Urine Chemistries

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KEYWORDS

• Urine electrolytes • Urine chemistries • Potassium • Sodium • Osmolality
• Acute kidney injury • Hyponatremia

HOSPITAL MEDICINE CLINICS CHECKLIST

1. Use urine chemistries to help diagnose and manage patients with acute kidney injury, polyuria, hyponatremia, metabolic acidosis, metabolic alkalosis, and disorders of potassium balance. Proper interpretation requires integration with clinical data and an understanding of the appropriate uses for each test.
2. Urine chemistry values, measured in units of concentration, are dependent on both the absolute amount of a substance excreted and the urine concentration.
3. Use the fractional excretion of sodium (FENa) in cases of acute oliguric renal failure to distinguish between prerenal azotemia and acute tubular necrosis. The FENa should not be used as a surrogate for the clinical assessment of volume status.
4. In metabolic alkalosis, urine chloride concentration may be a better marker of volume status than urine sodium concentration.
5. When managing patients with hyponatremia, use timely and repeated measurements of urine sodium concentration and osmolality to avoid iatrogenic complications.
6. Measure the urine osmolality when evaluating a patient with polyuria to determine whether the polyuria is caused by solute diuresis or water diuresis.
7. For cases of non–anion-gap metabolic acidosis measure urine pH, sodium, potassium, and chloride concentrations. Calculate the urine anion gap to help distinguish between gastrointestinal loss of bicarbonate and renal tubular acidosis related to impaired ammoniagenesis.
8. For cases of hypokalemia, calculate a transtubular potassium gradient to help distinguish between gastrointestinal and renal loss of potassium.

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APPROPRIATE USE

1. What are urine chemistries?

Clinicians often refer to urine chemistries as urine electrolytes. Interpreted strictly, electrolytes are charged ions or small molecules that render a solution electrically conductive. The commonly measured urine electrolytes are sodium, potassium, and chloride. This article uses the term urine chemistries broadly to refer to true urine electrolytes as well as noncharged particles, including creatinine and urea, and urine osmolality. Other urine electrolytes measured less frequently and usually in the context of specific disorders include calcium, phosphorus, magnesium, and bicarbonate. Urinary ammonium ion concentration is a useful tool in the evaluation of non–anion-gap metabolic acidosis, but is generally estimated or calculated rather than directly measured.

2. What are normal values for urine chemistries?

The framework for interpretation of serum versus urine chemistries is distinctly different. First, unlike serum chemistries, which generally have narrow normal-range values, urine chemistries tend to have wider expected ranges because the concentration of a substance in the urine depends on the absolute quantity excreted as well as the urine concentration, both of which can vary significantly. The amount of a substance in the urine may vary depending on diet, medications, or alterations to and from steady-state conditions, and the concentration of the urine may vary 20-fold depending on the action of antidiuretic hormone (ADH). The urine osmolality in healthy subjects ranges from 50 to 1200 mOsm/kg. Concentrated urine will result in higher measured concentrations of any substance regardless of the absolute quantity excreted. Dilute urine will produce the opposite result.

Second, interpretation of serum chemistries is rather straightforward in that the normal ranges apply to all patients regardless of diet, medications, renal function, or other factors. However, urine chemistries cannot be interpreted in isolation but instead often require concurrent serum chemistries, including renal function and key clinical information such as medications. A single value may be normal in one patient but abnormal in another, and urine chemistry values that fall within the “normal range” may actually reflect significant abnormalities in renal function. For example, a patient’s urine potassium may be in the “normal” range but if the patient has hypokalemia, the appropriate renal response would be potassium conservation and low urinary potassium excretion. Changes in the intake of certain electrolytes, sodium and potassium in particular, can influence urine measurements.

Third, the clinician needs to consider a patient’s baseline renal function, degree of acute kidney injury (or recovery from renal injury), and whether the patient is or is not in steady state with regard to acid-base or electrolyte balance when interpreting urine chemistries. Urine chemistries can significantly inform the understanding of the physiology of several conditions, but if used improperly can be misleading.[1] Finally, please note that urine chemistry values provided in the text and tables are intended as guidelines and do not reflect absolute cut off values in diagnosing the relevant disorders.

