REVIEW

The Use of Selected Urine Chemistries in the Diagnosis of Kidney Disorders

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Abstract

Urinary chemistries vary widely in both health and disease and are affected by diet, volume status, medications, and disease states. When properly examined, these tests provide important insight into the mechanism and therapy of various clinical disorders that are first detected by abnormalities in plasma chemistries. These tests cannot be interpreted in isolation, but instead require knowledge of key clinical information, such as medications, physical examination, and plasma chemistries, to include kidney function. When used appropriately and with knowledge of limitations, urine chemistries can provide important insight into the pathophysiology and treatment of a wide variety of disorders.

Clin J Am Soc Nephrol 14: 306–316, 2019. doi: https://doi.org/10.2215/CJN.10330818

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Introduction

Urine chemistries can provide valuable insight into a wide range of clinical conditions. These tests are often underutilized because of the difficulty many physicians find in their interpretation. Whereas a basic metabolic profile obtained from a blood sample has well defined normal values, there are no such values for urine chemistries. Urinary excretion of electrolytes vary widely as the kidney adjusts the rate of excretion to match dietary intake and endogenous production. The excretion of a dilute or concentrated urine or administration of a drug can markedly alter the concentration of urine electrolytes, potentially misleading the clinician as to the absolute quantity in the urine over a given amount of time. This review will be limited in scope and will concentrate on discussing the clinical use and interpretation of urine chemistries to include sodium, potassium, chloride, pH, creatinine, urea, and osmolality. Urine chemistries are best interpreted with knowledge of the clinical setting at the time they are obtained. These tests can be diagnostic and offer mechanistic insight in the evaluation of AKI, volume status, disorders of plasma sodium and potassium, and acid-base disorders.

Urine Sodium

Assessment of Effective Circulating Volume

Under normal conditions, sodium excretion by the kidney equals dietary intake minus the small amount lost in sweat and feces, and typically ranges from 40 to 220 mEq/d. The ability to match dietary intake with excretion enables extracellular fluid volume to be maintained within a narrow range. When effective circulatory volume is reduced, activation of effector mechanisms such as sympathetic nerves and the renin-angiotensin-aldosterone system causes avid sodium retention in the kidneys, lowering urine sodium concentration to values <15 mEq/L. On the other hand, volume expansion suppresses effector mechanisms and stimulates release of atrial natriuretic peptide, leading to a reduction in sodium reabsorption, causing urinary sodium concentration to be high. Thus, the urine sodium concentration is an indirect measure of volume status and reflects the integrity of the kidney to regulate that status.

There are specific circumstances where measurement of urine sodium no longer accurately reflects volume status. The urine sodium concentration is dependent on the amount of free water in the urine and is therefore influenced by the rate of water reabsorption in the kidneys. Under conditions of a water diuresis, the urine sodium concentration may be reduced even though daily excretion is high, falsely suggesting the presence of a low volume state. Similarly, a concentrated urine can increase urine sodium concentration even though the total amount of sodium is low, potentially masking the presence of volume contraction and falsely suggesting euvolemia or volume expansion. The fractional excretion of sodium (FE_{Na}) accounts for the effect of water reabsorption in the kidney on urine sodium concentration:

$$FE_{Na} = (U_{Na} \times P_{Creatinine} / P_{Na} \times U_{Creatinine}) \times 100\%.$$

This formula expresses the percentage of filtered sodium excreted in the urine and provides a measure of sodium handling that is independent of urinary concentration.

Differentiation of Prerenal Azotemia versus Acute Tubular Necrosis

Measurement of urine sodium concentration and FE_{Na} are frequently utilized to determine whether AKI is prerenal and correctable by restoring intravascular volume, or whether it is secondary to acute tubular necrosis, where administration of fluids might

be harmful by causing volume overload (1). A random urine sodium concentration of <15 mEq/L and a FE_{Na} of <1% suggest the presence of a volume-responsive component to a reduced GFR. In patients with established acute tubular necrosis, loss of tubular function will prevent maximal sodium retention even when extracellular fluid volume depletion is present. These tests remain useful when evaluating a change in kidney function in patients with previously stable CKD; however, the response to decreased kidney perfusion is delayed and the reduction in urine sodium will be less maximal as compared with normal kidneys (2) (Supplemental Material, Case 1).

There are situations where the urine sodium concentration and FE_{Na} inadequately distinguish between azotemia due to kidney parenchymal injury from volume responsive azotemia (3). These conditions are characterized by vasoconstriction in the kidney causing a reduction in GFR and filtered load of sodium in the setting where tubular function remains relatively intact (4–12) (Figure 1). The biochemical profile in the urine can change in a time dependent manner from a prerenal picture to that of acute tubular necrosis. Variability in timing of measurements likely explains disparities in the literature as to sensitivity and specificity of these tests in patients with AKI (13–15). The sensitivity and specificity of the FE_{Na} is greatest when applied to patients with oliguria and a reduced GFR (discussed further in Supplemental Material, Cases 1 and 2).

In patients with severe congestive heart failure, advanced cirrhosis of the liver, and extensive burns, a reduction in the filtered load of sodium brought about by intense neurohumoral activation can cause sodium retention in the kidneys to be of such a degree that urine sodium concentration and FE_{Na} remain low even when tubular necrosis is present, as manifested by granular casts and tubular cells in the urine (16–19). Despite volume expansion, a low urinary sodium concentration is typically present early in acute GN when tubular function is intact and the filtered load of sodium is reduced because of the decrease in glomerular surface area available for filtration (11).

Active diuretic use is another situation where the urine sodium concentration and FE_{Na} may not accurately reflect effective circulatory volume. In congestive heart failure and cirrhosis, the urine sodium concentration and the FE_{Na} may be increased because of administration of diuretics and yet effective circulatory volume is reduced (17). In such patients, calculation of the fractional excretion of urea (FE_{Urea}) can be helpful:

$$FE_{Urea} = (U_{Urea} \times P_{Creatinine} / P_{Urea} \times U_{Creatinine}) \times 100\%.$$

Under conditions of volume depletion, proximal reabsorption of water and urea increases in association with decreased kidney perfusion and increased filtration fraction. Thiazide and loop diuretics act distal to the proximal tubule and therefore leave urea reabsorption unaffected. As a result, the FE_{Urea} is reduced even though urine sodium concentration and FE_{Na} are increased. An FE_{Urea} <35% suggests low effective volume (20,21). A low FE_{Urea} is also present in adrenal insufficiency where impaired distal reabsorption of sodium due to mineralocorticoid deficiency leads to salt wasting and decreased effective circulatory volume (Supplemental Material, Case 2).

The utility of the FE_{Urea} to assess effective circulatory volume is lost when proximal reabsorption of salt and water is impaired (22). This situation occurs after either administration of acetazolamide, an osmotic diuresis due to administration of mannitol, glycosuria as in uncontrolled diabetes, or increased urea excretion resulting from high protein intake or catabolism. Proximal tubule salt reabsorption may also be impaired in patients with cerebral salt wasting (23).

The FE_{Urea} has also been used to discriminate between volume responsive azotemia and tubular necrosis in the absence of diuretic use. How this test compares to the FE_{Na} for this purpose is difficult to determine because studies included patients who were highly selected and excluded those with interstitial nephritis, GN, urinary obstruction, and exposure to radiocontrast material (19,20). Another potential limitation of the FE_{Urea} is its use in elderly patients and those with sepsis. Studies in experimental models show downregulation of urea transporters in the nephron with endotoxemia and aging. This effect would tend to increase the FE_{Urea} in septic and elderly patients even when volume depletion was the only cause of azotemia (24,25).

Conditions in which volume contraction coexists with a nonreabsorbable anion also cause urine sodium concentration and FE_{Na} to be increased. As discussed below, urinary chloride concentration is typically low in this setting.

Urinary Chloride

Urinary excretion of chloride mirrors sodium excretion in response to dietary intake. In a manner similar to sodium, the urinary concentration of chloride and fractional excretion of chloride (FE_{CL}) can be used as indirect markers of effective circulatory volume. Despite these similarities, there are situations when the directional change in urinary concentration may differ, such that reliance solely on one or the other can lead to an erroneous assessment of effective volume status. These differences are particularly evident when volume disturbances are accompanied by acid-base disorders (26). For this reason, both urine sodium and chloride should be obtained when using urine electrolytes to assess volume or acid-base status.

