Chapter 15
Kidney Excretions: The Lyter Side of Urine

Jeremy Steinman, Carly Kuehn, and Lisa M. Antes

Objectives

- Understand the categories to classify hypokalemia, the differential diagnosis in each category and the use of urine potassium to help narrow the differential
- Understand the relevance of hypokalemia associated with hyperaldosteronism and initial testing considerations
- Recognize Type I, II and IV renal tubular acidosis (RTA), some common causes of each and the implications for obtaining a urine anion gap when evaluating patients with suspected RTA

J. Steinman
Department of Internal Medicine, Division of Endocrinology, University of Virginia, Charlottesville, VA, USA

C. Kuehn
Department of Internal Medicine, Division of General Internal Medicine, University of Iowa, Iowa City, IA, USA

L. M. Antes (✉)
Department of Internal Medicine, Division of Nephrology, University of Iowa, Iowa City, IA, USA
e-mail: lisa-antes@uiowa.edu

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- Use urine osmolarity to sort polyuria into a solute or water diuresis and describe common causes of each
- Understand the basic physiologic principles behind a water deprivation test
- Understand the limitations and use of fractional excretion of sodium and fractional excretion of urea in patients with acute kidney injury

Overview

The evaluation of serum electrolytes is part of a basic laboratory workup for various conditions and clinical signs or symptoms. Urine testing can be a powerful tool to further delineate some conditions not clearly understood from history, physical exam and serum electrolyte evaluation alone. This chapter shows the clinician the physiology behind metabolic conditions commonly evaluated with urine electrolytes (hypokalemia, renal tubular acidosis, acute kidney injury) and how urine testing aids in evaluation (polyuria).

Case 1: Hypokalemia Evaluation

A 20 year old female with no past medical history presents to your clinic for an evaluation of muscle cramps. She has no other complaints. BP is 113/80 and physical exam is unremarkable. A basic metabolic panel (BMP) reveals a potassium (K) of 2.9 mEq/L (normal 3.5–5 mEq/L). What else would you ask her and how would you proceed with the evaluation?

Hypokalemia is a common issue encountered in both the primary care and inpatient settings. The differential diagnosis is broad, but can be narrowed with a few key clinical clues. There are **4 main categories**:

Cause of hypokalemia	Common example
1. Increased renal losses of potassium	Diuretic use
2. Increased extrarenal losses of potassium (mostly GI tract)	Diarrhea (e.g., enterocolitis)
3. Decreased dietary intake	Malnourishment
4. Transcellular shifts	Continuous insulin infusions

Renal losses are most easily evaluated with assessment of urine K excretion. In this regard, it is important to understand the context and the response expected by the kidneys. In the face of low serum potassium, the kidney should be conserving (or reabsorbing) potassium and the urine potassium value should therefore be low (< 20 mEq/day or a random urine specimen with < 15mEq/L). If the urinary potassium is high or within the normal range in the face of hypokalemia, this represents pathologic potassium loss in the urine.

Renal losses comprise a diverse category, including medication associated urine K losses, osmotic diuresis, renal tubular defects and mineralocorticoid excess states [1]. A thorough medication history is imperative when evaluating renal losses of potassium, as several drugs are known to cause renal K wasting. In addition, several medications are known to cause hypomagnesemia (Table 15.1), which in turn can contribute to hypokalemia. Magnesium (Mg) facilitates K reabsorption by the kidney. Checking a serum Mg level is a simple way to explore this possiblity. Patients with medication associated hypokalemia may have concomitant acid-base disorders, as is the case with diuretic therapy or normal acid-base status, as is the case with proton pump inhibitors (PPI). Osmotic diuresis (e.g., hyperglycemia) can result in renal K losses as well.

Two important causes of excessive renal potassium losses are type I and II renal tubular acidosis (RTA) and hyperaldosteronism. These can be differentiated by evaluation of acid-base status and blood pressure. Patients with RTA have

Table 15.1 Medications associated with hypomagnesemia

Renal Mg losses
Diuretics (loop and thiazide type)
Aminoglycosides
Calcineurin inhibitors
Cisplatin/carboplatin
Foscarnet
Amphotericin B
GI Mg losses
Proton pump inhibitors

a non-anion gap metabolic acidosis. Patients with hyperaldosteronism have hypertension and either a normal acid-base status or metabolic alkalosis. There are also rarer conditions, both genetic and acquired, in which patients have a syndrome of primary renal potassium losses, metabolic alkalosis and salt wasting: Bartter and Gitelman syndromes are the most common (see Chap. 1). While the lab abnormalities may mimic hyperaldosteronism, these latter conditions are characterized by low or normal blood pressures and not hypertension.

Extra-renal losses of potassium can be seen with GI tract losses of K either from the upper tract or lower tract. Upper tract losses include nasogastric tube drainage or vomiting resulting in volume depletion and increase in aldosterone; aldosterone then increases urinary losses of K. Such a patient may also have a concomitant metabolic alkalosis. Lower tract causes such as diarrhea or surreptitious laxative use can also be considered, and may have an associated non-anion gap metabolic acidosis (NAGMA).

It is always important to assess **diet** when evaluating patients with hypokalemia. Normal intake of potassium ranges from 80 to 120 mEq per day in patients with nor-

mal renal function. Patients with malnutrition as a cause of hypokalemia are likely to have other abnormal parameters, including unexplained weight loss, a low serum blood urea nitrogen (BUN) and low serum phosphorus, as well as low prealbumin.

Transcellular shifts may occur for a variety of reasons. In the hospitalized setting, transcellular shifts can occur in those receiving excessive beta-2 agonism (e.g., albuterol use in status asthmaticus) or continuous insulin infusions used to treat diabetic ketoacidosis. The exchange of potassium between the extracellular space and skeletal muscle is mediated by specific membrane transporters (sodium-potassium ATPase = Na^+-K^+ pump). Another rare type of transcellular shift, hypokalemic periodic paralysis, causes muscle cramps after a high carbohydrate meal in certain populations due to a fall in blood K levels. Other causes of transcellular shifts result from increased cellular formation (e.g., red blood cell proliferation post vitamin B12 therapy or white blood cell proliferation post granulocyte colony stimulating factor treatment) or hypothermia related hypokalemia in critically ill patients.

