidence to support the use of urine sodium, fractional excretion of sodium, urine osmolality, and fractional excretion of urea in critically ill patients with acute kidney injury (AKI) to inform about diagnosis and response to interventions (i.e., differentiate between transient and established AKI).
2. Discuss the role of urine sodium and urine osmolality in the diagnosis and evaluation of disorders of sodium and water balance.
3. Discuss the use of urine chloride in the evaluation of metabolic alkalosis.
4. Review the role of urine anion gap and urine osmolality in the evaluation of a nonanion gap metabolic acidosis.
5. Describe the role of urine potassium, urine magnesium, and urine calcium in the evaluation of disorders of potassium, magnesium, and calcium.

The kidneys are sensitive organs that tightly regulate the body's electrolytes, volume, and acid-base status. When one of those deviates from the normal range, the kidneys adjust the urine excretion composition to restore homeostasis. As such, these changes can be tracked by urine biochemistry. The composition of urine biochemistry must match net dietary intake and endogenous production to maintain balance. There are no normal values for urine biochemistry, only appropriate or inappropriate response by the kidneys to a physiologic change.

Although urine biochemistry can be a helpful diagnostic tool, it has many limitations, including being influenced by kidney function, urine output, and nutritional status, all factors that are often abnormal in critically ill patients. Findings therefore must be taken in clinical context by way of thorough history, physical examination, and other laboratory investigations. The main clinical uses of urine biochemistry in the intensive care unit (ICU) are summarized in Table 55.1.

This chapter discusses how urine biochemistry can assist in investigating various critical care pathologies but will not discuss the management of these conditions. It will provide an overview of situations when urine biochemistry may provide diagnostic information and should be interpreted.

URINE SODIUM

Context in the Literature

Studies that defined the values used for urine sodium[3] and fractional excretion of sodium[4] were published many years ago but still stand as the values to differentiate between low renal perfusion states (as in early transient acute kidney injury [AKI] or prerenal) and intrinsic renal states (persistent AKI or acute tubular necrosis [ATN]). These studies were small and included patients with severe AKI. Since then, our knowledge of the pathophysiology of AKI in critical illness has changed to understand that in certain conditions, such as sepsis, reabsorption of sodium does not necessarily correlate with renal perfusion.[3,4] Some therefore have questioned the utility of urine sodium in ICU practice.[5–8] Some studies have not found any utility of routinely testing urine sodium measurement in the ICU,[9–11] whereas others

TABLE 55.1

Urine Biochemistry in the Intensive Care Unit

URINE BIOCHEMISTRY	CLINICAL CIRCUMSTANCE OF USE
Urine sodium	Assessment of volume status or effective circulating volume, assessment of early transient AKI versus persistent AKI state (i.e., prerenal states versus ATN), diagnosis of hyponatremia Other less common ICU uses: dietary compliance in patients who are salt restricted (hypertension, cirrhosis), evaluation of calcium, and uric acid stone formers
Urine chloride	Assessment of volume status or effective circulating volume, diagnosis of etiology of metabolic alkalosis
Urine urea	Fractional excretion of urea calculation to differentiate between early transient AKI versus persistent AKI state in patients receiving diuretics
Urine osmolality	Estimates the effect of ADH on the kidneys and therefore clinically helps in assessing effective circulating volume and in the evaluation of dysnatremia
Urine potassium	Evaluation of hypokalemia and hyperkalemia
Urine anion gap and urine osmolal gap	Evaluation of non-anion gap metabolic acidosis (urine anion gap requires urine sodium, potassium and chloride while urine osmolal gap requires urine osmolality, sodium, potassium, urea, glucose)
Urine calcium and urine magnesium	Rarely performed in the ICU. Fractional excretion of magnesium can help elucidate renal versus non renal losses of magnesium. Urinary calcium is used in hypercalcemia and in the evaluation of renal stones.

have claimed its utility by demonstrating significant renal sodium retention in the early phase of AKI.[12–16] Some of the literature also has shown that a drop in urine sodium often precedes a rise in serum creatinine,[17] therefore advocating for early urine sodium measurement to identify patients at risk of AKI. Furthermore, some have encouraged frequent monitoring of urine sodium to better reflect its response to constant hemodynamic variations[18–21] or to monitor urine sodium indices before and after interventions.[22]

Although no specific values exist for a normal urine sodium excretion, a urine sodium below 10 to 20 signifies a very active sympathetic and renin-angiotensin-aldosterone pathway, which often is seen in low effective circulating volume state, such as volume depletion, cardiac disease (cardiorenal), or liver disease (hepatorenal). Despite all these controversies, many studies have shown that single-spot urine sodium evaluation may help in the management of AKI in the ICU,[16,17,23,24] and therefore understanding its interpretation is important for the intensivist.