3. When are urine chemistries indicated?

Urine chemistries can be useful in the following clinical circumstances: acute kidney injury, disorders of intravascular volume, polyuria, hypernatremia, hyponatremia, acid-base disorders, and abnormalities of serum potassium concentration. Prompt measurement, often in the emergency department before therapy has been instituted,

is very important. Repeated measurements are generally helpful as well. Remember that urine can be saved either at the bedside or preferably in the laboratory, and appropriate urine chemistries ordered at a later time.

ACUTE KIDNEY INJURY

4. What is the impact of hypovolemia on urine sodium concentration?

In states of hypovolemia, the glomerular filtration rate (GFR) initially falls, stimulating the release of renin, which increases angiotensin II–mediated aldosterone release from the adrenal gland. Aldosterone causes increased sodium resorption to maintain intravascular volume and GFR. If volume depletion is severe enough, ADH is released, which concentrates the urine by augmenting water resorption. The net effect is concentrated urine with low sodium content. These changes in urine composition may precede the presence of clinical signs of volume depletion.[2] Thus, intravascular volume depletion (hypovolemia) is suggested in patients with appropriate clinical signs and symptoms who have a low urine sodium concentration. When volume depletion is severe, the GFR falls and oliguria may develop.

5. How is measurement of urine sodium concentration useful in diagnosing the cause of acute kidney injury?

It is not always clear clinically whether a patient with acute kidney injury and oliguria is experiencing prerenal azotemia, which might be responsive to increased intravascular volume, or has acute tubular necrosis (ATN), whereby additional volume might be harmful by inducing pulmonary edema. Measurement of the urine sodium concentration is helpful in such situations. Low urine sodium concentration (<20 mEq/L), suggests prerenal azotemia with renal tubular cells functioning to appropriately reabsorb sodium. High urine sodium concentration (>40 mEq/L) is consistent with (but not diagnostic of) ATN.[3] Urine osmolality greater than 500 mOsm/kg also supports prerenal azotemia and volume-stimulated ADH action. In advanced ATN, the ability to generate concentrated urine may be lost and the urine osmolality will approach that of serum (<350 mOsm/kg)[3]; this is known as isosthenuria.

6. When can the urine sodium concentration be misleading in the diagnosis of the cause of acute kidney injury?

In states of metabolic alkalosis and volume depletion, such as in vomiting, the urine sodium concentration may not be maximally reduced because of obligate urinary sodium excretion with bicarbonate. In such situations, measurement of urine chloride concentration may be useful, with values less than 20 mEq/L suggesting volume depletion.[4]

Another pitfall to consider is that urine sodium concentration may be high (>20 mEq/L) in prerenal azotemia in patients with preexisting chronic kidney disease[5,6] or volume depletion induced by diuretic therapy.

7. When is fractional excretion of sodium helpful?

The fractional excretion of sodium (FENa) is the percentage of filtered sodium that is excreted in the urine. The FENa is considered the most accurate test to distinguish prerenal azotemia from acute tubular necrosis, the two most frequent causes of acute kidney injury.[3,7] Differentiating prerenal azotemia from ATN is clinically important

because only patients with prerenal azotemia are likely to have improved renal function with volume infusion. In oliguric acute kidney injury, FENa values of less than 1% (ie, 99% of filtered sodium is resorbed by the renal tubules) support prerenal azotemia whereas values greater than 1% to 3% support ATN.[7,8] In clinical practice, a value of greater than 2% is generally accepted as evidence of ATN.[2,9]

$$\text{FENa \%} = [(\text{Urine sodium} \times \text{Serum creatinine})/(\text{Urine creatinine} \times \text{Serum sodium})] \times 100$$

8. When is fractional excretion of sodium misleading?

There are several pitfalls to the use of the FENa, so it must be used and interpreted in the correct contexts. Note that FENa has only been validated to distinguish prerenal azotemia from ATN in patients with oliguric renal failure[10] (generally recognized as urine output <400 mL in 24 hours when obligated to excrete about 500–600 mOsm in 24 hours).[2] FENa is not a surrogate for clinical assessment of volume status in general.

Extension of FENa to other diseases or to patients with multiple coexisting disorders requires clinical judgment. For example, FENa in a healthy person is often less than 1% depending on sodium intake and is not a marker of volume depletion.[5] Note also that FENa tends to be low in patients with several renal conditions not associated with volume depletion, including glomerulonephritis,[3,8,11,12] renal failure due to radiocontrast media,[11] pigment nephropathy,[13] vascular disease, vasculitis, liver disease,[3] and various forms of nonoliguric acute kidney injury.[8,10,12,14] Although the FENa may be less than 1%, such patients are not necessarily volume depleted and may in fact be volume overloaded, as in glomerulonephritis where there is primary sodium retention.