Returning to case 1, this young woman with normal blood pressure had labs with persistent hypokalemia and serum bicarbonate of 28 mEq/L (normal 23–25). Her urine potassium was >40 mEq/L (consistent with renal loss). Her serum magnesium was 2.0 mEq/L (normal range 1.5–2.5 mEq/L). She was on no medications. Since the primary physician felt this was a renal loss of potassium, the patient was referred to nephrology clinic. Patient underwent a diuretic screen to exclude surreptitious use of diuretics, which was negative. She was suspected to have Gitelman syndrome, a condition in which there is a defect in the thiazide sensitive NaCl cotransporter. She was given potassium supplements and told to ensure adequate intake of dietary sodium chloride, and was referred for further genetic testing (done in specialized centers).

Case 2: Hypokalemia Associated with Hypertension

A 21 year old female with a blood pressure of 152/84 presents to your clinic. Her labs are as follows: sodium 141 meq/L (normal 135–145 mEq/L), potassium 3.2 mEq/L (normal 3.5–5 mEq/L), chloride 101 mEq/L (normal 95–107 mEq/L), bicarbonate 33 mEq/L (normal 23–25 mEq/L), BUN 13 mg/dL (normal 7–20), creatinine 0.7 mg/dL (normal 0.5–1.1). What are the next steps in evaluation?

While 90–95% of cases of hypertension (HTN) are termed essential or primary, secondary HTN may be suggested by **symptoms** (e.g., flushing and sweating suggestive of a pheochromocytoma), **physical exam findings** (e.g., renal bruit suggestive of renal artery stenosis) or **laboratory abnormalities** (e.g., unprovoked hypokalemia suggestive of hyperaldosteronism). Secondary HTN should also be considered in patients with resistant HTN, a severe or accelerated course of HTN, early or late onset HTN or specific anti-hypertensive intolerances. It is important to consider secondary causes because these imply an underlying, potentially correctable cause (Table 15.2).

Table 15.2 Evaluation of secondary causes of hypertension [2]

Etiology	Signs and symptoms	Screenings tests/ findings
Renal parenchymal disease	Edema, HTN	Elevated serum creatinine or decreased eGFR. Abnormal urine sediment (cells, casts) Abnormal urine dipstick (proteinuria, hematuria)

Table 15.2 (continued)

Etiology	Signs and symptoms	Screenings tests/ findings
Renovascular Hypertension (Renal Artery Stenosis)	Previously well controlled HTN, now uncontrolled or resistant; recent onset HTN in elderly with vascular disease or in very young (esp females with fibromuscular dysplasia); increased risk in smokers or those with extensive vascular disease; possible abdominal renal bruit	Continued rise in serum creatinine with initiation of RAS blocking agents. US may show disparity in kidney size. Renal dopplers may show elevated resistive indices and parvus tardus waveforms
Drug-Induced	Active NSAID use or catecholamine releasing drugs (cocaine, amphetamines)	Drug screening
Aldosterone Excess	Unprovoked hypokalemia	Abnormal aldosterone:renin ratio (ARR> 20); abnormal response to sodium loading
Pheochromocytoma	Flushing, palpitations, paroxysms of HTN (labile), diaphoresis	Abnormal urinary fractionated catecholamine excretion (metanephrines and normetanephrines); abnormal plasma free metanephrines

(continued)

Table 15.2 (continued)

Etiology	Signs and symptoms	Screenings tests/ findings
Cushing's Syndrome	Central obesity, striae, muscle weakness, moon facies, elevated blood glucose, fluid retention	Increased 24-hour urinary cortisol; positive low dose dexamethasone suppression test or midnight salivary cortisol
Thyroid under or overactivity	Tachycardia, weight loss, anxiety, elevated SBP for overactive thyroid vs bradycardia, weight gain, fatigue, elevated DBP for underactive thyroid	Abnormal TSH and sometimes abnormal free T4
Obstructive Sleep Apnea (OSA)	Snoring, interrupted sleep, daytime somnolence, stout neck, obesity	Abnormal polysomnography (sleep study), Sleep Apnea Clinical Score with nighttime pulse oximetry
Coarctation of the aorta	Brachial:femoral pulse differential/ delay, systolic bruits in back/chest, arm to leg SBP difference > 20 mmHg	Imaging of chest (rib notching); abnormal ECHO (children) or MRI (adults)

ACE-i angiotensin converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *ARR* aldosterone:renin ratio, *DBP* diastolic blood pressure, *ECHO* echocardiogram, *eGFR* estimated glomerular filtration rate, *Hypertension* hypertension, *MRI* magnetic resonance imaging, *NSAIDs* nonsteroidal anti-inflammatory drugs, *SBP* systolic blood pressure, *T4* thyroxine, *TSH* thyroid stimulating hormone, *US* ultrasound

Returning to case 2, HTN in an otherwise healthy young woman should prompt consideration of a secondary cause of HTN. Additional history is elicited and a thorough physical exam is performed. She is taking no medications that can elevate blood pressure (e.g., herbal supplements, sympathomimetics, oral contraceptives). Her body mass index (BMI) is 21 and she has no symptoms or body features to suggest OSA. Similarly, she has no symptoms or exam findings of cortisol or thyroid hormone excess. She has no arm to leg BP difference. The main differential diagnosis for a secondary cause of her HTN would rest between renovascular HTN and hyperaldosteronism. The latter is particularly suggested by HTN associated with unprovoked hypokalemia and metabolic alkalosis.

Case 3: Hyperaldosteronism Diagnosis and Evaluation

The patient in case 2 had a random urine K of 80 mEq/L, which indicates an inappropriately high K excretion in the face of hypokalemia. This supports the previous suspicion that her metabolic abnormalities and hypertension are due to some form of hyperaldosteronism, resulting in renal K wasting.