A high urine sodium and low chloride concentration in the setting of volume depletion suggests the presence of a nonreabsorbable anion. The nature of the anion can be distinguished using the urine pH and clinical context. A urine pH of 7 or 8 indicates significant bicarbonaturia, as with active vomiting or nasogastric suction (27–29). The extrarenal generation of metabolic alkalosis leads to excretion of bicarbonate into the urine, which obligates a component of filtered sodium to accompany the base whereas urine chloride remains low in response to neurohumoral activation resulting from volume contraction. A urine sodium-to-chloride ratio of >1.6 is typical in such patients (26). A urine pH <6 suggests another nonreabsorbable anion is responsible, such as ketoanions, or drugs such as ticarcillin disodium clavulanate, piperacillin tazobactam, or carbenicillin disodium. When given in the setting of low effective volume, these antibiotics couple increased delivery of sodium to increased aldosterone levels in the distal nephron, leading to generation of metabolic alkalosis of a kidney origin, accounting for the low urine pH (Figure 2). In metabolic alkalosis, the urine chloride concentration can be used as a marker as to whether

the alkalosis is responsive or resistant to administration of a chloride-containing solution (30,31). A low urine chloride indicates a chloride responsive metabolic alkalosis such as vomiting, chloride wasting diarrhea, remote use of diuretics, and posthypercapneic metabolic alkalosis. By contrast, a high urine chloride concentration indicates a chloride resistant alkalosis, as seen in genetic disorders such as Bartter and Gitelman syndrome and hypertensive disorders caused by increased mineralocorticoids or mineralocorticoid-like effect.

A high urine chloride and low sodium concentration in the setting of volume depletion suggests the presence of another cation in the urine. As discussed below, this situation most commonly occurs in diarrhea where development of hypokalemia and metabolic acidosis lead to high rates of ammonium excretion, obligating the excretion of chloride despite depletion of intravascular volume (Figure 3). A urine sodium-to-chloride ratio of <0.76 is typical in such patients (26).

Urine Potassium

Urinary potassium excretion by the kidney can vary from 10–15 mEq/d to as high as 400 mEq/d, depending on dietary intake. Determining the urine potassium concentration in a patient with dyskalemia can help determine whether the kidney is responding appropriately or is responsible for the disorder. A random urine potassium concentration of 5–15 mEq/L is consistent with an extrarenal etiology of hypokalemia, whereas values >40 mEq/L favor a kidney cause of the disorder. These cutoffs to include intermediate values require the clinical context and sometimes the response to therapy for proper interpretation. In general, hypokalemia due to a nonkidney disorder will be more easily corrected, assuming the underlying disturbance is no longer present, whereas ongoing losses in the urine make correction of hypokalemia more difficult. As with urine sodium concentration, a limitation of a random value is the degree of urinary concentration. A urine potassium concentration of 40 mEq/L may be an appropriate response in a patient with hypokalemia with a maximally concentrated urine due to decreased water intake or if obtained in the setting of decreased effective volume. Although decreased volume stimulates aldosterone production, the absolute amount of potassium in the urine remains relatively low because of decreased delivery of sodium and water to the distal nephron. By the same token, a random urine value of <15 mEq/L may represent potassium wasting by the kidneys if obtained in the setting of a water diuresis.

The transtubular potassium gradient (TTKG) is a method designed to overcome the limitations of a random urine potassium concentration in the evaluation of a patient with dyskalemia:

$$\text{TTKG} = U_{\text{Potassium}} \times P_{\text{Osmolality}} / P_{\text{Potassium}} \times U_{\text{Osmolality}}.$$

The formula estimates the ratio of potassium in the lumen of the cortical collecting duct to that in the peritubular capillaries at a point where tubular fluid is isotonic relative to plasma (32,33). In a patient with hypokalemia, a value of <3 is consistent with an appropriate kidney response to the disorder whereas a value >7 indicates potassium wasting by the kidneys. Mineralocorticoid activity and TTKG correlate positively, and in a patient with hyperkalemia, a value of <6 generally indicates an inappropriate response by the collecting duct, although studies vary as to the precise cutoff value. This calculation requires the urine sodium concentration to be at least 25 mEq/L and urine osmolality to be equal to or greater than the plasma osmolality.

Recognizing that urea and sodium are reabsorbed in the downstream medulla has led some to question the utility of this calculation because the validity of this formulae assumes absorption of osmoles distal to the collecting duct is negligible. For this reason, a urine potassium-to-creatinine ratio is used to assess potassium handling by the kidneys (34). This formula takes advantage of the near constant rate of urinary secretion of creatinine and therefore the ratio corrects for variability in urine concentration. A ratio of <13 mEq potassium/g creatinine (<2.5 mEq potassium/mmol creatinine) is considered an appropriate response to gastrointestinal potassium loss, remote use of diuretics, decreased dietary intake, and potassium shift into cells. Higher values suggest an inappropriate response of the kidney (Figure 4).

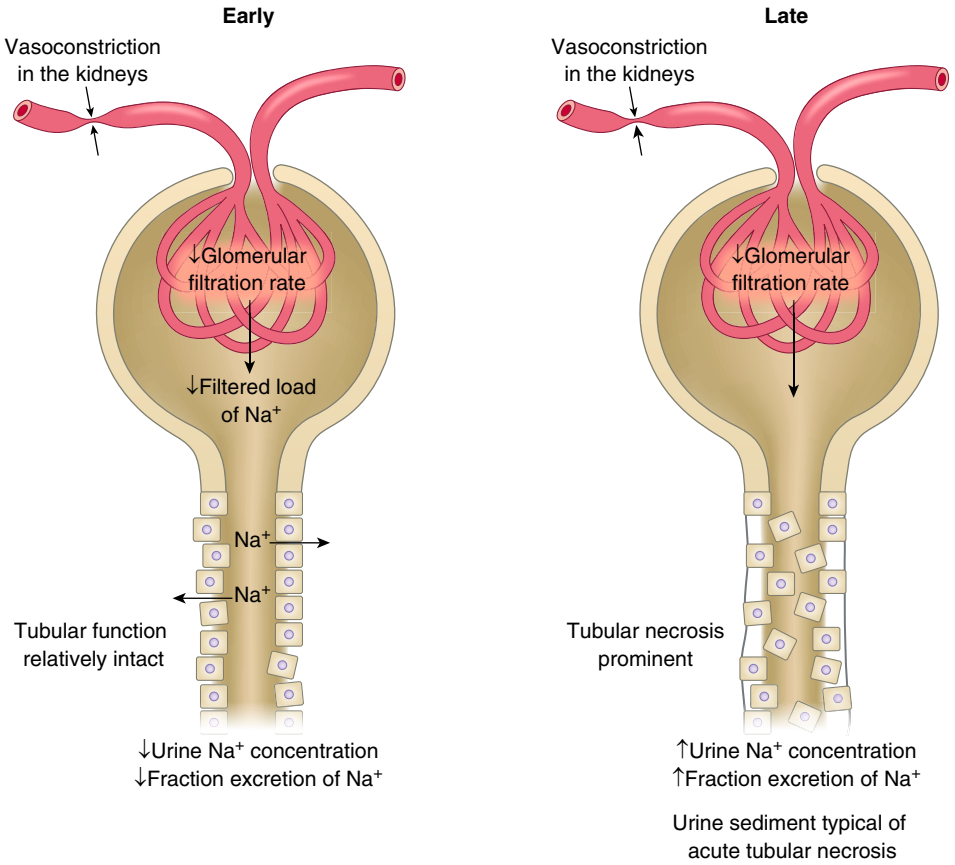
Urine Chemistries in the Evaluation of Metabolic Acidosis

Analysis of urine chemistries can provide information as to the amount of ammonium excretion by the kidney and therefore are useful in distinguishing between renal and extrarenal causes of a nonanion gap hyperchloremic metabolic acidosis. Metabolic acidosis of a kidney origin is characterized by low ammonium excretion rates, whereas ammonium excretion is elevated in metabolic acidosis of an extrarenal origin. Direct measurement of ammonium in the urine is the most appropriate way to make this distinction, but if this assay is unavailable, then urinary ammonium excretion can be indirectly assessed by measuring the urinary anion gap (UAG):

$$\text{UAG} = U_{\text{Sodium}} + U_{\text{Potassium}} - U_{\text{Chloride}}.$$

The UAG is normally positive, ranging from 30 to 50 mmol/L, because of the urinary excretion of unmeasured anions such as phosphate, sulfate, and organic anions. In the setting of metabolic acidosis, ammonia production by a normal kidney increases from baseline values of 30–40 to >200 mmol/d. Ammonium is excreted into the urine with chloride and the increased concentration of ammonium chloride will cause the UAG to become negative, indicating the acidosis is of an extrarenal origin (35,36) (Figure 5). A positive UAG indicates an impairment in ammonium production and identifies the kidney as the cause of the acidosis. An increased plasma chloride and low bicarbonate concentration also develops as a compensatory response in chronic respiratory alkalosis. In this setting, the UAG is positive because urinary ammonium excretion is appropriately low (37).