Conversely, some patients who are hypovolemic will not have a low FENa. Because FENa is the ratio of excreted sodium to filtered sodium, its value is inversely proportional to the GFR such that as GFR decreases, the FENa will increase for any given excretion rate of sodium.[5] Thus, elderly patients and patients with preexisting chronic kidney disease with low GFR may not be able to generate a FENa less than 1% even under conditions of volume depletion.

$$\text{FENa} = \text{Excreted Na}/\text{Filtered Na}$$

$$\text{FENa} = (\text{Urine volume}) \times (\text{Urine Na})/\text{Serum Na} \times \text{GFR}$$

9. When is fractional excretion of urea helpful?

Interpretation of the FENa (or urine sodium concentration) is challenging in patients receiving diuretics because of relatively high urinary sodium concentration even in the presence of volume depletion. To distinguish prerenal azotemia from ATN in patients on diuretics, use of fractional excretion of urea (FEUrea) has been proposed. In volume depletion, proximal tubular resorption of urea is increased via several mechanisms, leading to a decrease in urine urea and an increase in serum urea. The resorption of urea, however, is not directly affected by diuretics.[15] Therefore, volume depletion will result in a decrease in FEUrea.

$$\text{FEUrea \%} = [(\text{Urine urea} \times \text{Serum creatinine})/(\text{Serum urea} \times \text{Urine creatinine})] \times 100$$

FEUrea values of less than 35% in the setting of oliguric acute kidney injury support the diagnosis of prerenal azotemia.[15]

10. Which is more useful, FENa or FEUrea?

There are conflicting comparative data regarding the test performance of the FENa versus the FEUrea in distinguishing prerenal azotemia from ATN.[16] In a recent prospective study, 99 patients with acute kidney injury were evaluated with FENa and FEUrea. In patients not on diuretics, FENa less than 1% had a sensitivity and specificity of 78% and 75%, respectively, for predicting reversible prerenal azotemia while FEUrea less than 30% had a sensitivity and specificity of 48% and 75%, respectively. In patients on diuretics, FENa less than 1% had a sensitivity and specificity of 58% and 81%, respectively, for identifying prerenal azotemia while FEUrea less than 30% had a sensitivity of 79% and specificity of 33%.[16] The investigators suggest that FENa is better able to distinguish reversible prerenal acute kidney injury and that FEUrea does not have high enough specificity to be useful. In practice, however, both tests are frequently used (**Table 1**).

HYPERNATREMIA AND HYPONATREMIA

11. How can urine chemistries clarify the etiology of disorders of water balance (hypernatremia and hyponatremia)?

Hyponatremia is a common condition present in 15% to 30% of hospitalized patients.[17] Often, hyponatremia develops or worsens in the hospital because hospitalized patients have many potential barriers to water excretion and may receive hypotonic fluids.[18,19] Prompt measurement of appropriate urine chemistries is essential to the management of patients who present with hypernatremia or hyponatremia. Complications such as cerebral edema and central pontine myelinolysis may occur with improper management.[20–22] Serial measurement of serum and urine chemistries is important in the assessment of patients' response to therapy.

Hyponatremia represents an excess of water relative to solute in the body. Because sodium is the major extracellular cation and is the most abundant serum electrolyte, it is common to use serum sodium concentration as a measure of free water balance. Note, however, that the concentration of any substance in the serum will tend to decrease as total-body free water increases owing to a dilutional effect. Recall also that serum sodium concentration is not useful by itself in assessing volume status or total-body sodium content.

Hypernatremia is simply a relative deficiency of free water with respect to total-body solute. A patient may be clinically hypovolemic, euvolemic, or hypervolemic at any level of serum sodium concentration.

Unless a patient is anuric, is consuming very low quantities of solute, or is drinking massive quantities of water, hyponatremia develops as a result of the action of ADH in the kidney to diminish free water excretion. ADH action may be either appropriate

Table 1
Urine chemistries in the evaluation of acute kidney injury

	Urine Sodium (mEq/L)	FENa (%)	FEUrea (%)	Urine Osmolality (mOsm/kg)
Prerenal	<20	<1	<30–35	>500
Acute tubular necrosis	>40	>2	>30–35	<350
Prerenal plus diuretics	Variable	Variable	<30–35	Variable

(related to an identifiable volume or osmotic stimulus) or inappropriate (contrary to a volume or osmotic stimulus and attributable to stimuli such as pain, medications, pulmonary or central nervous system disease, or syndrome of inappropriate antidiuretic hormone [SIADH]). Patients with hyponatremia should have maximally suppressed ADH because of an osmotic stimulus, and be producing urine that is dilute relative to serum. If the urine is not maximally dilute in a patient with hyponatremia, one must seek the stimulus for the ADH release.