Spot Urine Sodium and Fractional Excretion of Sodium

The kidneys respond to a decrease in effective circulating volume by avidly reabsorbing sodium with the goal to increase volume status (appropriately or inappropriately). Decreased effective circulation may be due to decreased volume status from fluid losses (e.g., bleeding, gastrointestinal [GI] losses, pancreatitis, crush injuries) or from poor perfusion resulting from a low-flow state (e.g., low cardiac output or heart failure, advanced cirrhosis, hypoalbuminemia). Regardless of the cause of the low-perfusion state, the kidney response is to conserve sodium, which theoretically should manifest by a low sodium content in the urine (<10 mEq/L). The only circumstances in which a low urine sodium concentration may be seen despite preserved effective circulation are from dilution secondary to polyuria and in malnourished patients with inadequate sodium and other solute intake. Even in prerenal states, urine sodium has limitations. Although in selected circumstances, a low urine sodium may suggest the kidneys are sensing low perfusion (prerenal cause); this assessment often is confounded, in particular in ICU settings (e.g., resuscitation, diuretic exposure, vasoactive exposure). Similarly, another limitation would be increased sodium excretion during metabolic alkalosis. As the kidneys eliminate bicarbonate, sodium must accompany it to maintain electroneutrality. This would result in increased urinary sodium excretion regardless of effective circulating volume. This also may occur when an alternative anion to chloride is excreted in the urine.

The last clinical circumstances in the ICU in which urine sodium is essential are when elucidating the cause of hyponatremia (in conjunction with urine osmolality). A low urine sodium (<10 mEq/L) may suggest a reduced effective circulating volume (except in primary polydipsia, in which the urine sodium is low despite normal volume status) cause, whereas a high urine sodium (>40 mEq/L) suggests syndrome of inappropriate antidiuretic hormone (ADH) secretion or with renal losses (e.g., mineralocorticoid deficiency, salt wasting, diuretics).

Urine electrolytes often are measured to differentiate between prerenal states (or low effective circulation volumes) and established AKI. In this situation, the fractional excretion of sodium has been considered more reliable than urine sodium alone in differentiating these entities because it directly measures sodium handling.

BOX 55.1

Urine Sodium and Fractional Excretion of Sodium in Acute Kidney Injury

Urine sodium <10 or fractional excretion of sodium <1%

Prerenal states: Volume depletion (e.g., GI losses, renal losses, skin losses, third spacing), GI bleeding, hypotension/shock, drugs, renal artery stenosis, CHF, cirrhosis, hypoalbuminemia

Additional causes: Early or less severe AKI or if combined with chronic low flow state (heart failure, cirrhosis, or burns), AKI resulting from radio contrast or heme pigments, acute glomerulonephritis, acute interstitial nephritis, and acute urinary tract obstruction

Urine sodium >20 or fractional excretion of sodium >2%

Established AKI

Pre-renal state with chronic kidney disease or diuretic use

AKI, Acute kidney injury; *CHF,* congestive heart failure; *GI,* gastrointestinal.

$$\text{Fractional excretion of sodium:}\quad \frac{\text{urinary sodium} \times \text{plasma creatinine}}{\text{plasma sodium} \times \text{urinary creatinine}}$$

Theoretically, a fractional excretion of sodium of less than 1% indicates the kidneys are retaining sodium and can be found in early AKI (prerenal causes), whereas a fractional excretion of sodium more than 2% may be found with more established AKI when tubular damage disrupts the kidneys' capacity to retain sodium (Box 55.1). However, clinicians also should recognize that fractional excretion of sodium has significant limitations and may have limited value in ICU settings. Numerous additional AKI causes have been shown to manifest a fractional excretion of sodium less than 1% across a range in AKI severity, including AKI in association with a chronic low-flow state (i.e., heart failure, cirrhosis), AKI associated with radio contrast or heme pigments, acute glomerulonephritis, acute interstitial nephritis, and acute urinary tract obstruction. Similarly, fractional excretion of sodium may be elevated in transient AKI or prerenal diseases when a patient has chronic kidney disease or has received diuretic therapy. Clinicians should recognize that fractional excretion of sodium is not dynamic and is based on a single value for creatinine, which may not reflect significant changes in glomerular filtration rate.