The UAG can be misleading when other unmeasured ions are excreted. For example, increased urinary excretion of sodium keto acid salts in diabetic and alcoholic ketoacidosis and urinary excretion of sodium hippurate and sodium benzoate in toluene exposure can keep the UAG positive



Condition (reference)	Mechanism
Sepsis (5)	Vasoconstriction in the kidneys due to activation of vasoconstrictors such as angiotensin II, sympathetic nerves, arginine vasopressin, and vasoactive eicosanoids followed by ischemic, cytokine, and oxidant-induced tubular injury
Radiocontrast agents (6)	Production of endothelin and angiotensin II in the kidneys followed by ischemic and contrast-induced tubular injury
Nonsteroidal anti-inflammatory drugs (7)	Unopposed vasoconstriction from angiotensin II and sympathetic nerves followed by ischemic injury when given in setting of low effective volume
Rhabdomyolysis (8)	Sequestration of fluid in muscle decreases kidney perfusion followed by direct tubular injury from hematin, oxygen radicals, and tubular obstruction
Acute urinary obstruction (9,10)	Vasoconstriction in the kidneys due to angiotensin II and thromboxane followed by ischemic tubular injury
Acute glomerulonephritis (11)	Vasoactive inflammatory cytokines reduce glomerular filtration rate causing a lowering in the filtered load of sodium
Acute kidney allograft rejection (12)	Decreased glomerular blood flow from vasoactive cytokines followed by tubular dysfunction

Figure 1. | Causes of AKI where urine sodium concentration and fractional excretion of sodium may be initially reduced, only to later increase. In these conditions, the GFR is reduced because of activation of systemic and/or intrakidney vasoconstrictors causing a reduction in filtered load of sodium at a time when tubular function is relatively intact. As the insult persists, tubular injury becomes more widespread, resulting in an increase in urine sodium concentration and fractional excretion of sodium.

despite an appropriate increase in urinary ammonium excretion (38,39). A similar effect can occur in D-lactic acidosis. The stereospecificity of the sodium-L-lactate cotransporter in the luminal membrane of the proximal tubule results in less efficient reabsorption of filtered D-lactate as compared with L-lactate, causing excretion of

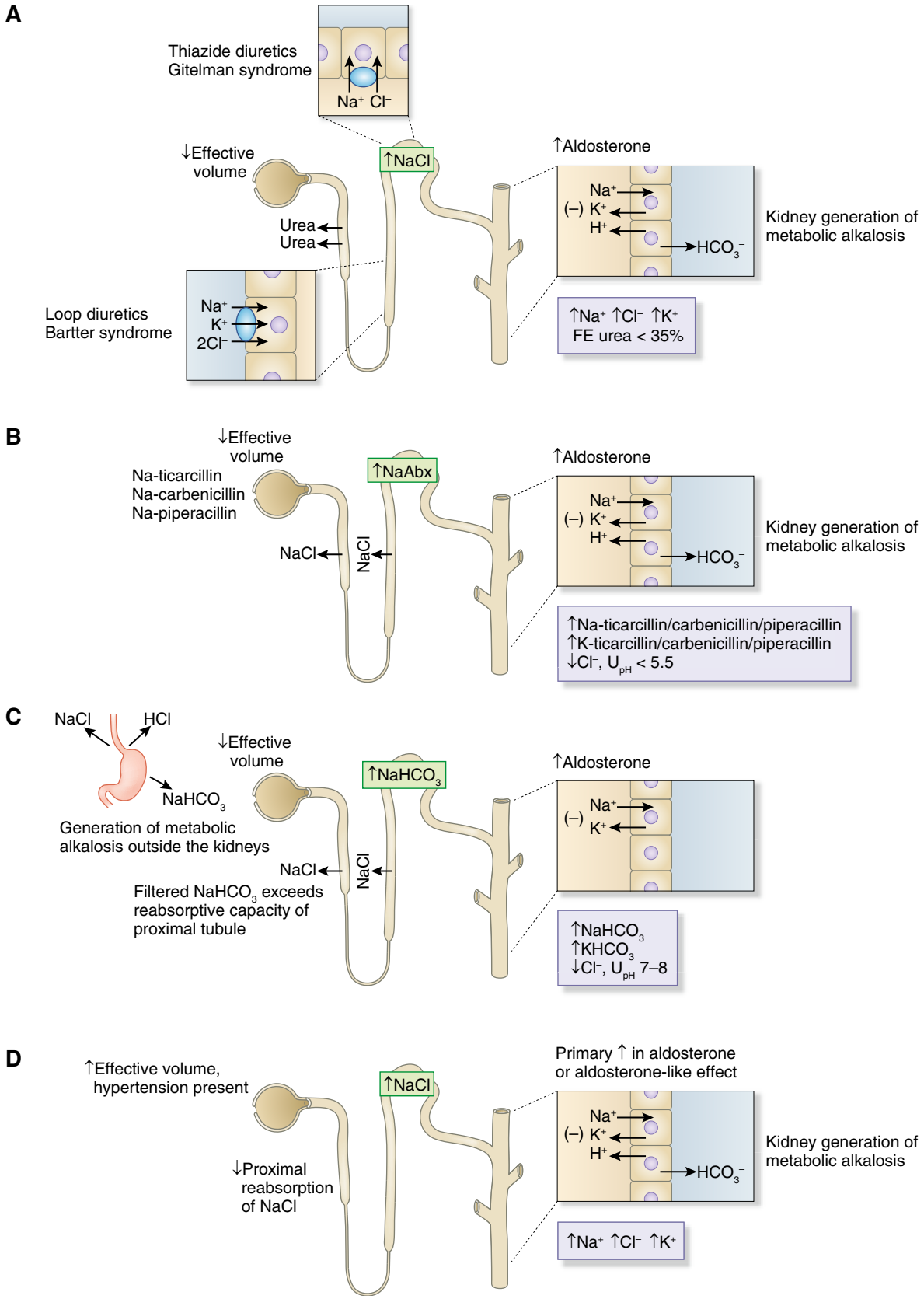


Figure 2. | **Urine chemistry profile in metabolic alkalosis.** (A) Loop and thiazide diuretics and their genetic equivalent (Bartter and Gitelman syndrome, respectively) cause contraction of effective circulatory volume and activation of the renin-angiotensin-aldosterone axis. Increased distal delivery of sodium coupled with increased mineralocorticoid levels causes increased potassium secretion and an increased rate of