12. How does one interpret urine chemistry findings to distinguish SIADH, volume depletion, and water intoxication?

As soon as hyponatremia is identified, urine osmolality and sodium and potassium concentrations should be measured, ideally before the administration of intravenous fluids or diuretics. A low urine sodium concentration (<20 mEq/L) supports true or effective volume depletion and thus a volume stimulus to ADH release. Urine osmolality will be low (<100 mOsm/kg) only in water intoxication and perhaps in disorders of very low solute intake. The urine will be less than maximally dilute in all other disorders because of the action of ADH.

Urine sodium concentration is helpful in distinguishing true or effective volume depletion from SIADH. Note that volume depletion and SIADH may coexist, making repeated measurement of serum sodium and urine sodium and osmolality important. A urine sodium level of less than 20 mEq/L generally distinguishes patients whose hyponatremia corrects with isotonic saline from those who do not respond and therefore are more likely to have SIADH.[23] **Table 2** shows typical findings in each disorder. It is important to monitor response to the treatment of acute hyponatremia with repeated serum sodium values as well as urine osmolality and sodium concentration to prevent overly rapid correction of hyponatremia.

Table 2
Urine chemistries in hyponatremia

	Urine Sodium (mEq/L)	Urine Osmolality (mOsm/kg)	Initial Treatment
Volume depletion	<20	>300	Isotonic saline
Effective circulating volume depletion	<20	>300	Treat underlying condition and water restriction
SIADH	>40 if consuming regular diet	>100–150, not maximally dilute	Hypertonic saline, oral salt, fluid restriction, ADH blocker, protein/urea
Volume depletion and SIADH	Variable, may be <20 until volume depletion corrected	>300	Isotonic saline until urine sodium rises
Water intoxication	Variable, may be low due to dilute urine	<100	Restrict water
Low solute intake (tea and toast)	May be <20	Low (less than serum osmolality)	Restrict water, provide salt and/or protein

Abbreviations: ADH, antidiuretic hormone; SIADH, syndrome of inappropriate antidiuretic hormone.

13. How can urine chemistries be useful in patients with hypernatremia?

Hypernatremia is less common than hyponatremia. It is present in about 1% of hospitalized patients and may account for 0.2% of hospital admissions.[24] Hypernatremia simply reflects a deficit of free water relative to solute. In the hospitalized patient, hypernatremia is often caused by inadequate free water intake because of impaired access (such as nil-by-mouth status, delirium, or bed rest) in the context of ongoing free water loss from the kidneys, skin, respiratory tract, or gastrointestinal tract.

Hypernatremia may be initiated by an osmotic diuresis caused by glucosuria in severe hyperglycemia, renal excretion of accumulated urea and sodium during recovery from acute kidney injury, or an osmotic diuretic such as mannitol. Patients with nephrogenic or central diabetes insipidus may develop hypernatremia while hospitalized if their condition is unrecognized on admission and if their ability to access free water is compromised. Most adult patients with hypernatremia also have concurrent volume depletion. Hypervolemic hypernatremia related to acute salt intoxication is rarely seen in adults. In all cases, hypernatremia (water depletion) is perpetuated by inadequate free water intake. Impaired thirst may play a role in elderly patients.[25]

In hypernatremia, urine sodium concentration is variable but is often low (except in salt intoxication or iatrogenic administration of hypertonic fluids), because of concurrent volume depletion that may be related to poor oral sodium intake or ongoing salt losses. Unless diabetes insipidus is present, urine osmolality will be high under the influence of ADH, secreted appropriately to increase water resorption by the kidney to correct the hypernatremia. In hypernatremia, administration of water is almost always appropriate. The rate of administration is determined by both the magnitude of the deficit and the rate of ongoing electrolyte free water loss.[26(pp746–93)]

Excretion and Clearance of Electrolyte Free Water

An important point that is often misunderstood is that a patient with urine osmolality greater than serum osmolality may be actually losing free water in the urine. The concept of electrolyte free water clearance (EFWC) applies here.[27–32] A full discussion is beyond the scope of this article, but is well summarized by Bodonyi-Kovacs and Lecker.[27]