FRACTIONAL EXCRETION OF UREA

Context in the Literature

Considering the concerns about the reliability and accuracy of fractional excretion of sodium, in particular among patients receiving diuretic therapy, the fractional excretion of other molecules (urea, lithium, uric acid) therefore has been investigated. The fractional excretion of urea is the most studied in critically ill patients.[9–11,25–28]

$$\text{Fractional excretion of urea:}\quad \frac{\text{urine urea} \times \text{plasma creatinine}}{\text{urine creatinine} \times \text{plasma urea}}$$

Urea is reabsorbed primarily in the proximal tubule, which is proximal to the site of action of loop and thiazide diuretics, making it theoretically a better surrogate marker of effective circulating volume in patients receiving diuretics. A fractional excretion of urea less than 35% has been suggested

to be compatible with low effective circulating volume, whereas a value of more than 50% to 65% is more consistent with established AKI.[27–28] An important caveat in the use of fractional excretion of urea, as in the use of any marker that is reabsorbed principally in the proximal tubule, is that it requires an intact proximal tubule for accuracy. For example, in patients with Fanconi syndrome or any acquired defect in which proximal tubular function is impaired, the fractional excretion of urea would be elevated regardless of effective circulating volume and unreliable.

URINE CHLORIDE

Context in the Literature

Urine chloride and urine sodium normally are reabsorbed in response to decreased effective circulation. Measurement of urine chloride therefore can provide additional information about proximal tubular reabsorption, in particular where urine sodium is elevated in response to bicarbonate excretion in metabolic alkalosis.

Urine Chloride

Urine chloride can be an important adjuvant in the diagnosis of metabolic alkalosis and differentiate states of low effective circulating volume and mineralocorticoid excess.[29–32]

Saline-responsive contributors to metabolic alkalosis (e.g., vomiting, diuretic use) generally have a low associated urine chloride (<25 mEq/L), whereas saline-resistant metabolic alkalosis (e.g., primary and secondary aldosteronism, Bartter syndrome, Gitelman syndrome, exogenous alkali administration) has a high urinary chloride concentration (>40 mEq/L) resulting from the excess mineralocorticoid effect (Table 55.2).

TABLE 55.2

Metabolic Alkalosis

URINE CHLORIDE	CAUSE
Urine chloride <25 mEq/L	*Saline responsive* Vomiting, nasogastric tube drainage Rarely diarrhea (usually causes a nonanion gap metabolic acidosis) from laxative abuse or villous adenoma Prior diuretic use Posthypercapnia Cystic fibrosis
Urine chloride >40 mEq/L	Saline resistant • Primary hyperaldosteronism (Conn syndrome) • Secondary hyperaldosteronism (renovascular disease, hypovolemia, CHF, cirrhosis combined with diuretics) • Non-aldosterone mineralocorticoid excess: Cushing syndrome, Liddle syndrome, licorice ingestion • Severe hypokalemia • Exogenous alkali • Current diuretic use • Bartter or Gitelman syndrome

CHF, Congestive heart failure.

In a few circumstances urine chloride is elevated despite decreased effective circulation. This occurs when a cation must be excreted to maintain electroneutrality. For example, in a patient with significant GI losses resulting from diarrhea contributing to a low effective circulating volume who also develops a nonanion gap, metabolic acidosis prompting increased renal excretion of ammonia to restore the acid base balance (excretion of ammonia is the renal mechanism to excrete excess acid). Ammonia (a cation) must be excreted with an accompanying anion, most often in the form of ammonium chloride, hence raising urinary chloride.

URINE OSMOLALITY

The kidneys are the primary source of water regulation in the body. ADH plays a central role in regulation of plasma osmolality and sodium by controlling water excretion. Osmoreceptors in the hypothalamus are stimulated by changes in plasma osmolality, which influences thirst and secretion of ADH from the posterior pituitary gland. Conversely, these mechanisms are downregulated by decreases in plasma osmolality. Urine osmolality therefore can represent a surrogate for the action of ADH on the kidneys. ADH acts on the collecting tubule to reabsorb water, concentrate the urine, and in the process increase urine osmolality. Urine osmolality can range from 50 mOsm/kg (maximally dilute) to about 1200 mOsm/kg (maximally concentrated) depending whether the kidneys are trying to eliminate or retain water (Box 55.2). Thus, when urine osmolality is less than plasma osmolality, water is excreted. Conversely, when urine osmolality exceeds plasma osmolality, water is preserved.

Assessment of urine osmolality may have value for discriminating transient and established AKI.

In established AKI, greater tubular dysfunction will contribute to an impaired response to ADH, despite a decreased effective circulation, leading to lower urine osmolality than expected (most often below 400 mOsm/kg). In contrast, when tubular function remains largely preserved, as in mild or transient AKI, the urine osmolality will increase above 500 mOsm/kg in the setting of a decreased effective circulation (e.g., hypovolemia).