The next step in evaluation would be to obtain labs for plasma aldosterone concentration (PAC) and plasma renin activity (PRA). Her PAC returns at 35 ng/dL (reference range, upright: 4–31 ng/dL) and her PRA returns at 0.4 ng/mL/h (reference range, upright: 0.5–4.0 ng/mL/h). Her PCA: PRA ratio is 70. With a high PAC and a suppressed renin activity, primary hyperaldosteronism should be considered. (Table 15.3) Typical cut-offs to consider this entity are a PAC > 15 ng/dL and a PAC: PRA ratio of > 20. The latter ratio is also called an aldosterone-renin ratio (ARR) [3].

It is important to note that many medications can interfere with the ARR (Fig. 15.1) Medications that impair renin release, like NSAIDs and β-blockers, may elevate the

Table 15.3 Evaluation of aldosterone/renin axis

Disorder	Aldosterone	Renin	Examples
Primary hyperaldosteronism*	High	Low	**Aldosterone producing adenoma** **Bilateral idiopathic hyperaldosteronism** Familial hyperaldosteronism
Secondary hyperaldosteronism	High	High	**Renovascular HTN** (atherosclerotic RAS, fibromuscular dysplasia) Renin secreting tumor
Pseudohyperaldosteronism[a]	Normal	Normal	**Cushing's syndrome** (pituitary Cushing's, adrenal overproduction, ectopic ACTH secretion)
	Low	Low	**Exogenous mineralocorticoids** Liddle syndrome Glycyrrhizic acid (found in black English licorice) Apparent mineralocorticoid excess syndrome

Commonly encountered diagnoses are bolded
RAS renal artery stenosis, *ACTH* adrenocorticotropic hormone
*PAC/PRA must be greater than 20 and PAC must be higher than 15 ng/dL to diagnose primary hyperaldosteronism (*PAC* plasma aldosterone concentration, *PRA* plasma renin activity)
[a]Pseudohyperaldoseronism can be characterized by normal aldosterone/normal renin or low aldosterone/low renin conditions

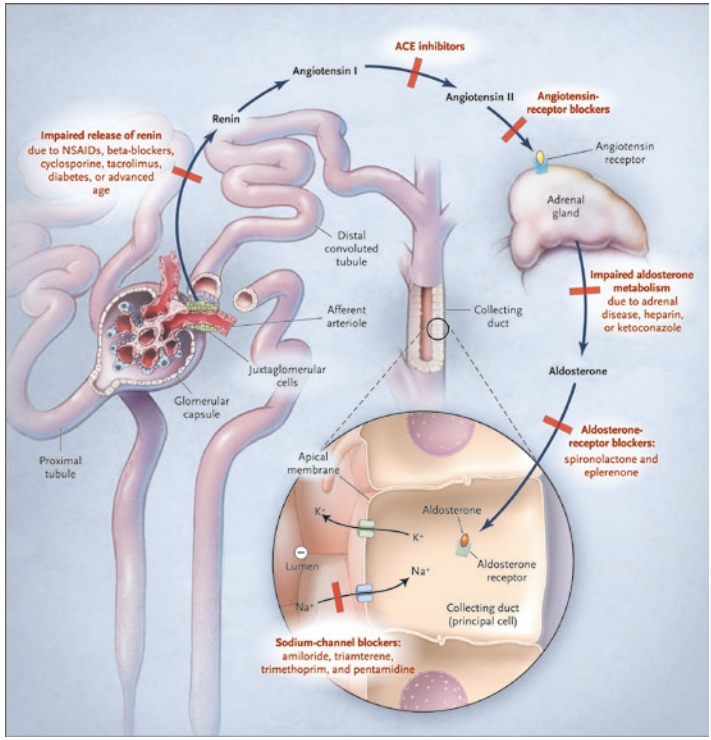


Figure 15.1 Medications acting on Renin-Angiotensin-Aldosterone System. This figure illustrates the normal Renin-Angiotensin-Aldosterone System (RAAS). The red rectangles show locations where drugs/medications/diseases/conditions can disrupt the pathway. The first step in the RAAS is the release of renin from the juxtaglomerular cells in the afferent arteriole in response to low blood volume (e.g., true volume depletion) or low effective arterial blood volume (e.g., congestive heart failure). Renin then acts as a proteolytic enzyme to convert angiotensinogen to angiotensin I. Under the influence of ACE, angiotensin I is converted to angiotensin II. Angiotensin II has a myriad of effects, including enhancing aldosterone release form the adrenal gland. The round circle highlights the site of action of aldosterone in the principal cell of the collecting duct, where it acts to reabsorb sodium and secrete potassium. In addition to low blood volume/low effective arterial blood volume, aldosterone release can also be stimulated by high plasma potassium levels. (From Ref. [4], Copyright @ 2004 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society)

ARR. Diabetes or advanced age have a similar mechanism. Medications that may lower the ARR include ACE-inhibitors (by blocking the conversion of angiotensin I to angiotensin II) and ARBs (by blocking the action of angiotensin II at its receptor). In addition, other drugs can lower the ARR by impairing aldosterone metabolism (eg, heparin) or by blocking the aldosterone receptor (eg, spironolactone). Interpretation of the ARR must take this into account.

In patients in whom there is a high clinical concern for hyperaldosteronism but lab criteria are not met (i.e., PAC is not >15 and PAC:PRA is not >20), a salt loading test (saline suppression test) can be done. Typically this involves infusion of 2L of normal saline (NS) intravenously over 4 hours. The PAC and PRA are then repeated; an adequate test to interpret results would require a urine Na > 200 mEq. If the patient has hyperaldosteronism, administration of NS would not suppress the PAC and PRA. (See box for specifics of this testing).

Saline Suppression Test (Salt Loading to confirm suspicion of hyperaldosteronism)

This can be achieved by either infusion of normal saline (NS), generally 2L over 4 hours, or with oral salt loading. Patients are instructed to add 1 flat teaspoon of salt to their daily food intake and to consume salty foods like potato chips, pretzels and pickles for 72 hours. Urine is collected after 3 days to ensure urine sodium > 200 mEq/24 h to ensure test validity and then a PRA and PAC are obtained. Many centers prefer the saline infusion as it is practically easier to administer and can ensure the validity without a 24 hour urine collection; however, this test is more expensive. A test is thought to be positive if the aldosterone remains unsuppressed (i.e., remains elevated) and the renin continues to be suppressed (i.e., remains low) [3].