The formula is as follows:

EFWC = The amount of free water lost in the urine (and that would need to be replaced to prevent worsening hypernatremia)

$$EFWC = \text{Urine volume } [1 - (\text{Urine Na} + \text{Urine K}/\text{Serum Na})]$$

Note that if the urine sodium plus potassium is less than the serum sodium, the EFWC will be positive, that is, free water is being lost in the urine. If the urine sodium plus potassium is greater than serum sodium then free water is not being lost. The clinician should consider the possibility of additional free water loss in the urine, especially in the context of recovery from ATN or glucosuria. Hypernatremia is also frequently encountered in patients receiving high-protein enteral feeding (**Table 3**).

POLYURIA

14. What is polyuria?

Polyuria is generally considered to be a urine output of greater than 3 L per day in adults. This situation is frequently encountered in patients receiving intravenous fluids,

Table 3
Urine chemistries in hypernatremia

	Urine Osmolality (mOsm/kg)	Urine Sodium (mEq/L)
Diabetes insipidus (nephrogenic or central)	<300 (<100 in complete nephrogenic diabetes insipidus)	Variable (depends on intake)
Water depletion	>600–800	Variable
Water and volume depletion	>600–800	<20
Osmotic diuresis (hyperglycemia)	>300	Variable
Salt Intoxication (rare in adults)	>600–800	>20 (very high)

recovering from acute kidney injury, or receiving diuretics. It is helpful to categorize polyuria as either a water diuresis or a solute diuresis. A water diuresis is seen in polydipsia and diabetes insipidus. A solute diuresis may be the result of intravenous administration of sodium chloride, hyperalimentation (tube feeding), hyperglycemia, high protein intake, or during recovery from acute kidney injury from ATN or urinary obstruction. It is also useful to consider whether the polyuria is appropriate (such as after water intoxication or recovery from ATN, whereby polyuria is due to excretion of accumulated water and solute), or inappropriate (as in diabetes insipidus and hyperglycemia, with primary loss of free water).[26]

15. How can urine chemistries be used to diagnose the cause of polyuria?

Patients with a water diuresis will have urine that is dilute with respect to serum. A solute diuresis will usually present with higher urine osmolality. Total solute excretion on a standard diet is typically less than 900 mOsm/d. Therefore, daily solute excretion in patient with polyuria that exceeds 900 mOsm/d suggests an osmotic diuresis. The total daily urinary osmoles excreted can be measured with a 24-hour collection or estimated by multiplying a spot urine osmolality by the 24-hour urine volume (urine osmolality $\times$ urine volume).

Note that primary renal sodium wasting (as in cerebral salt wasting) is extremely rare. Polyuria in the hospitalized patient is often mediated by a solute diuresis related to the administration of sodium chloride, hyperalimentation, or recovery from ATN (**Table 4**).

Table 4
Urine chemistry findings in polyuria

	Urine Osmolality (mOsm/kg)	Urine Sodium	Urea/Other
Osmotic diuresis	Usually >300	Variable (high if sodium diuresis)	High urea, glucose, mannitol, or other osmole
Water diuresis	<300	Low (total daily excretion matches intake)	Low/absent

ACID-BASE DISORDERS

16. How are urine chemistries used to evaluate and manage patients with acidosis?

Many acid-base disorders can be diagnosed and treated without measurement of urine chemistries. Most cases of anion-gap metabolic acidosis can be diagnosed and managed using history, physical examination, and serum electrolytes without direct measurement of urine chemistries. In certain conditions, for example, diabetic ketoacidosis, measurement of urine chemistries such as ketones may be important.

Urine electrolytes are often measured when non–anion-gap (hyperchloremic) metabolic acidosis is suspected, and can help distinguish between gastrointestinal bicarbonate losses and impaired renal acid excretion (renal tubular acidosis [RTA]).

17. How are urine chemistries used to manage a patient with alkalosis?

In metabolic alkalosis, urine chloride concentration may be more useful than urine sodium concentration in assessing volume status. In an effort to correct the alkalosis, the kidneys excrete bicarbonate, which is negatively charged. In this circumstance sodium is the accompanying cation, which leads to higher urine sodium levels that are not reflective of the volume status. A urine chloride concentration of less than 20 mEq/L suggests volume depletion.[4]

18. How can urine electrolytes in non–anion-gap metabolic acidosis differentiate renal tubular acidosis from gastrointestinal bicarbonate losses?