Assessment of urine osmolality is important for diagnosing the cause of hyponatremia and hypernatremia. Urine osmolality, in the context of serum osmolality and serum sodium, reflects whether ADH is appropriately or inappropriately active. For example, in a patient with hypo-osmolar hyponatremia and a high urine osmolality (exceeding serum osmolality), ADH is active. This could be in response to either a decreased effective circulation or from the syndrome of inappropriate ADH secretion (SIADH). Alternatively, in a patient with hypo-osmotic hyponatremia and low urine osmolality (<100 mOsm/kg), the kidneys are excreting free water. This may be the normal response to correcting hyponatremia. However, persistent hyponatremia in the setting of low urine osmolality occurs in two circumstances: (1) the patient has overwhelmed the body's normal response to excrete all ingested free water (primary polydipsia, generally occurs in patients with preserved kidney function who ingest in excess of 10 to 12 L of water per day); (2) the patient has extremely low solute intake (e.g., severely malnourished, beer potomania) and excretes only a small amount of solute (urine osmolality 100 to 150 mOsm/kg).

In hypernatremia, ADH secretion should be elevated to stimulate water reabsorption. This would manifest as an

BOX 55.2

Urine Osmolality in Common Clinical Situations

High Urine Osmolality
AKI or when assessing effective circulating volume
Prerenal states
Volume depletion (GI losses, renal losses, skin losses, third spacing)
Heart failure
Cirrhosis
Hypoalbuminemia
Hyponatremia
Prerenal states
Volume depletion (GI losses, renal losses, skin losses, third spacing)
Heart failure
Cirrhosis
Hypoalbuminemia
Syndrome of inappropriate ADH secretion
Hypernatremia
GI losses (vomiting, diarrhea, nasogastric tube, fistula)
Skin losses (fever, exercise, ventilation)
Sodium overload (received excess normal saline or sodium bicarbonate)
Mineralocorticoid excess
Seizures (↑ intracellular osmoles → water shifts → transient increase in serum Na)

Low Urine Osmolality
AKI or when assessing effective circulating volume
Euvolemic or hypervolemic
Established AKI
Chronic kidney disease
Hyponatremia
In process of correcting hyponatremia
Primary polydipsia
Extremely low solute intake (tea and toast diet or beer potomonia)
Hypernatremia
Osmotic diuresis (glucose, mannitol, urea)
Loop diuretics
Nephrogenic DI
Central DI

ADH, Antidiuretic hormone; *AKI,* acute kidney injury; *DI,* diabetes insipidus; *GI,* gastrointestinal.

elevated urine osmolality. Hypernatremia in the context of a high urine osmolality suggests it is either extrarenal water loss leading to ADH release to conserve water or excretion of a high sodium load (e.g., excess salt ingestion or administration saline solutions). A low urine osmolality in the context of hypernatremia suggests that the kidneys are inappropriately excreting water. This would indicate either states where diuresis is intended (e.g., osmotic or loop diuretics) or unintended (e.g., central or nephrogenic diabetes insipidus).

URINE SPECIFIC GRAVITY

A quick way to estimate urine osmolality is by looking at the urine specific gravity on urinalysis. A specific gravity value of 0.001 is approximately equal to urine osmolality of 30 to 35 mOsm/kg.[33] Thus a specific gravity of 1.010 usually correlates to a urine osmolality of 300 to 350 mOsmol/kg. Exceptions to this would be when large particles (glucose, radiocontrast media) are present, rendering urine specific gravity disproportionately high.[34]

BOX 55.3

Urine Potassium in Hypokalemia

Low 24-hour urinary potassium (<25 mEq/day) or low spot urine potassium (<15 mEq/L) or low potassium to creatinine ration (<1.5 mEq/mmol)
GI losses: vomiting, diarrhea, nasogastric tube
Sweat losses: extreme heat, cystic fibrosis
Low intake
High 24-hour urinary potassium (>25 mEq/day) or high spot urine potassium (>40 mEq/L) or high potassium to creatinine ration (>1.5 mEq/mmol)
Renal potassium wasting
- Diuretics, amphotericin B
- Increased mineralocorticoid activity
- Excretion of bicarbonate (vomiting, RTA)
- Excretion of other nonreabsorbable anion (hippurate, beta-hydroxybutyrate, penicillin derivative)

Transcellular shifts
Hypomagnesemia
Bartter, Gitelman, Liddle syndromes
High 24-hour urinary potassium (>25 mEq/day) and high potassium to creatinine ratio (>1.5 mEq/mmol) but low spot urine potassium (<15 mEq/L)
Established AKI (tubular dysfunction +/– dilutional)
Primary polydipsia (dilutional)
Other polyuric states (osmotic and water diuresis)

AKI, Acute kidney injury; *RTA,* renal tubular acidosis.