Returning to case 3, as this patient had biochemical evidence for primary hyperaldosteronism, cross-sectional imaging with a CT scan or MRI is indicated to help elucidate whether an adrenal adenoma is present. Adrenal vein sampling can also be considered in the right clinical context but is typically recommended by and performed by specialists.

Case 4: Renal Tubular Acidosis

A 60 year old male with type 2 diabetes mellitus on lisinopril 20 mg daily with CKD stage 3 (with baseline creatinine 1.7 mg/dL) presents to his physician with labs significant for sodium 136 mEq/L (normal 135–145 meEq/L), potassium 5.2 mEq/L (normal 3.5–5 mEq/L), chloride 108 mEq/L (normal 97–107 mEq/L), bicarbonate 18 mEq/L (normal 22–26 mEq/L) and normal albumin. What further evaluation would you pursue to understand the etiology of his metabolic acidosis?

Abnormal serum laboratory values can often lead to questions of what testing may be needed next. If labs differ dramatically from prior values, early recheck of the lab is most helpful to ensure that the lab value is consistently abnormal and not due to a processing error. *For case 4, we first would investigate whether the acidosis is a high anion gap metabolic acidosis (HAGMA) or a normal anion gap metabolic acidosis (NAGMA).*

The anion gap is determined by the following equation:

$$\text{Serum Anion Gap} = \left[\text{Na}^+\right] - \left[\text{Cl}^-\right] - \left[\text{HCO}_{3^-}\right]$$

which in this patient is calculated to be 10 (using case values, 136 − 108 − 18 = 10). The normal anion gap (AG) is 10–12 and thus this person has a NAGMA.

NAGMA causes can be recalled using the ACCRUED mnemonic. A NAGMA mainly occurs through (1) loss of bicarbonate in the GI tract (2) impairment of acid excretion

or excessive loss of bicarbonate in the kidneys, or (3) either acid gain or dilutional acidosis due to rapid administration of high volumes of sodium chloride (Table 15.4). A Medication Administration Record (MAR) typically assists with the latter, however if the history does not provide obvious delineation between the first two, then a urine anion gap can be helpful.

$$\text{Urine Anion Gap} = \left[Na^+ \right] + \left[K^+ \right] - \left[Cl^- \right]$$

The urine anion gap is essentially an "ammonium detector" for the urine [7]. Ammonium cannot be directly measured in the urine by clinical labs, but its presence can be inferred by checking a urine anion gap. On a typical Western diet, we generate about 100 mEq of nonvolatile acid each day (acids other than carbon dioxide) that we must excrete to stay in acid-base balance. Ammonia (NH_3) is produced and secreted

Table 15.4 Causes of non-anion gap metabolic acidosis using the ACCRUED mnemonic (number after etiology refers to pathophysiologic cause of NAGMA described in text)

Mnemonic	Etiology	Examples
A	Acid infusion (3)	Hyperalimentation
C	Chronic kidney disease (2)	Diabetic nephropathy
C	Carbonic anhydrase inhibitor (2)	Acetazolamide
R	Renal tubular acidosis (2)	Type IV RTA
U	Ureteral diversion (1)	Ileal conduit
E	Expansion/Extra chloride (3)	High/rapid volume sodium chloride infusion
D	Diarrhea (1)	Viral gastroenteritis

by the proximal tubule and serves as one of the principal urinary buffers. Ammonia (uncharged) traps the hydronium ion (H^+) excreted by the kidney in the urine as charged ammonium (NH_4^+). Urine NH_4^+ and urine chloride (Cl^-) bond to form a soluble salt ($NH_4^+Cl^-$) that is excreted in the urine.

In cases of a NAGMA resulting from loss of bicarbonate from the GI tract, the urine anion gap will be negative. In these instances, the kidneys will function normally and try to compensate for the NAGMA by excreting more acid. This attempt at NAGMA compensation will result in more $NH_4^+Cl^-$ in the urine resulting in a higher chloride measurement. Looking at the urine anion gap equation, the higher than normal urine chloride measurement leads to a negative urine anion gap. Simply stated, the kidney is working, and the problem is the GI tract when the urine anion gap is "neGUTive."

In cases of a NAGMA resulting from either renal impairment of acid excretion or excessive loss of bicarbonate, the urine anion gap will be positive (generally > 20). In these instances, the kidneys are not functioning appropriately and are likely the culprit of the metabolic acidosis. This is likely the result of a renal tubular acidosis (RTA).

There are some caveats to the urine anion gap that should be noted. To avoid confusion, use of the urine anion gap calculation should only be used in the setting of a NAGMA. Normal patients without a NAGMA have a positive urine anion gap due to normal physiologic excretion of $NH_4^+Cl^-$ and should not mistakenly be considered to have an RTA. The interpretation of the urine anion gap may also be difficult in states of volume depletion, in proximal RTA (type II RTA) or in the presence of excess negative charges (e.g., beta-hydroxybutyrate).

Returning to case 4, the following urine tests were obtained: Urine sodium 110 mEq/L, urine potassium, 13 mEq/L, urine chloride: 95 mEq/L. Urine anion gap was calculated to be 28 (using case values 110 + 13 – 95 = 28), which in the face of a NAGMA is consistent with an RTA.

RTA occurs as a result of the failure of the kidney to reabsorb all the filtered bicarbonate, failure to synthesize new bicarbonate to keep up with daily metabolic demands (protein metabolism from our dietary daily acid load consumes bicarbonate and must be replaced) or failure to excrete acid. Table 15.5 lists the 3 general types of RTA, types I, II and IV. Two features to differentiate the RTAs are the serum potassium and urine pH. If serum potassium is elevated, the patient most likely has a type IV RTA. If normal or low, the patient may have a type I or II RTA. If the urine pH >5.5, the RTA is a distal or type 1 RTA. The urine pH in proximal or type 2 RTA can be variable depending on the severity of the acidosis. In mild cases, urine pH will be relatively alkaline (urine pH >5.5), but in severe cases will be acidic (urine pH <5.5).