The kidneys play a key role in maintaining acid-base balance through three main mechanisms: resorption of filtered bicarbonate, secretion of protons, and the production of ammonia to buffer the urine. Ammonia buffers protons to produce ammonium ($NH_3 + H^+ \rightarrow NH_4^+$). In non–anion-gap metabolic acidosis from bicarbonate loss in diarrhea, the clinician would expect low urine pH and increased quantities of ammonium. If renal acid-base handling is impaired, however, urinary findings during metabolic acidosis may differ. Therefore in a patient with non–anion-gap metabolic acidosis, measurement of urinary pH and estimation of urinary ammonium are helpful tools. Urine pH is measured using a dipstick. Urinary ammonium is not measured directly but instead is estimated using the calculated urine anion gap.[33–35]

The urine anion gap depends on the principle of electroneutrality, and is simply the difference between the major measured cations (sodium and potassium) and anions (chloride) in the urine.[33] As the amount of ammonium (an unmeasured cation) increases, the amount of chloride (its accompanying anion) increases. In steady state, the urine anion gap is usually positive because of the presence of unmeasured anions such as phosphate, sulfate, and organic anions. In metabolic acidosis, however, with elevated urinary chloride accompanying elevated urinary ammonium, the urine anion gap becomes less positive and even negative.

$$\text{Urine anion gap (UAG)} = \text{Urine sodium} + \text{Potassium} - \text{Chloride}$$

It may be restated:

$$\text{UAG} = \text{Measured cations} - \text{Measured anions}$$

$$\text{UAG} = \text{Unmeasured Anions} - \text{Unmeasured cations}$$

In healthy subjects consuming a Western diet, the urine anion gap is positive with a mean of 41 ± 9.[33,34] In severe diarrhea with metabolic acidosis, urine ammonium ion will increase and be excreted with an anion (mostly chloride, although sulfates and phosphates may be present).[35] The urine chloride concentration will increase and the ammonium excretion will be reflected by a less positive or negative urine anion gap. The urine anion gap, however, will be positive in patients with some forms of RTA whereby renal ammoniagenesis is impaired. Impaired ammoniagenesis is the defect in type 4 RTA and is also seen in distal (type 1) RTA (**Table 5**).[26(pp578–646),33] It should be noted that the urine anion gap may not be a reliable indicator of ammonia excretion in normal physiologic conditions and mild acidosis (see **Table 5**).[34]

The authors advise nephrology consultation when an RTA is suspected, to guide hospital management as well as to secure appropriate outpatient follow-up in treating long-term complications, including bone disease.

POTASSIUM DISORDERS

19. How can urine potassium concentration help distinguish between gastrointestinal and renal losses in hypokalemia?

Potassium disturbances may be related to an absolute excess or deficiency of potassium, or shift between intracellular and extracellular compartments. Most of the dietary potassium load (80–120 mEq) is excreted in the urine with the remainder in the stool. The appropriate response of the kidney is to excrete more potassium during hyperkalemia and less potassium during hypokalemia. Measurement of urine potassium concentration can help determine whether the kidney's response to the serum potassium concentration is appropriate or inappropriate, and therefore whether the derangement is a result of renal potassium mishandling.

In a healthy human the kidney can increase potassium excretion to about 400 mEq daily. At this level of excretion the urine potassium concentration would be 200 mEq/L if 2 L of urine are produced.[36] Acute hyperkalemia is often related to shift of potassium from intracellular stores to the extracellular compartments. In chronic hyperkalemia there is generally a defect in renal excretion of potassium related to relative or absolute hypoaldosteronism. Hypokalemia is generally related to chronic potassium deficiency, gastrointestinal loss, or renal loss (under the influence of aldosterone or related to coexisting hypomagnesemia); however, cellular shift as is seen in alkalosis may contribute to acute changes.

The kidneys can decrease potassium excretion to about 10 mEq/day, or about 5 to 10 mEq/L.[37] Note that polyuria (induced by water or glucose diuresis) or volume depletion–induced hyperaldosteronism may augment urine potassium losses despite hypokalemia.