URINE POTASSIUM

Urinary potassium excretion is regulated by serum potassium concentration and by the effect of aldosterone. Urinary potassium levels are useful primarily when investigating hypokalemic state. In the setting of hypokalemia the appropriate renal response is to conserve potassium. This is best assessed using a 24-hour urine potassium collection (Box 55.3). The urinary potassium excretion of a patient with hypokalemia is lowered to less than 25 mEq/day.[35] A value above this suggests at least a component of renal potassium wasting. Because 24-hour urine collections are often impractical, a spot urine potassium may be performed. A spot urine potassium less than 15 mEq/L may indicate nonrenal losses (e.g., GI losses, transcellular shifts, poor dietary intake) or a remote diuretic effect.[36] Alternatively, a urine potassium concentration exceeding 40 mEq/L in the setting of hypokalemia suggests renal potassium wasting (e.g., diuretics, enhanced aldosterone action, renal tubular acidosis [RTA], hypomagnesemia). Spot urine potassium does have limitations and may not be accurate in selected circumstances: polyuria (resulting from relative dilution of potassium), low urine volumes (because of relative concentration of potassium), or in states of hyperaldosteronism (leading to increased sodium reabsorption distally and countercurrent potassium secretion).

Another compromise to performing a 24-hour urinary potassium collection is to measure a spot urine potassium-to-creatinine ratio. Given that creatinine theoretically is excreted at a near constant state, the urine potassium to creatinine ratio corrects for variations in urine volume, unlike a spot urinary potassium. Nonrenal sources of hypokalemia are associated with potassium to creatinine ratio of less than 1.5 mEq/mmol creatinine, whereas higher values are seen with renal potassium wasting.[37,38] Urinary potassium excretion is less informative in hyperkalemic states because kidneys are often capable of excreting excess potassium unless excretion is impaired (e.g., AKI).

The transtubular potassium gradient (TTKG) was proposed to estimate indirectly the effect of aldosterone in patients with dyskalemias by estimating the tubular fluid potassium concentration at the most distal site of potassium secretion at the end of the cortical collecting tubules.[39–41]

$$\text{TTKG} = \frac{\text{Urine potassium} / (\text{urine osmolality} / \text{plasma osmolality})}{\text{Plasma potassium}}$$

A TTKG less than 3 was perceived to be associated with a state of low aldosterone or low aldosterone effect (e.g., medications, type IV RTA), whereas a TTKG more than 7 was secondary to decreased effective circulating volume, where K excretion was limited by decreased distal tubular sodium delivery and low urine flow. TTKG also has been used in the evaluation of hypokalemic states in which a TTKG of more than 7 represented increased renal losses (e.g., hyperaldosteronism, diuretics), whereas a TTKG of less than 3 implied extrarenal losses (e.g., GI losses). However, evidence has suggested the assumptions underlying the TTKG were not valid and it is seldom used.[42]

URINE ANION GAP AND URINE OSMOLAL GAP

The kidneys excrete acid in the form of ammonium (NH_4Cl). In a nonanion gap metabolic acidosis, because urine ammonium levels cannot be directly measured, the urine anion gap (sometimes called urine net charge) can be used to estimate ammonium excretion.

$$\text{Urine anion gap} = \text{unmeasured anions} - \text{unmeasured cations}$$

$$\text{Urine anion gap} = (\text{urinary sodium} + \text{urine potassium}) - \text{urine chloride}$$

In metabolic acidosis, the urine ammonia (NH_4^+) (and accompanying urine chloride) should increase to excrete excess acid. Urine chloride therefore should increase relative to (urinary sodium + urine potassium) giving a negative value (–20 to –50 mEq/L) in the urine anion gap (e.g., GI or genitourinary losses, proximal RTA, rapid infusion of saline solutions). Alternatively, if the kidneys fail to excrete NH_4^+, the urine anion gap will be positive (e.g., type 1 and 4 RTA, advanced chronic kidney disease, AKI (Box 55.4).

There are circumstances when the urine anion gap may not reflect urinary acid excretion. For example, this may occur when there is increased urinary excretion of unmeasured anions (e.g., non-chloride anions) (e.g., hippurate after toluene inhalation [glue sniffing], hydroxybutyrate and acetoacetate in ketoacidosis, bicarbonate when proximal RTA is treated with alkali therapy, in neonates who excrete unmeasured anions at a high rate, D-lactate in D-lactic acidosis, and 5-oxoproline associated with chronic acetaminophen ingestion). The excretion of these anions may occur with $NH4^+$ and therefore will not reduce the anion gap as expected when chloride also is excreted. Furthermore, some of the anions are excreted with sodium and potassium, further contributing to a positive urine anion gap. In these circumstances, using the urine osmolal gap potentially can circumvent the pitfalls of the urine anion gap.

$$\text{Calculated urine osmolality} = (2 \times [\text{sodium} + \text{potassium}]) + \text{urea nitrogen} + \text{glucose}$$