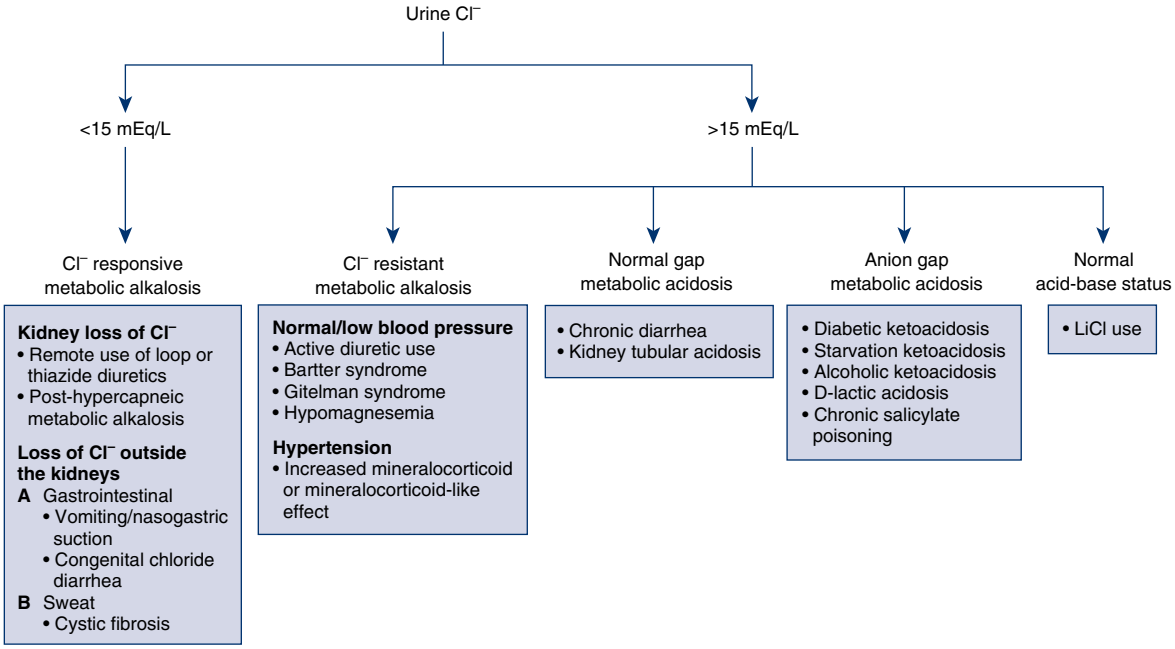


Figure 3. | The urine chloride concentration can be used to distinguish between a chloride responsive and resistant metabolic alkalosis. In a normal gap metabolic acidosis due to diarrhea, a high urine chloride is the result of increased excretion of NH_4Cl. Urine chloride is high in kidney tubular acidosis due to acidosis-induced decreased reabsorption of NaCl in the proximal tubule. In the indicated causes of anion gap metabolic acidosis, a high urine chloride is the result of increased excretion of NH_4Cl. In these settings, the urine sodium is typically higher than the chloride due to the excretion of sodium and potassium acid salts.

D-lactate into the urine as a sodium or potassium salt. Increased urinary excretion will also be missed when ammonium is excreted with an anion other than chloride, such as β-hydroxybutyrate or hippurate (Figure 5). In these settings, calculation of the urine osmolal gap is used as an indirect measure of ammonium excretion (40). The urine osmolal gap is the difference between the measured and the calculated urine osmolality:

$$\begin{aligned}\text{Urine osmolal gap} &= \text{Calculated urine osmolality(mosmol/kg)}\\ &= \left(2 \times \left[Na^+ + K^+\right]\right)\\ &+ (\text{Urea nitrogen in mg/dl})/2.8\\ &+ (\text{Glucose in mg/dl})/18.\end{aligned}$$

The urine osmolal gap normally ranges from approximately 10 to 100 mOsmol/kg. Because ammonium salts are generally the only other major urinary solute that contribute importantly to the urine osmolality, values appreciably >100 mOsmol/kg reflect increased excretion of ammonium salts. There are other osmotically active solutes that can increase the urinary osmolal gap in the absence of increased ammonium excretion. These include mannitol and alcohols such as ethanol, methanol, and ethylene glycol. Although ethanol is metabolized rapidly, urinary excretion of methanol and ethylene glycol, particularly during treatment with fomepizole, will significantly increase the urine osmolal gap. An increased plasma osmolal gap and clinical setting are important clues to the presence of toxic alcohol ingestion.

Urine pH does not reliably differentiate acidosis due to kidney disease from that of extrarenal origin (Figure 5). A small amount of distal H^+ secretion can lower urine pH to values <5 in the setting of decreased ammoniagenesis. Despite the acid urine pH, net acid excretion is low because of low ammonium excretion. Similarly, an alkaline urine does not necessarily imply a kidney acidification defect. When ammonia production is stimulated, distal H^+ secretion can be robust and yet the urine remains relatively alkaline because of the buffering effects of ammonia.

Figure 2. | Continued. hydrogen ion secretion in the distal nephron, leading to the development of hypokalemic metabolic alkalosis (27). The fractional excretion (FE) of urea is reduced to <35% because proximal reabsorption of urea is stimulated and unaffected by the downstream impairment in sodium chloride transport. Metabolic alkalosis due to remote use of diuretics is sensitive to chloride-containing solutions but resistant in genetic disorders. (B) Antibiotics such as carbenicillin, ticarcillin, and piperacillin given in the setting of decreased effective volume act as nonreabsorbable anions, causing increased delivery of sodium to the distal nephron, resulting in development of hypokalemia and a chloride-responsive from of metabolic alkalosis. The urine pH (U_{pH}) in this setting is acidic because of augmented hydrogen ion secretion. (C) Active vomiting or nasogastric suction generates a chloride-sensitive form of metabolic alkalosis. Bicarbonate acts as a nonreabsorbable anion, causing increased distal sodium delivery and development of potassium wasting (29). (D) A primary increase in mineralocorticoid levels (Conn syndrome) or effect (Liddle syndrome) leads to a chloride resistant form of metabolic alkalosis accompanied by kidney potassium wasting and hypertension. Increased distal delivery of sodium is due to inhibition of proximal reabsorption brought about by effective volume expansion.

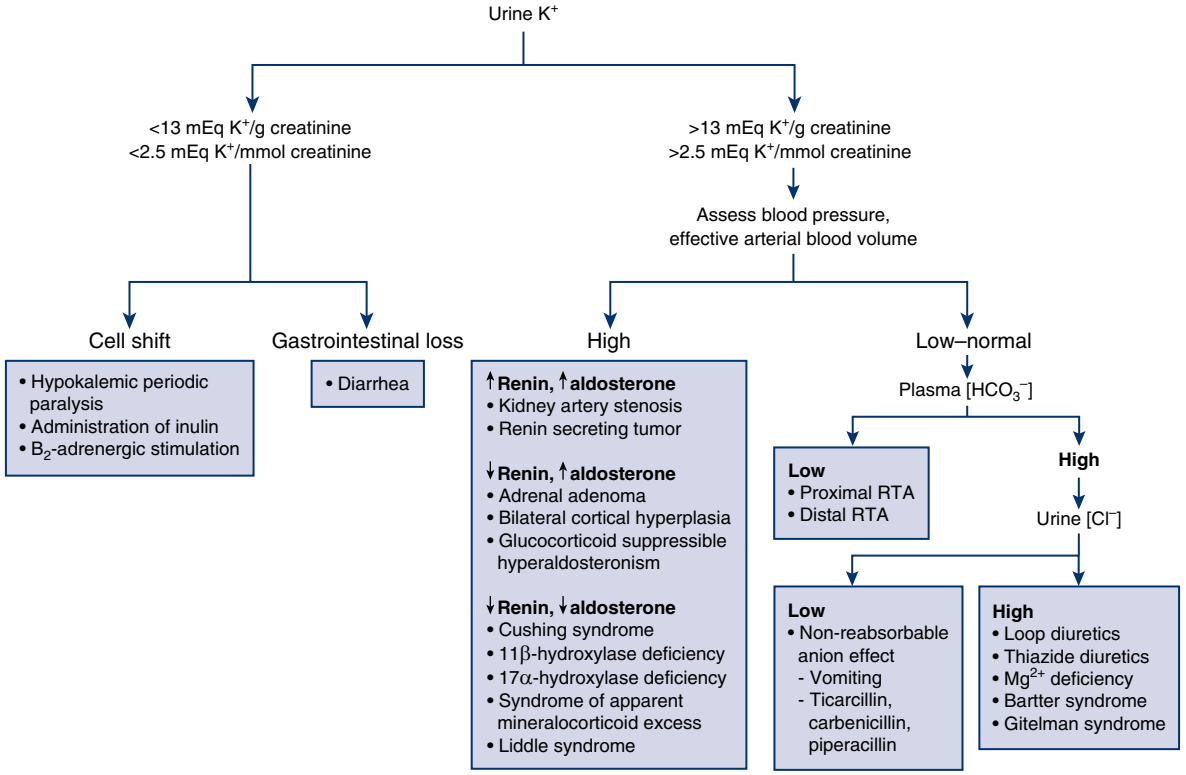


Figure 4. | **A flow diagram for the approach to patients with hypokalemia on the basis of the potassium-to-creatinine ratio in the urine.** RTA, renal tubular acidosis.

A severe reduction in distal sodium delivery, as in advanced cirrhosis, can limit H^+ secretion and also cause the urine to be relatively alkaline (Supplemental Material, Case 3).