Type I or distal RTA arises from the inability to secrete H^+ ions into the urine in the distal nephron for two possible reasons. First, H^+ ion channel disruption can occur in autoimmune conditions (e.g., Sjogren's syndrome or SLE) or genetic conditions (e.g., Liddle syndrome). Alternatively, membrane permeability may be altered due to medications like amphotericin B, topiramate, or lithium [5, 6]. Patients with type I RTA may have a propensity to form calcium phosphate stones or develop nephrocalcinosis. Type 1 or distal RTAs often require nephrology consultation.

Type II or proximal RTA is the result of inability to reabsorb bicarbonate in the proximal tubule, resulting in wasting of bicarbonate. The differential of type II RTA includes Fanconi syndrome, which is a generalized proximal tubular dysfunction resulting in urine loss of glucose, bicarbonate and phosphates, amino acids, uric acid and potassium. This may be caused by both genetic mutations and medications such as tenofovir or ifosfamide [7], but also may be associated with clinical entities like amyloidosis and multiple myeloma [5]. A nephrology consult may be necessary in these patients for further testing to delineate these conditions. Lastly, practitioners should be aware of patients presenting with osteomalacia who might need consideration for an underlying type

Table 15.5 Renal tubular acidosis (RTA) types, lab abnormalities, causes and clinical features

RTA type	Location of disorder	Dysfunction	Serum K/ HCO3 (mEq/L)	Urine pH	Differential diagnoses	Other clinical features
I	Distal tubule	Low H^+ secretion	Low/<12	>5.5	Autoimmune (Sjogren's syndrome, SLE), Drugs (amphotericin B, lithium, topiramate)	Calcium phosphate stones, nephrocalcinosis, hypocitraturia
II	Proximal tubule	Low HCO_3 resorption	Low/14–18	>5.5, but may be <5.5 in severe cases	Fanconi Syndrome, Mutiple myeloma, Amyloidosis, Drugs (carbonic anhydrase inhibitors, tenofovir, topiramate, ifosfamide), Familial/Hereditary, Heavy metal poisoning	Osteomalacia, rickets
IV	Collecting duct	Low aldosterone activity or level	High/~18	Usually <5.5	Diabetes, Urinary obstruction, Drugs (ACE-i, NSAIDs, cyclosporine)	Hyperkalemia

Abbreviations: *HCO3* bicarbonate, *ACE-i* angiotensin converting enzyme inhibitor, *NSAIDs* nonsteroidal anti-inflammatory drugs, *SLE* systemic lupus erythematosus
Normal serum HCO_3 = 23–25 mEq/L; Normal serum K = 3.5–5 mEq/L

II RTA. Treatment of RTA due to a medication effect may involve discontinuation of the contributing medication, but this often requires multi-disciplinary conversation to assess risk-benefit to the patient.

Type IV RTA is the most common RTA providers will encounter. Aldosterone may be less effective or deficient resulting in poor excretion of potassium and retention of hydronium ion in the collecting duct, resulting in a NAGMA with hyperkalemia [8]. The common causes of type IV RTA are urinary obstruction, chronic kidney disease, medications like ACE-i, and diabetes mellitus (even with mild nephropathy).

Returning to case 4, the presence of hyperkalemia and an RTA in the context of diabetes should prompt the clinician to suspect type IV RTA. The clinical history of chronic kidney disease and exposure to ACE-i would be consistent with this as well.

Treatment of Type 4 RTA

A decision to treat the metabolic derangements in type IV RTA depends on the severity of the metabolic acidosis and the degree of the hyperkalemia. To better address the hyperkalemia, it is important to understand the regulation of potassium excretion in the kidney and the role of the Renin-Angiotensin-Aldosterone System (RAAS) (Fig. 15.1). While potassium is freely filtered at the glomerulus, about 90% undergoes reabsorption before reaching the distal nephron. The handling of potassium in the kidney is very unique in that potassium can be secreted into the distal nephron, depending on physiological needs. Two important regulators of this process are aldosterone and the amount of sodium delivered to the distal area of the nephron. In the principal cell of the collecting duct, under the stimulation of aldosterone, sodium is reabsorbed through a sodium channel on the urine, or lumen, side of the membrane. This creates more electronegativity

in the lumen (due to sodium travelling as a positive charge into the cell) and creates a favorable gradient for potassium to be secreted from inside the cell into the urine through a potassium channel. How much potassium excreted is also dependent on distal sodium delivery to that area of the nephron. Thus in situations of low sodium delivery, as in volume depletion, potentially less potassium will be secreted.

There are many drugs that can interfere with potassium excretion by disrupting any of the pathways along the RAAS (see red rectangular markings in Fig. 15.1). Examples include: NSAIDs can impair renin release; ACE-i and ARB can impair production of angiotensin II or the effect of angiotensin II at its receptor (respectively); heparin can impair aldosterone biosynthesis/metabolism in the adrenal gland; spironolactone can block the aldosterone receptor in the principal cell; trimethoprim can block the sodium channel on the lumen side of the principal cell. Patients who may be particularly prone to developing hyperkalemia associated with these drugs include those with underlying chronic kidney disease, diabetes mellitus, advanced age or states of true or effective circulating volume depletion. Further risk is imposed by diets high in potassium or use of salt substitutes that contain potassium. Thus a careful assessment of diet, volume status and medications that may impair urinary K secretion is necessary in evaluating hyperkalemia.

In a patient with diabetes mellitus and type IV RTA with proteinuria, it can get even more complicated. The goal is to reduce proteinuria to slow progression of renal disease and perhaps reduce cardiovascular risk. ACE-i or ARBs are common anti-proteinuric therapies, however their use may be limited by hyperkalemia or their implementation impaired by pre-existing hyperkalemia (see Chap. 5). As illustrated in Fig 15.1, it is important to discontinue all unnecessary agents like NSAIDs or trimethoprim that can cause hyperkalemia. Initiation of anti-proteinuric therapies may first require additional strategies to lower serum K level, focusing on potassium balance: decreasing intake of potassium, facilitating transcellular shifts of potassium or enhancing urinary potassium excretion.