BOX 55.4

Urine Anion Gap in Nonanion Gap Metabolic Acidosis

Positive Urine Anion Gap
Type 1 and type 4 RTA
Chronic kidney disease and tubular dysfunction
Excretion of nonchloride anion (hippurate, beta-hydroxybutyrate, 5-oxoproline). The urine osmolal gap will pick up these abnormalities and will be >400 mOsmol/kg

Negative Urine Anion Gap
Diarrhea
Intestinal or pancreatic fistula
Ureteral diversions
Proximal type 2 RTA
Rapid infusion of bicarbonate free intravenous fluids (saline solutions)

RTA, Renal tubular acidosis.

$$\text{Urine osmolal gap} = \text{Measured urine osmolality} - \text{Calculated urine osmolality}$$

If the measured urine osmolality differs from the calculated urine osmolality, then additional osmoles are present (e.g., ammonium salts as NH_4Cl or NH_4 with another anion). When the urine osmolal gap is less than 150 mOsm/kg in the presence of a metabolic acidosis, urinary NH_4^+ excretion may be impaired (e.g., distal RTA), whereas, if the urine osmolal gap is more than 400 mOsmol/kg, urinary NH_4^+ concentration is elevated, suggesting the kidneys are excreting acid (e.g., GI loss, non-chloride anion excretion).

The urine osmolal gap, similar to the urine anion gap, is imperfect and may be confounded in selected circumstances. For example, urinary excretion of osmotically active acids (e.g., alcohols, mannitol), urinary tract infections by bacteria that produce urease (e.g., urease catalyzes urea and water to NH_4 and bicarbonate, thereby falsely elevating NH_4^+, which does not represent real renal acid secretion as the ammonium is formed outside the kidneys) or when large quantities of intact acids are excreted (e.g., beta-hydroxybutyric acid in ketoacidosis when the increased osmolal gap is due to beta-hydroxybutyric acid rather than ammonium salts).

OTHER URINE ELECTROLYTES

Other urine electrolyte measurements are of limited value in the ICU. Urinary magnesium can sometimes be assessed to calculate the fractional excretion of magnesium in patients with hypomagnesemia.

$$\text{Fractional excretion of magnesium} = \frac{100 \times (\text{urinary magnesium} \times \text{plasma creatinine})}{(0.7 \times \text{plasma magnesium}) \times \text{urinary creatinine}}$$

The plasma magnesium is multiplied by 0.7, because only 70% of the serum magnesium is unbound to albumin and therefore filtered across the glomerulus.

A $FeMg_2^+$ of more than 2% suggests hypomagnesemia may be due to renal losses of magnesium, whereas a value less than 2% supports GI losses. Urinary calcium also is evaluated less frequently in the ICU. It can be used in the evaluation of hypocalcemia and hypercalcemia; however, this usually begins with an evaluation of parathyroid hormone

concentration and 24-hour urine collection generally once critical illness has resolved. The other common indication to measure urinary calcium is in patients predisposed to formation of urinary stone; however, this occurs predominantly in an outpatient setting.

CONCLUSION

Urine biochemistry can play an important adjuvant diagnostic role in the evaluation of a number of clinical problems; however, recent data have suggested a number of the most commonly performed tests (e.g., urine sodium, fractional excretion of sodium, fractional excretion of urea), in particular in settings of AKI, may be unreliable and confounded in ICU settings. Accordingly, clinicians should recognize urine biochemical tests require careful integration in ICU settings into the broader clinical context before directing or informing about diagnosis and therapeutic management.

Key Points

1. Urine sodium, fractional excretion of sodium, and fractional excretion of urea have been used as surrogate measures of kidney perfusion and for discriminating transient (prerenal) and established AKI (acute tubular necrosis); however, their value in ICU settings often is confounded and may be questionable.
2. Urine osmolality and urine sodium are important measures in the evaluation of sodium and water imbalance. Urine osmolality represents an important surrogate for presence of ADH action on the kidneys, where it acts on the collecting tubule to reabsorb water and concentrate the urine.
3. Urine chloride can aid in discriminating the cause of metabolic alkalosis and aid in the discrimination between states of low effective circulating volume and mineralocorticoid excess.