Urine Osmolality

Measurement of urine osmolality along with urine chemistries can provide important diagnostic information in approaching a patient with disorders in water balance. Because urine osmolality can normally range from <100 to approximately 1200 mOsm/kg, one measures urine osmolality to determine if the value is in the expected range for the given clinical situation. A maximally dilute urine in a patient with hypotonic hyponatremia is found in primary polydipsia where ingestion of large quantities of water (>20 L/d in the setting of normal kidney function) overwhelm the normal excretory capacity of the kidney. This threshold decreases as kidney function declines. A similar value is found with more moderate fluid intake when combined with extremely limited solute intake, a condition often referred to as "beer potomania" syndrome (39). Another example would be a "tea and toast" diet sometimes present in an elderly patient. Low urinary solute excretion limits water excretion by the kidneys because solute excretion determines the upper limits for the volume of water loss by the kidneys.

More commonly, the urine osmolality in hypotonic hyponatremia is some value >200 mOsm/kg resulting from the action of vasopressin to decrease free water excretion. Urine electrolytes can be used to assess volume status and determine whether the cause of increased vasopressin levels is secondary to a circulatory disturbance causing unloading of baroreceptors, or is baroreceptor independent as occurs in the syndrome of inappropriate antidiuretic hormone release (41).

The urine osmolality should be maximally concentrated (>1000 mOsm/kg H_2O) in patients with hypernatremia who have intact hypothalamic and kidney function due to increased plasma vasopressin levels. A lower maximum is seen in elderly patients because of age-related reductions in urine concentrating ability. If urine osmolality is <300 mOsm/kg, then either central or nephrogenic diabetes insipidus is present. These disorders are distinguished by examining the change in urine osmolality and urine volume after the administration of exogenous vasopressin. Urine osmolality will increase and urine volume decrease in central diabetes insipidus, whereas no response will occur in the nephrogenic form. Patients can present with incomplete forms of central and nephrogenic diabetes insipidus making the response to exogenous vasopressin less straightforward.

Urine osmolality can distinguish between a water diuresis and osmotic diuresis in patients with polyuria and polydipsia (42,43). A value <100 mOsm/kg indicates a water diuresis as seen in diabetes insipidus or primary polydipsia whereas a value between 300 and 600 mOsm/kg indicates an osmotic diuresis. Intermediate values between 100 and 300 mOsm/kg suggest a mixed polyuria as with a partial central or nephrogenic diabetes insipidus or simultaneous water and solute intake. Daily osmolar excretion averages 600–900 mOsm when ingesting a normal diet, and

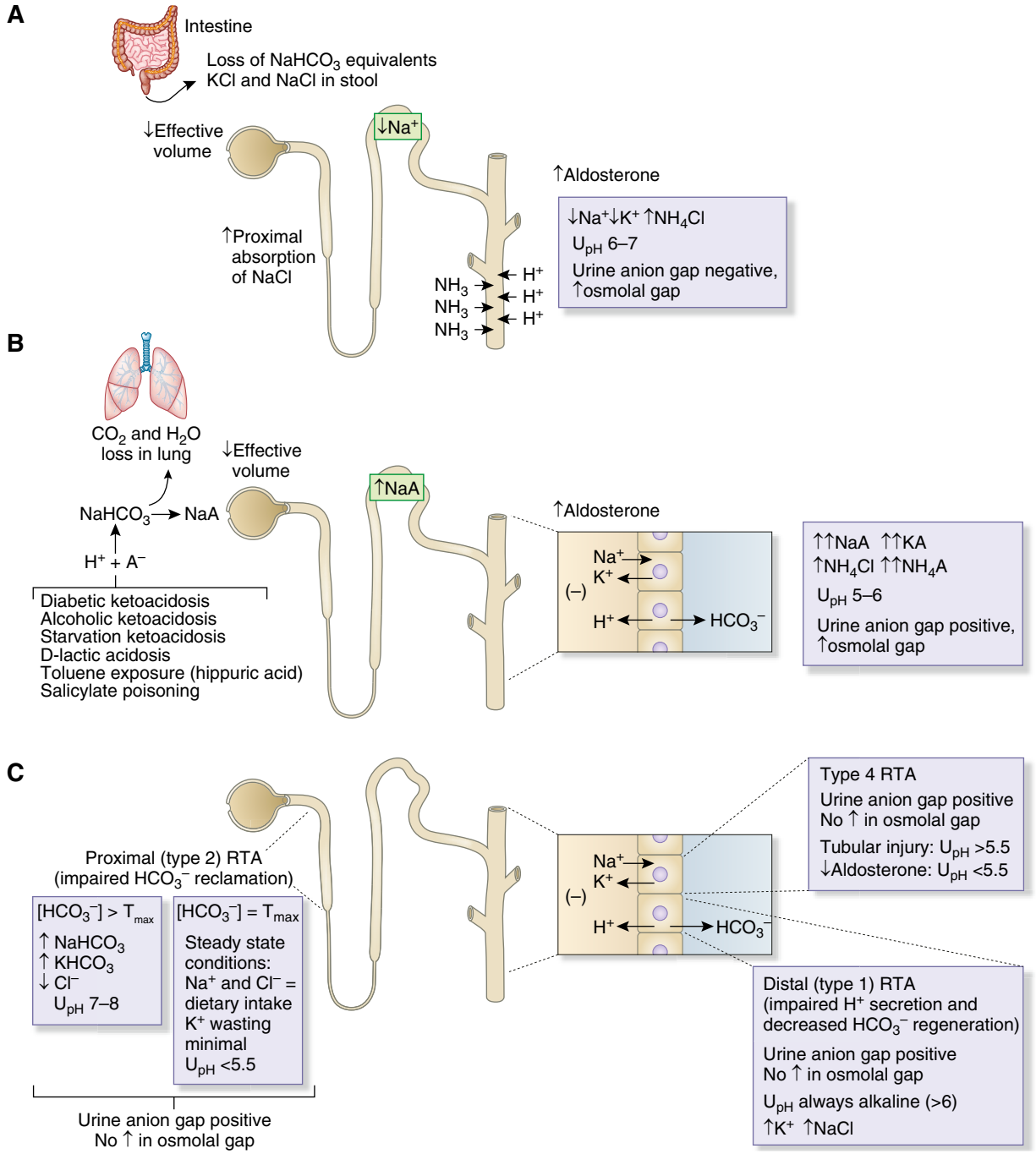


Figure 5. | **Urine chemistry profile in metabolic acidosis of kidney and nonkidney origin.** (A) In diarrhea, stool loss of potential bicarbonate, sodium chloride, and potassium lead to a normal gap hyperchloremic metabolic acidosis, hypokalemia, and extracellular fluid volume contraction. Acidemia and hypokalemia stimulate kidney ammoniagenesis allowing for increased amounts of distal hydrogen ion secretion to occur. Ammonium is excreted coupled to chloride, accounting for the development of a negative urinary anion gap and increased osmolal gap. The urine pH (U_{pH}) is not maximally acidic despite robust distal hydrogen ion secretion because the free hydrogen ion concentration is reduced due to the buffering effect of urinary ammonium. (B) Shown are various examples of overproduction aciduria. The excretion of the sodium or potassium salts of these acids (NaA) into the urine represent the indirect loss of bicarbonate from the body and cause the urine anion gap to remain positive despite large amounts of ammonium excretion. Urine sodium and potassium concentration will be greater than the urine chloride concentration because chloride is retained in response to volume contraction. Although some ammonium is excreted as NH_4Cl, a large amount of ammonium is excreted coupled to the anion salts of the acids. The urine osmolal gap is increased due to the large amount of ammonium in the urine indicating the acidosis is of extrakidney origin. (C) Distal (type 1) and proximal (type 2) renal tubular acidosis (RTA) are characterized by hypokalemic hyperchloremic normal anion gap metabolic acidosis. Distal (type 1) RTA results from defects in hydrogen ion secretion in the distal nephron interfering with bicarbonate regeneration. The urine pH is always alkaline (pH 6–7) and urine potassium is increased due to coupling of increased distal sodium delivery with increased aldosterone resulting from acidosis-induced decreased sodium reabsorption in the proximal tubule (36). Impairment in activity of the H^+-K^+-ATPase can also contribute to kidney K^+ wasting. Proximal (type 2) RTA is the result of impaired