Physiologic Focus	Strategy to facilitate lowering K
Diet	The patient can meet with a nutritionist to learn how to create a low potassium, low carbohydrate diet
Transcellular K shift	Excellent *control of diabe*tes Supplemental bicarbonate may help facilitate shift of K intracellularly and may help correct acidosis (chronic acidosis may be associated with progression of kidney disease, muscle wasting and osteoporosis)
Facilitate renal K excretion	Use of a thiazide or loop diuretic may be helpful to facilitate K excretion if the patient is hypertensive or fluid overloaded

With any of the above changes, it is important to recheck potassium within 2 weeks. Persistent elevations in K despite these changes may require expert consultation with a nephrologist.

Returning to case 4, he was started on furosemide, as he was also mildly hypervolemic. The furosemide helped to decrease his serum K to 4.9 mEq/L and he was able to continue his lisinopril. On discharge he was also started on sodium bicarbonate tablets with a nephrology referral to follow up on his type IV RTA, hyperkalemia, and chronic kidney disease.

Case 5: Evaluation of Polyuria

A 40 year old woman has been in the ICU for the past week following a trauma. Her urine output for the last several days has been 6 liters per day. Her serum sodium is 150 mEq/L (normal 135–145 mEq/L). What is the next step in diagnosis/management?

The case highlights the challenge of determining the cause of significant polyuria. Most define polyuria as >3 L of urine per day. Polyuria that is not addressed can lead to multiple medical problems. These include severe electrolyte derange-

ments and hypovolemia, and if the patient is unable to keep up with the water losses, severe dehydration can occur.

One must first determine whether polyuria is a water or solute diuresis, which can be evaluated with urine osmolality obtained on random urine specimen (Fig. 15.2). If the urine osmolality is <100 mOsm/L, then the polyuria is due to a water diuresis. If the urine osmolality is greater than 300 mOsm/L, then the polyuria is due to a solute diuresis.

History is crucial in determining the cause of the water diuresis. If the patient endorses compulsive water drinking, this may be consistent with primary polydipsia. In these individuals the polyuria is the normal response to habitually high water intakes. A water diuresis may also be due to diabetes inspidius (DI), which may be central or nephrogenic. [9]. Central DI is considered following intracranial insult (e.g. hemorrhage, trauma, or procedures) or primary pituitary deficiency (especially granulomatous disease such as sarcoidosis or tuberculosis). Nephrogenic DI can be considered in the context of chronic diuretic use, lithium therapy, or concomitant hypercalcemia. The polyuria in diabetes insipidus is inappropriate, thus the patient urinates alot and as a consequence then drinks alot.

In contrast to water diuresis, typified by a low urine osmolality, a urine osmolality >300 mOsm/kg suggests the diuresis is a solute diuresis. The solutes may be electrolytes (e.g. sodium) or nonionic compounds (e.g., glucose, urea, mannitol). The differential includes:

1. **high solute load**
   - large volume saline infusions
   - mannitol
2. **urea, particularly BUN >100**
   - renal failure
   - parenteral nutrition with protein content >100 g per day
3. **glucose (diabetes or glucose infusions)**
   - excessive serum glucose
   - use of sodium glucose co-transporter 2 inhibitors (SGLT2 inhibitors), the "-flozin" medications

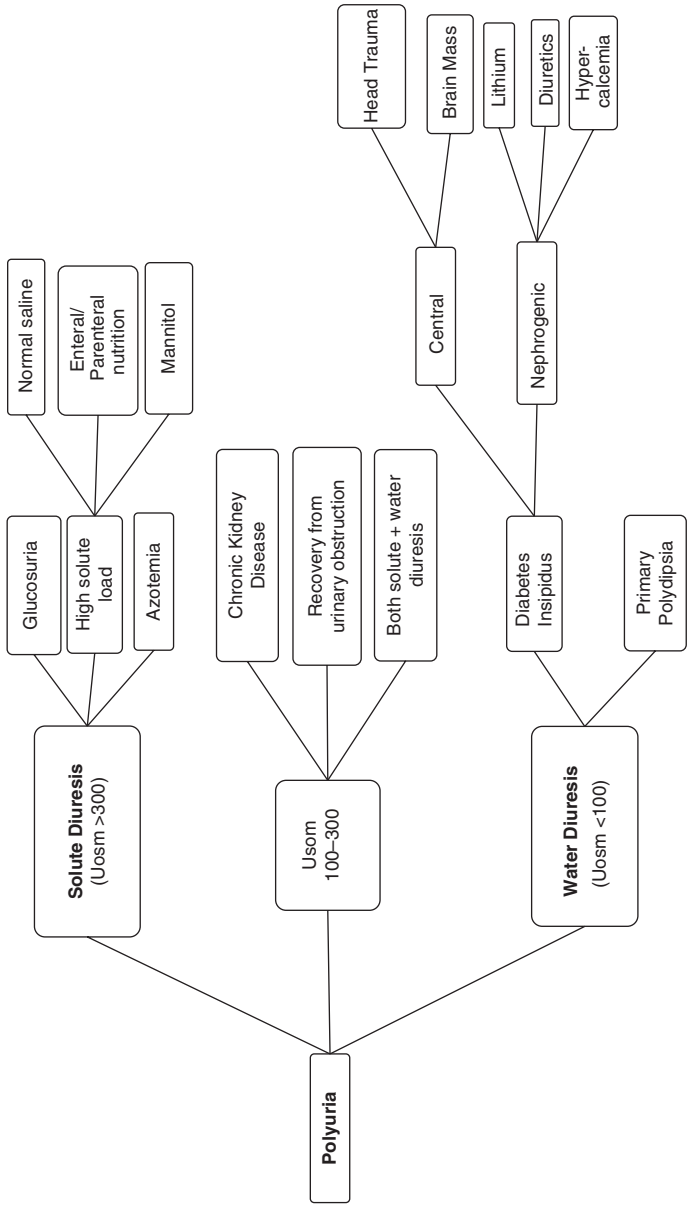


FIGURE 15.2 Polyuria: Solute versus water diuresis based on urine osmolality and appropriate differential diagnosis

Review of the MAR may help identify excess solutes or medications causing glucosuria. Routine labs (like blood glucose or blood urea nitrogen) are helpful at elucidating hyperglycemia and uremia, respectively. The most common causes of solute diuresis clinically are large volume saline infusions and hyperglycemia.