Key References

1. Darmon M, Vincent F, Dellamonica J, et al. Diagnostic performance of fractional excretion of urea in the evaluation of critically ill patients with acute kidney injury: a multicenter cohort study. *Crit Care*. 2011;15(4):R178.
2. Vanmassenhove J, Glorieux G, Hoste E, et al. Urinary output and fractional excretion of sodium and urea as indicators of transient versus intrinsic acute kidney injury during early sepsis. *Crit Care*. 2013;17(5):R234.
3. Langenberg C, Wan L, Egi M, et al. Renal blood flow in experimental septic acute renal failure. *Kidney Int*. 2006;69(11):1996-2002.
4. Langenberg C, Wan L, Bagshaw SM, et al. Urinary biochemistry in experimental septic acute renal failure. *Nephrol Dial Transplant*. 2006;21(12):3389-3397.
5. Prowle J, Bagshaw SM, Bellomo R. Renal blood flow, fractional excretion of sodium and acute kidney injury: time for a new paradigm? *Curr Opin Crit Care*. 2012;18(6):585-592.

A complete reference list can be found online at ExpertConsult.com.

References

1. Darmon M, Vincent F, Dellamonica J, et al. Diagnostic performance of fractional excretion of urea in the evaluation of critically ill patients with acute kidney injury: a multicenter cohort study. *Crit Care*. 2011;15(4):R178.
2. Vanmassenhove J, Glorieux G, Hoste E, et al. Urinary output and fractional excretion of sodium and urea as indicators of transient versus intrinsic acute kidney injury during early sepsis. *Crit Care*. 2013;17(5):R234.
3. Langenberg C, Wan L, Egi M, et al. Renal blood flow in experimental septic acute renal failure. *Kidney Int*. 2006;69(11): 1996-2002.
4. Langenberg C, Wan L, Bagshaw SM, et al. Urinary biochemistry in experimental septic acute renal failure. *Nephrol Dial Transplant*. 2006;21(12):3389-3397.
5. Prowle J, Bagshaw SM, Bellomo R. Renal blood flow, fractional excretion of sodium and acute kidney injury: time for a new paradigm? *Curr Opin Crit Care*. 2012;18(6):585-592.
6. Bagshaw SM, Bennett M, Devarajan P, et al. Urine biochemistry in septic and non-septic acute kidney injury: a prospective observational study. *J Crit Care*. 2013;28(4):371-378.
7. Bellomo R, Bagshaw S, Langenberg C, et al. Pre-renal azotemia: a flawed paradigm in critically ill septic patients? *Contrib Nephrol*. 2007;156:1-9.
8. Bagshaw SM, Langenberg C, Bellomo R. Urinary biochemistry and microscopy in septic acute renal failure: a systematic review. *Am J Kidney Dis*. 2006;48(5):695-705.
9. Pons B, Lautrette A, Oziel J, et al. Diagnostic accuracy of early urinary index changes in differentiating transient from persistent acute kidney injury in critically ill patients: multicenter cohort study. *Crit Care*. 2013;17(2):R56.
10. Darmon M, Vincent F, Dellamonica J, et al. Diagnostic performance of fractional excretion of urea in the evaluation of critically ill patients with acute kidney injury: a multicenter cohort study. *Crit Care*. 2011;15(4):R178.
11. Wlodzimirow KA, Abu-Hanna A, Royakkers AA, et al. Transient versus persistent acute kidney injury and the diagnostic performance of fractional excretion of urea in critically ill patients. *Nephron Clin Pract*. 2014;126(1):8-13.
12. Langenberg C, Wan L, Bagshaw SM, et al. Urinary biochemistry in experimental septic acute renal failure. *Nephrol Dial Transplant*. 2006;21(12):3389-3397.
13. Vanmassenhove J, Glorieux G, Hoste E, et al. Urinary output and fractional excretion of sodium and urea as indicators of transient versus intrinsic acute kidney injury during early sepsis. *Crit Care*. 2013;17(5):R234.
14. Vanmassenhove J, Glorieux G, Hoste E, et al. AKI in early sepsis is a continuum from transient AKI without tubular damage over transient AKI with minor tubular damage to intrinsic AKI with severe tubular damage. *Int Urol Nephrol*. 2014;46(10):2003-2008.
15. Maciel AT, Park M, Macedo E. Physicochemical analysis of blood and urine in the course of acute kidney injury in critically ill patients: a prospective, observational study. *BMC Anesthesiol*. 2013;13(1):31.
16. Vitorio D, Maciel AT. Acute kidney injury induced by systemic inflammatory response syndrome is an avid and persistent sodium-retaining state. *Case Rep Crit Care*. 2014;2014:471658.
17. Maciel AT, Park M, Macedo E. Physicochemical analysis of blood and urine in the course of acute kidney injury in critically ill patients: a prospective, observational study. *BMC Anesthesiol*. 2013;13(1):31.