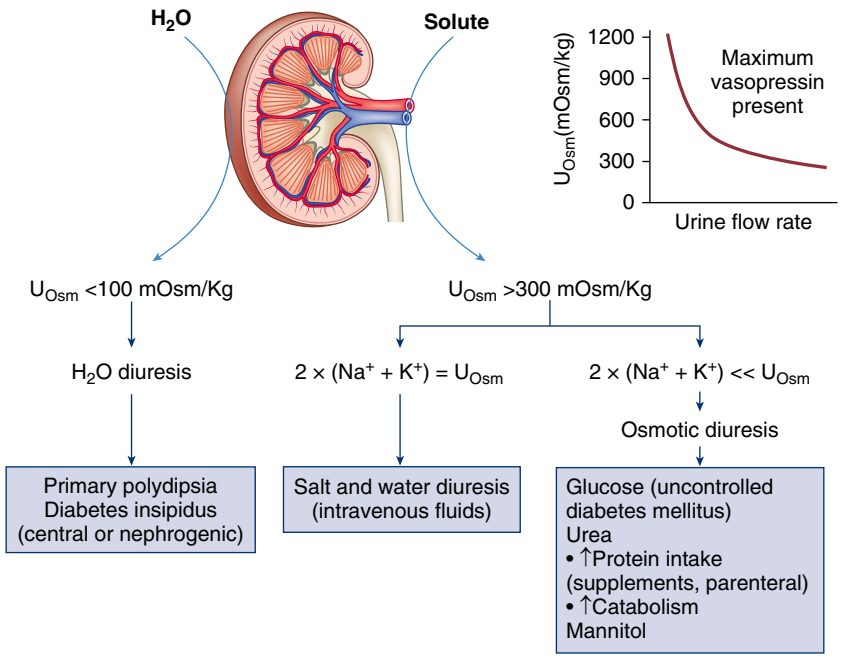


Figure 6. | **Urine chemistry tests for the diagnostic evaluation of a patient with polyuria.** Polyuria is generally said to be present when urine output is >3 L/d and can be due to either a water diuresis or an osmotic diuresis. A urine osmolality (U_{osm}) <100 mOsm/kg indicates a water diuresis. Restricting free water intake will cause a decrease in urine volume and an increase in urine osmolality in psychogenic polydipsia, whereas no effect is seen in diabetes insipidus. An increase in urine osmolality after the administration of desmopressin is found in central diabetes insipidus whereas no response is found in the nephrogenic form. A urine osmolality >300 mOsm/kg is observed in osmotic diuresis. Values between 100 and 300 mOsm/kg favor a mixed polyuria as with simultaneous water and solute intake or partial central or nephrogenic diabetes insipidus. Patients with CKD are unable to maximally dilute the urine and can also fall within this range when challenged with a water load. Administration of NaCl is responsible when the majority of osmoles can be accounted for by two times the sum of Na^+ and K^+ concentration in the urine. An osmotic diuresis due either to glucose, urea, or mannitol is present when there is a large gap between the urine osmolality and the urine electrolyte concentration. Even though urine osmolality is often greater than plasma values, hypernatremia can develop during an osmotic diuresis because the plasma Na^+ concentration is determined by the relative loss of water and electrolytes and not total solutes. Calculation of electrolyte free water excretion predicts the change in plasma Na^+ concentration in this setting. The graph demonstrates that with progressive osmotic diuresis the urine osmolality will progressively decrease to values that are isosmolar with plasma because high tubular flow rates prevent osmotic equilibrium with medullary interstitial fluid even when arginine vasopressin is not limiting (44).

is largely accounted for by urea, sodium, potassium, and ammonium salts. Another osmole is contributing to the polyuria when the product of urine volume and urine osmolality exceeds this range. Glycosuria as in uncontrolled diabetes, increased urea generation due to high protein nutritional supplementation, salt-containing intravenous fluids, or administration of mannitol can all lead to an osmotic diuresis (Figure 6). Polyuria in the absence of polydipsia can be seen in patients with hyponatremia undergoing a brisk aquaresis when the defect in water excretion is rapidly reversed as with discontinuation of thiazides, or after cortisol or thyroid hormone replacement.

Patients undergoing an osmotic diuresis may have a urine osmolality greater than the plasma osmolality and still be in negative water balance (44,45). Free water loss is present when the concentration of sodium and potassium in the urine is less than the plasma concentration. Calculation of electrolyte free water clearance is useful in predicting the directional change in plasma sodium concentration:

$$\text{Electrolyte free water clearance} = U_{Volume} \times (1 - [U_{Sodium} + U_{Potassium}/P_{Sodium}]).$$

A positive value indicates loss of free water from the body and predicts an increase in the plasma sodium concentration over time (46,47). A negative value suggests water intake would tend to lower the plasma sodium concentration after taking into account insensible water losses (Supplemental Material, Case 4).

Figure 5. | Continued. bicarbonate reclamation in the proximal tubule due to a decrease in the tubular maximum for reabsorption. When the plasma bicarbonate exceeds the tubular maximum, the urine pH will be alkaline and urine sodium and potassium will be increased whereas urine chloride is low. Once the plasma bicarbonate concentration falls to the reduced tubular maximum, the urine pH will become acidic and the degree of potassium wasting will decrease. Type 4 RTA is characterized by hyperkalemic normal anion gap metabolic acidosis. When the disorder results from a disturbance in the renin-angiotensin-aldosterone axis, the urine pH is acidic, whereas when it results from tubular dysfunction, the urine pH is more alkaline. In all types of RTA, urine ammonium excretion is reduced, reflected by a positive urine anion gap and no increase in the urine osmolal gap.

Conclusions

Urinary chemistries vary widely in both health and disease and are affected by diet, volume status, medications, and disease states. When properly examined these tests provide important insight into the mechanism and therapy of various clinical disorders that are first detected by abnormalities in plasma chemistries. These tests cannot be interpreted in isolation, but instead require knowledge of key clinical information, such as medications, physical examination, and plasma chemistries, to include kidney function. When used appropriately and with knowledge of limitations, urine chemistries can provide important insight into the pathophysiology and treatment of a wide variety of disorders.

Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.10330818/-/DCSupplemental.

Case 1. Use of the fractional excretion of sodium in a patient with pre-existing chronic kidney disease.

Case 2. Distinguishing between prerenal azotemia and acute tubular necrosis in the setting of diuretic therapy.

Case 3. Distinguishing whether metabolic acidosis is due to kidney disease or not.

Case 4. Use of urine chemistries in the approach to a polyuric patient with hypernatremia and a patient with hyponatremia.

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Published online ahead of print. Publication date available at www.cjasn.org.

Correction

Biff F. Palmer and Deborah Joy Clegg: The Use of Selected Urine Chemistries in the Diagnosis of Kidney Disorders. *Clin J Am Soc Nephrol* 14: 306–316, 2019; DOI: https://doi.org/10.2215/CJN.10330818.

The parameters utilized in Figure 4 (below) to distinguish appropriate potassium retention versus increased potassium excretion by the kidney (13 mEq K^+/g creatinine, 2.5 mEq K^+ /mmol creatinine) are two different thresholds reported in the literature and are not meant to indicate mathematical equivalence.

Published online ahead of print. Publication date available at www.cjasn.org.