If the cause of the solute diuresis is still unclear or there are multiple causes, it is possible to determine the exact solute causing the solute diuresis with a 24-hour urine collection of electrolytes (sodium, potassium) and nonionic compounds (glucose, urea nitrogen).

$$\text{Urine Osmolality} = 2\left[U_{Na} + U_{K}\right] + \left(\text{UUN} / 2.8\right) + \left(\text{Urine glucose} / 18\right)$$

UUN = urine urea nitrogen; U_K *= urine K;* U_{Na} *= urine Na*

A difference between calculated and measured osmolality suggests the presence of a nonionic agent like mannitol [9].

Polyuria with urine osmolality between 100–300 mOsm/kg is most commonly seen in patients with CKD isosthenuria, which is the inability to concentrate urine (see Chap. 7). It may also occur in situations of simultaneous excess water and solute intake, a partial DI or in patients recovering from urinary obstruction.

Returning to case 5, the patient's urine osmolality was elevated to >600 mOsm/kg. Review of recent medications revealed no new medications, however review of her intake/output (I/O) documentation showed that she had 5 L of normal saline per day over the past few days and she was euvolemic. As this appeared to be an appropriate solute diuresis, the team discontinued her saline and her urine output decreased to 2 L per day and her serum sodium normalized.

Case 6: Polyuria due to Water Diuresis

A 60 year old man is admitted after a head trauma to neurosurgical service and has been quite thirsty. He has been urinating 6L/day with stable serum sodium of 144 mEq/L (normal 135–145 mEq/L). His urine osmolality is measured and is <100 mOsm/kg. He is unsure of his medications. What is the next step in diagnosis and treatment?

Case 6 highlights a water diuresis. If urine osmolality is not available, a low urine specific gravity is a useful surrogate (see Chap. 7). The first line test, typical for any medical patient, is a clear history and physical exam; in this patient, given his intra-cranial trauma, this likely represents central DI but we cannot exclude nephrogenic DI. If the clinical context is unclear, one can consider a **water deprivation test** (pattern of results seen in Fig. 15.3a), which assesses the patient's ability to concentrate the urine when fluids are withheld [6]. Under normal circumstances, in response to dehydration, antidiuretic hormone (ADH) is secreted, resulting in conservation of water by the kidney. The result is the production of a small amount of concentrated urine, with a urine osmolality of >800 mOsm/kg. Similarly, patients with mild primary polydipsia will be able to concentrate their urine when deprived of fluids. An inability to maximally concentrate the urine with dehydration alone will be observed in patients who lack ADH (central DI), lack ADH responsiveness (nephrogenic DI) or have severe primary polydipsia. These last groups of patients can be administered a desmopressin challenge to further characterize and distinguish the etiology of their polyuria (Fig. 15.3b).

The basic principle of the water deprivation test involves baseline data including patient body weight, serum sodium concentration, plasma and urine osmolalities and ADH level. Then careful measurements of body weight, urine volume, and urine and plasma osmolalities every 1-2 hours are performed in the clinic setting under a state of water deprivation. It is crucial to monitor patients very closely

during the testing period as they can become profoundly volume depleted.

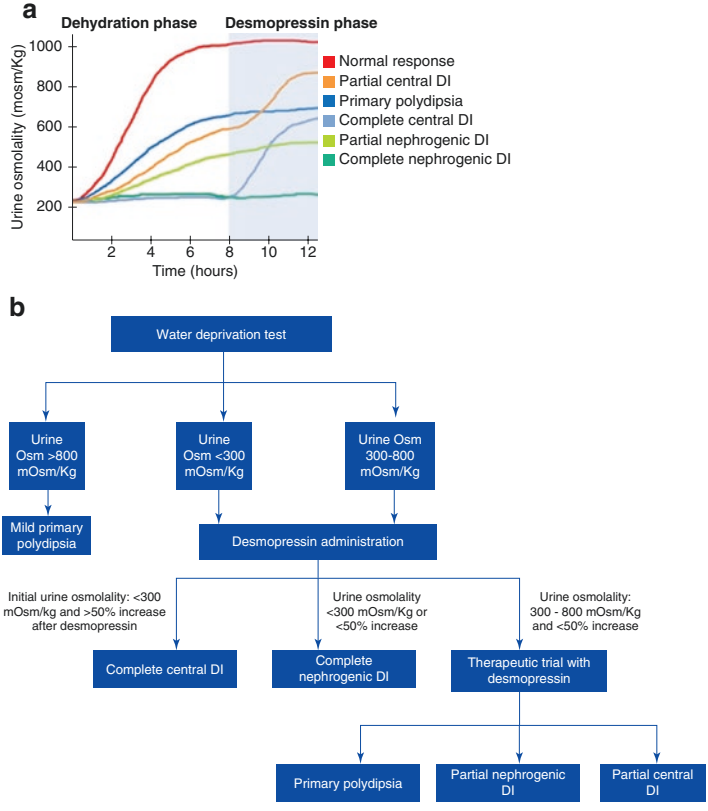
The test is continued until one of several endpoints is reached:

1. the patient has lost 3% of body weight.
2. the patient can achieve a urine osmolality of >600 mOsm/kg with water deprivation alone, indicating that both ADH release and effect are intact.
3. the plasma osmolality exceeds 295–300 mOsm/kg or the sodium concentration is at or exceeds 145 mEq/L with water deprivation alone, indicating that both ADH release and effect are intact.