18. Caironi P, Langer T, Taccone P, et al. Kidney instant monitoring (K.IN.G): a new analyzer to monitor kidney function. *Minerva Anestesiol*. 2010;76(5):316-324.
19. Maciel AT, Nassar AP, Vitorio D. Very transient cases of acute kidney injury in the early postoperative period after cardiac surgery: the relevance of more frequent serum creatinine assessment and concomitant urinary biochemistry evaluation. *J Cardiothorac Vasc Anesth*. 2016;30(1):56-63.
20. Maciel AT, Vitòrio D. Urine biochemistry in the early postoperative period after cardiac surgery: role in acute kidney injury monitoring. *Case Rep Crit Care*. 2013;2013:103450.
21. Horpacsy G, Zinsmeyer J, Mebel M. Continuous determination of various enzymes and sodium concentration in urine: a usable method for diagnosis of kidney graft rejection. *Eur Urol*. 1978;4(5):334-337.
22. Moviat M, Pickkers P, van der Voort PH, et al. Acetazolamide-mediated decrease in strong ion difference accounts for the correction of metabolic alkalosis in critically ill patients. *Crit Care*. 2006;10(1):R14.
23. Maciel AT, Park M, Macedo E. Urinary electrolyte monitoring in critically ill patients: a preliminary observational study. *Rev Bras Ter Intensiva*. 2012;24(3):236-245.
24. Toledo Maciel A, Vitorio D, Delphino Salles L. Urine sodium profile in the course of septic acute kidney injury: insights relevant for kidney function monitoring. *Minerva Anestesiol*. 2014;80(4):506-507.
25. Dewitte A, Biais M, Petit L, et al. Fractional excretion of urea as a diagnostic index in acute kidney injury in intensive care patients. *J Crit Care*. 2012;27(5):505-510.
26. Varela CF, Greloni G, Schreck C, et al. Assessment of fractional excretion of urea for early diagnosis of cardiac surgery associated acute kidney injury. *Ren Fail*. 2015;37(10):327-331.
27. Pepin MN, Bouchard J, Legault L, et al. Diagnostic performance of fractional excretion of urea and fractional excretion of sodium in the evaluations of patients with acute kidney injury with or without diuretic treatment. *Am J Kidney Dis*. 2007;50(4):566-573.
28. Carvounis CP, Nisar S, Guro-Razuman S. Significance of the fractional excretion of urea in the differential diagnosis of acute renal failure. *Kidney Int*. 2002;62(6):2223-2229.
29. Sherman RA, Eisinger RP. The use (and misuse) of urinary sodium and chloride measurements. *JAMA*. 1982;247(22):3121.
30. Koch SM, Taylor RW. Chloride ion in intensive care medicine. *Crit Care Med*. 1992;20(2):227.
31. Kassirer JP, Schwartz WB. The response of normal man to selective depletion of hydrochloric acid. Factors in the genesis of persistent gastric alkalosis. *Am J Med*. 1966;40(1):10.
32. Gladziwa U, Schwarz R, Gitter AH, et al. Chronic hypokalaemia of adults: Gitelman's syndrome is frequent but classical Bartter's syndrome is rare. *Nephrol Dial Transplant*. 1607;10(9): 1995.
33. Rose BD, Post TW. *Clinical physiology of acid-base and electrolyte disorders*. USA: McGraw-Hill Medical Publishing Division; 2001:412.
34. Zwelling LA, Barlow JE. Hypersthenuria in high-dose carbenicillin therapy. *Ann Intern Med*. 1978;89:225.
35. Squires RD, Huth EJJ. Experimental potassium depletion in normal human subjects. I. Relation of ionic intakes to the renal conservation of potassium. *J Clin Invest*. 1959;38(7):1134-1148.
36. Groeneveld JH, Sijpkens YW, Lin SH, et al. An approach to the patient with severe hypokalaemia: the potassium quiz. *QJM*. 2005;98(4):305.
37. Lin SH, Lin YF, Chen DT, et al. Laboratory tests to determine the cause of hypokalemia and paralysis. *Arch Intern Med*. 1561;164(14):2004.
38. Lin SH, Lin YF, Halperin ML. Hypokalaemia and paralysis. *QMJ*. 2001;94(3):133.
39. West ML, Marsden PA, Richardson RM, et al. New clinical approach to evaluate disorders of potassium excretion. *Miner Electrolyte Metab*. 1986;12(4):234.
40. Ethier JH, Kamel KS, Magner PO, et al. The transtubular potassium concentration in patients with hypokalemia and hyperkalemia. *Am J Kidney Dis*. 1990;15(4):309.
41. Choi MJ, Ziyadeh FN. The utility of the transtubular potassium gradient in the evaluation of hyperkalemia. *J Am Soc Nephrol*. 2008;19(3):424-426.
42. Kamel KS, Halperin ML. Intrarenal urea recycling leads to a higher rate of renal excretion of potassium: an hypothesis with clinical implications. *Curr Opin Nephrol Hypertens*. 2011; 20(5):547-554.