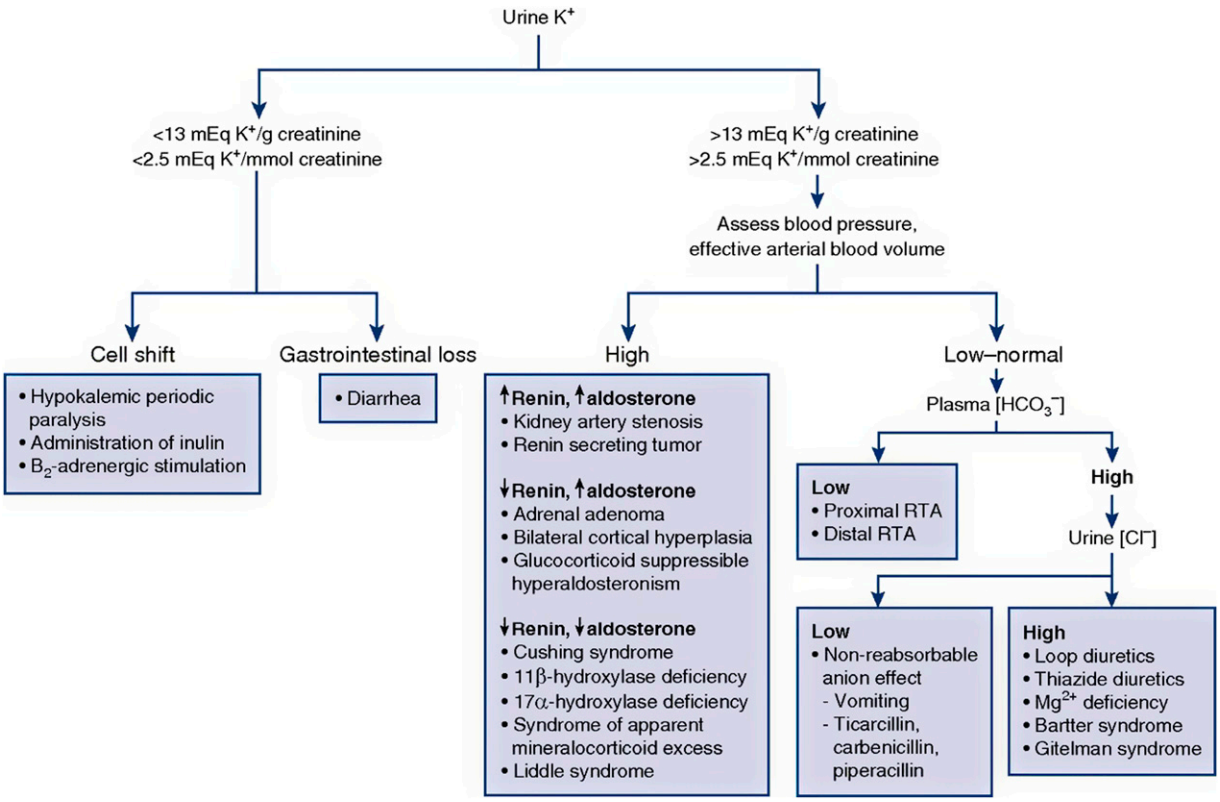

Figure 4. | A flow diagram for the approach to patients with hypokalemia on the basis of the potassium-to-creatinine ratio in the urine. RTA, renal tubular acidosis.

Supplemental Material: Table of Contents

Case 1: Use of the fractional excretion of sodium in a patient with pre-existing chronic kidney disease

A 52 year old man with known diabetic nephropathy and a baseline serum creatinine concentration of 2.2 mg/dl (eGFR 33 mL/min/1.73 m²) presents with a 3 day history of nausea, vomiting, and diarrhea described as 4-5 loose watery stools per day. Physical examination is significant for orthostatic changes in blood pressure and pulse, dry mucous membrane, and no peripheral edema. Laboratory studies show (mEq/L): Na^+ 142, K^+ 3.6, Cl^- l06, HCO_3^- 22 and serum creatinine concentration 2.8 mg/dl. The urinalysis shows 1+ protein but no cells and occasional hyaline casts. Urine output over the first 6 hours of evaluation is 500 ml. The urine sodium concentration is 55 mEq/L and the urine creatinine concentration is 75 mg/dl.

How does one utilize the fractional excretion of sodium in patients with chronic kidney disease?

The fraction excretion of sodium measures the percentage of the sodium filtered by the kidney that is excreted in the urine. When the glomerular filtration rate is normal (180 liters/day) and the filtered load of sodium is 27000 mEq/day (180 liters/d x plasma water sodium concentration of 150 mEq/L), the fractional excretion of sodium will always be <1% whenever dietary intake is <270 mEq/day, a value above the average dietary salt intake. The FE_{Na} would need to be <0.1% in order to reduce urinary sodium concentration to <25 mEq/day, indicating an appropriate response to a prerenal state. For this reason, the fractional excretion of sodium is most useful in distinguishing between prerenal azotemia from acute tubular necrosis when the glomerular filtration rate is markedly reduced. In a patient with a glomerular filtration rate of 20 liters/day, the filtered load of sodium would be only 3000 mEq/day. In this case, the fractional

excretion would only need to be <1% to indicate an appropriately reduced daily urine sodium excretion assuming a prerenal cause was the only problem.

Since baseline urine chemistries are not available in the described patient, one has to estimate the initial FE_{Na} based on the known eGFR and an estimate of dietary sodium intake. Assuming the patient was in balance on a dietary sodium intake of 175 mEq/day, the fractional excretion of sodium can be estimated to be 2.4% at baseline:

$$FE_{Na} = \text{daily sodium intake} / [\text{GFR (in liters/day)} \times \text{plasma water sodium content})$$

or

$$(175 \text{ mEq/day} / (33 \text{ ml/min} \times 1440 \text{ min/day}) \times 150 \text{ mEq/L}]$$

Upon presentation, the fractional excretion of sodium is 1.4%:

$$FE_{Na} = (U_{Na} \times P_{Creatinine} / P_{Na} \times U_{Creatinine}) \times 100\%$$

$$FE_{Na} = (55 \text{ mEq/L} \times 2.8 \text{ mg/dl} / 142 \text{ mEq/L} \times 75 \text{ mg/dl}) \times 100\%$$

Even though the urine sodium concentration is not less than 20 mEq/L and the fractional excretion of sodium is >1%, the clinical findings in this case are consistent with some degree of intact tubular function as reflected by the decrease in fractional excretion of sodium from 2.4% at baseline to the current value of 1.4%. Sodium balance is maintained in patients with chronic kidney disease through increases in the fractional excretion of sodium that can reach values of 25-30% when the glomerular filtration rate is approximately 10 ml/min. In chronic kidney disease, the kidney's

response to dietary sodium restriction or development of a prerenal state is delayed and not maximal but eventually the urine sodium concentration and fractional excretion will decrease over time in patients who are not at end stage (1,2). In addition to the change in fractional excretion of sodium, the history, clinical examination, urine microscopy, and, when appropriate, response to volume resuscitation, should be utilized in assessing the volume status of these patients.

Case 2: Distinguishing prerenal azotemia from acute tubular necrosis in the setting of diuretic therapy

A 58-year-old man with a history of heart failure with reduced ejection fraction is admitted with a 3-day history of worsening shortness of breath and edema. His past medical history is significant for a prior myocardial infarction and benign prostatic hypertrophy. He is found to be in pulmonary edema and requires intubation and mechanical ventilation. Medications on admission include aspirin, lisinopril, carvedilol, atorvastatin, and furosemide. On physical examination, he is afebrile, blood pressure is 92/60 mm Hg, and pulse rate is 112/min. There is jugular venous distention, an S3 gallop, diffuse crackles throughout both lung fields, and lower extremity edema to the knees. A urinary catheter is inserted and intravenous furosemide is given. Urine output over the next 4 hours is 300 ml. Laboratory evaluation shows the following (mEq/L): Na^+ 140, K^+ 4.8, Cl^- 103, HCO_3^- 22, creatinine 3.0 mg/dl (baseline 1.9 mg/dl), blood urea nitrogen 76 mg/dl. Urine chemistries show a Na^+ 64 mEq/L, creatinine 72 mg/dl, urea 159 mg/dl. Urinalysis shows 1+ protein, 1-2 RBC/hpf, 2-4 WBC/hpf, and occasional hyaline and fine granular casts.

How can one distinguish between prerenal azotemia and acute tubular necrosis in the setting of diuretic therapy?

This patient presents with acute kidney injury in the setting of decompensated heart failure. The worsening azotemia during the hospitalization is most likely due to decreased effective blood volume causing a prerenal state. Acute tubular necrosis from hypotension and urinary obstruction from prostate disease also need to be considered in assessing the change in kidney function. The fractional excretion of sodium is a useful test to distinguish between a prerenal cause of acute kidney injury from acute tubular necrosis. This test becomes less reliable in the setting of diuretic

therapy because the urine sodium may not accurately reflect attempts by the kidney to retain sodium. Under condition of low flow to the kidney, there is increased urea reabsorption by the proximal tubule accounting for the disproportionate rise in the blood urea nitrogen compared to the serum creatinine concentration. The fractional excretion of urea will be unaffected by loop diuretic therapy since the site of action of these drugs is in the downstream thick ascending limb. In this patient, the fractional excretion of sodium is higher than expected in a prerenal state at 1.9%, but the fractional excretion of urea is only 8.7% (<35%), suggesting an underlying prerenal state.