If the plasma osmolality reaches >300 mOsm/kg and the urine osmolality remains <600 mOsm/kg, or if the urine osmolality on 2–3 successive hourly measurements is stable despite a rise in plasma osmolality, then desmopressin (DDAVP) is administered. A patient with central DI will have a consistently low urine osmolality (<300 mOsm/kg) with water deprivation, but will increase to >600 mOsm/kg after DDAVP administration, since they are responsive to ADH but simply lack the hormone (orange and light blue lines, Fig. 15.3a). It is classified as partial or central based on how much concentration occurs in the dehydration phase. Central DI is classically seen in association with a hypothalamic/pituitary insult (after pituitary surgery or trauma for example). A patient with nephrogenic DI will exhibit low urine osmolality with water deprivation (<300 mOsm/kg) with only partial response to ADH since ADH is secreted normally, but the kidney is less responsive to ADH in this condition (light and dark green lines, Fig. 15.3a). Nephrogenic DI is again classified as partial or complete based on the ability to concentrate urine in the dehydration phase of the test. A classic cause of nephrogenic DI is chronic lithium therapy. A patient with primary polydipsia (dark blue line, Fig. 15.3a) should be able to concentrate their urine to >600 mOsm/kg with the water deprivation part of the test alone [6]. Primary

polydipsia classically is associated with certain mental health conditions, like schizophrenia.

Returning to case 6, he was found to have a urine osmolality of 80 mOsm/kg. When deprived of water, his urine osmolality increased to 90 mOsm/kg. When serum sodium was 146 mEq/L (>145 mEq/L) and plasma osmolality was 305 mOsm/kg (>295 mOsm/kg) DDAVP was administered. After DDAVP was given, his urine osmolality increased to 650 mOsm/kg and the urine output decreased. This is consistent with complete central DI as the cause; the etiology was felt to be secondary to his



brain trauma. For treatment, access to free water was restored and desmopressin 100 mcg twice daily was administered. With this treatment his serum sodium concentration improved to 138 mEq/L and his urine output decreased to 2–3 L per day. In the setting of intracranial trauma, the central DI may be transient, so close monitoring of patient in the outpatient setting is required to prevent hyponatremia.

Fractional Excretion of Sodium and Urea "Do's and Don'ts"

Under normal circumstances, of the approximate 25,000 mEq of sodium the kidney filters daily, less than 1% is excreted in the urine. The kidney has a remarkable ability to reabsorb almost all the filtered sodium daily through the actions of sodium transport in the kidney tubules (see Chap. 1). When

FIGURE 15.3 (**a**) Graphical representations of the water deprivation test for diabetes insipidus [6]. (**b**) Algorithm for Diagnosis of the Main Types of Polyuria Using Results from Water Deprivation Testing and Desmopressin Administration. [Modified with permission from from 6]. The normal response to dehydration is a rise in the urine osmolality to > 800 mOsm/kg (red line). In patients with primary polydipsia, with water deprivation the urine will concentrate to ranges between 300 and 800 mOsm/kg depending on the severity of the problem (in milder forms will be able to concentrate the urine more); there is only a small further increment in urine osmolality (dark blue line) after desmopressin administration. In patients with complete DI (central or nephrogenic), during the dehydration phase the urine osmolality stays < 300 mOsm/kg with a concomitant rise in plasma osm to > 300; patients with complete central DI will have >50% increase in urine osm after desmopressin administration (light blue line), while patients with complete nephrogenic DI will have a <50% increase due to insensitivity to the hormone (dark green line). In patients with partial central (orange line) or nephrogenic DI (light green line), the urine osmoality after water deprivation increases to usually 300–600 mOsm/kg, with <50% increase in urine osmolality after desmopressin administration.

the kidney tubules are damaged or injured, more sodium will appear in the urine. The test that calculates how much of the filtered sodium appears in the urine is called the Fractional Excretion of Sodium (FeNa). The FeNa is often used clinically to differentiate pre-renal acute kidney injury (AKI) from acute tubular necrosis (ATN).

The FeNa is calculated by the following equation:

$$\text{FeNa}: \left(U_{Na} \times P_{cr}\right) / \left(P_{Na} \times U_{cr}\right) \times 100$$

P = plasma, U = urine, Na = sodium, cr = creatinine, Fe = fractional excretion

The values are obtained from a simultaneous lab draw for plasma sodium and creatinine and a random urine sample for urine sodium and creatinine. The general principle is that a FeNa <1% indicates prerenal causes and a FeNa >2% is suggestive of ATN. A value in between may be suggestive of a transition from pre-renal to ATN [10].

It is important to know the limitations of this equation:

1. **Do not use in nonoliguric patients.** It can only be used in patients who are oliguric (i.e., urine output <400–500 ml daily). The sensitivity and specificity change markedly if, for example, the patient is making 2 L urine daily and should therefore not be used in nonoliguric patients.
2. **Do not use in patients with AKI superimposed on CKD.** The values in patients with underlying CKD can be misleading. The remaining nephrons need to manage the daily solute load with less functioning nephrons and thus the values may be higher and may not be interpretable in CKD.
3. **Do not use in proximity to diuretics.** If a diuretic is given just prior to sampling, error may occur as loop diuretics block sodium reabsorption and more sodium will appear in the urine, i.e., the FeNa may be high. The sensitivity and specificity change markedly when using this as a tool in patients with AKI who have received diuretics [11].

Some conditions are known to be associated with a low FeNa that are not pre-renal in nature. These include early contrast nephrotoxicity (due ot vasoconstriction) and acute glomerulonephritis (due to sodium avidity). In these conditions the FeNa is poorly reflective of the actual cause of the AKI. Similarly, the FeNa should not be checked after large amounts of normal saline are administered. For any clinical condition, however, a thorough history and physical exam and putting the AKI in the clinical context is the most helpful. Tools such as the FeNa are used to help support the clinical suspicion but should never replace it and should be interpreted in that light.

An alternative equation is the fractional excretion of urea (FeUrea), performed the same way but just with urea checked in substitution for the sodium. The values for the equation are <35 for identifying pre-renal and >50 for ATN.

$$\text{FeUrea}: \left(U_{\text{Urea}} \times P_{\text{cr}}\right) / \left(P_{\text{cr}} \times U_{\text{Urea}}\right) \times 100$$

P = plasma, Fe = fractional excretion, cr = creatinine

Summary

Overall, urine electrolytes are powerful diagnostic tests when used in the correct setting to help taper differentials. They can help further characterize incidental lab findings, such as a urine potassium in a patient with hypokalemia, but more importantly they can help guide treatment, as is the case for obtaining urine osmolality in the evaluation of acute polyuria. While these tests are not always at the front of our minds, they are overall fairly inexpensive ways to limit the financial and emotional burden of further testing and in some cases help our patients' quality of life.

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