20. What is the transtubular potassium gradient and how is it used clinically?

A spot measurement of urine potassium concentration is hard to interpret in the absence of data about daily urine volume and urine concentration. To assess the kidney's tendency to reabsorb or excrete potassium, the concept of transtubular potassium gradient (TTKG) has been developed.[38,39] The TTKG estimates the ratio between the tubular and serum potassium concentrations at the level of the collecting duct, as a surrogate measure of aldosterone effect. Serum and urine osmolality and potassium concentrations are measured concurrently. The ratio of urine (luminal potassium) to serum potassium needs

Table 5
Urine chemistry findings in non–anion-gap metabolic acidosis due to RTA

	Name	Urine pH	Urine Anion Gap	Serum Bicarbonate (mEq/L)	Serum Potassium	Causes
Normal		5.0 (western diet)	Positive	24		
Proximal RTA (decreased HCO_3^- resorption)	Type 2	<5.5 (will increase under bicarbonate load)	Negative "normal"	12–20	Normal but low under bicarbonate load	Genetic, acquired (myeloma, drugs, metals)
Type 4 Hyporenin-hypoaldosterone	Type 4	<5.5	Variable to positive	Mildly low, >17	High	Diabetes, ACEI/ARB
Distal RTA (tubular pump defects)	Type 1	>5.5, usually higher	Positive	May be <10	Usually low but depends on specific defect	Familial, Sjögren, rheumatoid arthritis
Mixed disorder/ renal failure		Variable to high	Variable to positive	Mildly low	Normal to high	Renal failure

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; RTA, renal tubular acidosis.

to be corrected for water absorption between the distal tubule and the final urine under the stimulus of ADH by including osmolality in the equation.

TTKG = [(Urine potassium/Serum potassium)/(Urine osmolality/Serum osmolality)]

Higher values suggest the kidney is excreting potassium whereas lower values support the conservation of potassium.

The TTKG is used to approximate the gradient between tubular lumen and serum potassium concentrations in the distal tubular capillary, and thus the net excretion or retention of potassium. Suggested normal values have been determined by the response of study subjects to potassium loading and depletion as well as in patients with hypokalemia caused by intracellular shift.[40,41] It must be noted that the response of patients with underlying kidney disease may vary and that the renal response to a given change in serum potassium may be delayed by up to 24 hours.[39] Also, urine must be isotonic or hypertonic to serum ($\geq$300 mOsm/kg) for proper interpretation.[38] Another key point to remember is that urine sodium concentration should be greater than 25 mEq/L.[38] Recall that sodium resorption takes place in the distal tubule, creating an electronegative potential in the lumen that drives potassium secretion. If distal sodium delivery is decreased, there will be less potassium excretion independent of aldosterone effect. A urine sodium concentration of greater than 25 mEq/L ensures that distal sodium delivery does not limit potassium excretion (**Table 6**).

MISCELLANEOUS DISORDERS

21. What other disorders have characteristic urine chemistry findings?

In surreptitious diuretic use, patients have high urine sodium and potassium concentrations that wax and wane in the face of clinical volume depletion.

Patients with Gitelman syndrome or Bartter syndrome have high urine sodium and potassium concentrations in the face of persistent clinical volume depletion. Urine calcium tends to be relatively low in Gitelman syndrome.

Patients with Fanconi syndrome have a relatively high urinary excretion of phosphate, potassium, and glucose in the context of hypophosphatemia, hypokalemia, and euglycemia. Tubular proteinuria and aminoaciduria are also common. A simple clinical clue can be a urine dipstick that is positive for glucose when serum glucose is less than <180 mg/dL.

Table 6
Urine chemistry findings in hypokalemia and hyperkalemia

	Hypokalemia		Hyperkalemia	
Transtubular Potassium Gradient	**<2**	**>2**	**<7**	**>10**
Cause	Gastrointestinal loss	Hyperaldosteronism	Hypoaldosteronism	Normal aldosterone effect
Example	Diarrhea	Conn syndrome	ACEI, spironolactone	Potassium shift/ overload

FUTURE DIRECTIONS

22. Are there other urine tests that might become available to help distinguish the etiology of acute kidney injury?

Fractional excretion of lithium and uric acid have been proposed as potentially useful indices to distinguish prerenal azotemia from ATN, but are either not practical (lithium) or less well characterized (uric acid).[42] Also, novel nonelectrolyte urinary biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) or kidney injury molecule 1 (KIM-1) may prove useful in the future, but are not currently in clinical use.[43,44]

Direct measurement of urinary ammonia may become available, obviating the calculation of the urine anion gap.[45]

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