The use of FE_{Urea} and FE_{Na} do have limitations as discussed in the main text. The initial report establishing a value <1% for a prerenal etiology and >3% to indicate tubular injury came from a small study of highly selected patients excluding those on diuretics and patients with chronic kidney disease, glomerulonephritis, and urinary obstruction (3). A larger subsequent study validating the use of FE_{Na} also excluded the use of diuretics within 24 hours of study entry (4). More recent studies have reported a sensitivity and specificity for the FE_{Na} of 78% and 75% in patients not administered diuretics and 58% and 81% in those administered diuretics (5,6). By comparison the sensitivity and specificity of the FE_{Urea} is 48% and 75% in patients not administered diuretics and 79% and 33% in patients administered diuretics. These observations emphasize the need to use the FE_{Urea} and FE_{Na} as an adjunct to the clinical history, physical examination, urine microscopy, and, when appropriate, response to volume resuscitation in the assessment of the azotemic patient.

Case 3: Distinguishing whether metabolic acidosis is due to kidney disease or not

A 19-year-old woman is transported to the emergency room after being found on the floor of her apartment unable to move. The patient states she was in her usual state of health up until 36 hours ago when she noticed the onset of episodic but progressively worsening generalized weakness. There was no history of bladder or bowel incontinence or loss of consciousness. Past medical history was unremarkable and the patient denied ingestions, however, the roommate who accompanies her says she has been acting "a little crazy" recently. Vital signs on admission showed: temperature of 37 C, blood pressure of 110/60 mmHg and pulse 95. Physical exam is remarkable for erythematous discoloration around her lips and nose and erythema of the oral and pharyngeal mucosa. Conjunctival injections are present. There was 2/6 weakness in both upper and lower extremities and generalized hyporeflexia. Laboratory data show: (mEq/L) Na^+ 136, K^+ 1.5, Cl^- 105, HCO_3^- 10, creatinine 1.4 mg/dl, BUN 32 mg/dl, pH 7.1, pCO_2 35 mmHg, pO_2 110, Urine (mEq/L): Na^+ 42, K^+ 38, Cl^- 65, pH 6.0, urea 38 mg/dl, creatinine 62 mg/dl, osmolality 610 mOsm/kg.

How can one determine whether the metabolic acidosis is due to kidney disease or not in this patient?

This patient presents with severe hypokalemia and a triple acid-base disturbance to include an anion gap metabolic acidosis, hyperchloremic normal gap metabolic acidosis, and respiratory acidosis. This determination can be made by taking a systematic approach to the basic metabolic profile (7). Examination of the plasma sodium concentration suggests a mild increase in total body water. Normally changes in hydration status will lead to a similar change in chloride concentration, however, in this case the chloride concentration is increased. A change in chloride

concentration in a direction opposite or disproportionate to the change in plasma sodium suggests an acid-base disorder is present. The two causes to consider when the chloride concentration has increased relative to the sodium are chronic respiratory alkalosis or normal anion gap metabolic acidosis. One should always calculate the anion gap when given a basic metabolic profile. In this case, the anion gap is 21, thus identifying the presence of an anion gap metabolic acidosis as at least one of the acid-base disturbances in this case. In general, the serum bicarbonate concentration will fall by an amount equal to the increase in anion gap. In this patient the anion gap has increased by nine assuming a normal value of 12. As a result one would predict the plasma bicarbonate should be approximately 15 mEq/L (24 – 9 = 15). Since the measured value is 10 mEq/L, one can conclude a normal gap hyperchloremic metabolic acidosis is also present which was suggested by the disproportionate rise in plasma chloride concentration noted above. The expected degree of respiratory compensation for a bicarbonate of 10 mEq/L in the setting of metabolic acidosis is a pCO_2 of approximately 25 mmHg. The measured value of 35 mmHg indicates an insufficient respiratory response confirming the presence of respiratory acidosis.

The laboratory findings along with the erythema around the mouth and oropharynx are consistent with inhalation of toluene. Metabolism of toluene generates benzoic and hippuric acid which are buffered by endogenous bicarbonate. The subsequent excretion of the sodium or potassium salts of these acids into the urine is equivalent to the indirect loss of bicarbonate from the body. While chronic exposure to toluene can lead to tubular injury and a type 1 distal renal tubular acidosis, examination of urine chemistries demonstrates a normal response of the kidney to the acidosis as manifested by robust excretion of ammonium in the urine.

Calculating the urine anion gap allows for indirect assessment of the amount of urinary ammonium. Metabolic acidosis of extrarenal origin leads to a marked increase in urinary

ammonium excretion and normally would be reflected by a large negative value for the UAG. In this patient, the UAG is 15 suggesting the acidosis is due to intrinsic kidney disease. The UAG is misleading in the setting of toluene exposure due to increased urinary excretion of Na^+ and K^+ coupled to hippurate and or benzoate (8,9). In addition, the stimulatory effect of acidemia and hypokalemia progressively increase the amount ammoniagenesis so that large quantities of ammonium hippurate and benzoate are also present in the urine further limiting the utility of the UAG to accurately reflect urinary ammonium excretion. A similar situation occurs in diabetic ketoacidosis where the UAG may remain positive despite an appropriate increase in urinary ammonium excretion due to the increased urinary excretion of Na^+, K^+, and NH_4^+ ketoacid salts.

The urine osmolal gap is a more useful method to semiquantitatively estimate the amount of ammonium in the urine under conditions of organic acid anion loss in the urine. In this case, the urine osmolal gap is significantly increased at 436 mOsmol/kg indicating large amounts of ammonium in the urine and an extrarenal source of the acidosis.

The severe hypokalemia is due to the poorly reabsorbable anion effect of hippurate and benzoate causing increased distal Na^+ delivery in the setting of increased mineralocorticoid activity, the latter being due to volume depletion. The urine K^+/creatinine ratio of 6.9 (38 mEq/5.5 mmol) indicates K^+ wasting by the kidneys.

Case 4: The use of urine chemistries in the approach to a polyuric patient with hypernatremia and a patient with hyponatremia

A 73 year-old man with dementia is transferred from a nursing home to the hospital with a diagnosis of pneumonia. On admission serum electrolytes were normal. In addition to treating the infection, hyperalimentation with high-protein supplements (solution contains 30 mEq/l each of Na^+ and K^+) is begun in an attempt to improve the patient's poor nutritional status. Five days later it is noted the urine output is averaging 4 liters/d. Laboratory evaluation shows (mEq/L): Na^+ 156, K^+ 4.6, Cl^- 116 HCO_3^- 26, BUN 35 mg/dl, creatinine 1.2 mg/dl. Urine chemistries show (mEq/L): Na^+ 12, K^+ 42, osmolality 505 mOsm/Kg.

How can one use urine chemistries to determine the cause of free water lose in this patient?

This patient presents with a water deficit in association with polyuria. When approaching a polyuric patient one needs to distinguish between a water diuresis and an osmotic diuresis. In the setting of a water diuresis the urine osmolality will be maximally dilute at <100 mOsm/kg. The urine osmolality of 505 mOsm/kg in this patient suggests an osmotic diuresis. Even though the urine is concentrated, calculating the electrolyte free water excretion indicates this patient is losing 2.6 liters of free water per day exacerbating the water deficit. In the setting of a normal diet daily solute excretion averages 900 mOsm. This patient is excreting 2020 mOsm/day (Uosm (505 mOsm/kg) x 4 liters/24 hr = 2020 mOsm). The most likely cause of the polyuria is an osmotic diuresis due to urea excretion derived from the metabolism of protein in the hyperalimentation.

Calculating electrolyte free water clearance can also be useful in the management of patients with hyponatremia. Consider a patient with SIADH who presents with a plasma sodium concentration of 123 mEq/L and has a urine output of 1 liter/day. Urine studies show osmolality

of 550 mOsm/kg, Na^+ 95 mEq/L, and K^+ 58 mEq/L. The daily solute excretion is 1 liter x 550 mOsm or 550 mOsm/day.

$$\text{Electrolyte free water clearance} = U_{volume} \times [1 - (U_{sodium} + U_{potassium} / P_{sodium})]$$

$$\text{Electrolyte free water clearance} = 1 \text{ liter} \times [1 - (95 + 58 / 123)]$$

$$\text{Electrolyte free water clearance} = -240 \text{ ml}$$

The negative value indicates water restriction would not be an effective strategy to correct the hyponatremia. In fact, any water intake in excess of insensible losses would aggravate the hyponatremia. The administration of urea to increase urinary solute excretion or administration of a vasopressin receptor antagonist would be effective treatments in this setting.

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