

## ACID-BASE AND ELECTROLYTE TEACHING CASE

### A Physiologic-Based Approach to the Evaluation of a Patient With Hypokalemia

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Hypokalemia is a common electrolyte disorder. Transient causes of hypokalemia are due to cell shift, whereas sustained hypokalemia is caused by either inadequate intake or excessive potassium loss. Evaluation of the intake, distribution, and excretion of potassium should include the following: (1) a careful history, including use of drugs, medications, and the presence of vomiting or diarrhea; (2) physical examination, including orthostatic changes in blood pressure and heart rate; and (3) measurement of urine and plasma electrolytes. Urinary potassium wasting is caused by pathophysiologic conditions that couple increased distal sodium delivery with increased plasma aldosterone levels or aldosterone-like effects. If urinary potassium loss is identified, the next step is to determine whether the loss is caused by a primary increase in distal delivery of sodium or a primary increase in mineralocorticoid level. A primary increase in distal delivery should be associated with volume depletion, whereas a primary increase in mineralocorticoid level generally is associated with volume expansion and hypertension. In patients with a primary increase in mineralocorticoid activity, it is useful to measure plasma renin activity and plasma aldosterone levels. Complications of hypokalemia include muscle weakness, rhabdomyolysis, cardiac arrhythmias, impaired urinary concentrating ability, and glucose intolerance. *Am J Kidney Dis* 56:1184-1190. © 2010 by the National Kidney Foundation, Inc.

**INDEX WORDS:** Hypokalemia; aldosterone; distal sodium delivery; mineralocorticoid; urine electrolytes.

Note from Feature Editor Jeffrey A. Kraut, MD: This article is part of a series of invited case discussions highlighting either the diagnosis or treatment of acid-base and electrolyte disorders.

#### INTRODUCTION

Hypokalemia frequently is encountered in clinical practice. Transient causes of hypokalemia are due to cell shift, whereas sustained hypokalemia is caused by either inadequate intake or excessive potassium loss. Hypokalemia resulting from excessive potassium loss can be caused by renal or extrarenal losses. Clinical

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history, physical examination with particular emphasis on determination of volume status, and assessment of acid-base status will allow the cause of hypokalemia to be readily determined in most cases.

#### CASE REPORT

##### Clinical History and Initial Laboratory Data

A 38-year-old woman is referred for refractory hypokalemia. Three months ago, she presented to her primary care physician reporting weakness, and a routine metabolic profile laboratory test showed the following values: sodium, 138 mEq/L (138 mmol/L); potassium, 2.5 mEq/L (2.5 mmol/L); chloride, 90 mEq/L (90 mmol/L); bicarbonate, 32 mEq/L (32 mmol/L); serum creatinine, 0.9 mg/dL (79.56  $\mu$ mol/L); serum urea nitrogen, 20 mg/dL (7.14 mmol/L); and estimated glomerular filtration rate of 81 mL/min/1.73 m<sup>2</sup> (1.35 mL/s/1.73 m<sup>2</sup>), calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. During the next 12 weeks, she was treated with oral potassium, 20 mEq/d; losartan, 50 mg/d; and spironolactone, 25 mg/d. Despite this therapy, serum potassium levels remained in the range of 2.5-3.0 mEq/L (2.5-3.0 mmol/L). On evaluation, blood pressure was 110/72 mm Hg and heart rate was 88 beats/min. The rest of the physical examination findings were unremarkable, with no skin discoloration or edema. Laboratory test results were unchanged from previous measurements.

##### Additional Investigations

Plasma renin activity was 6.5 ng/mL/h (1.8 ng/L/s; reference range, 0.5-4 ng/mL/h [0.1-1.1 ng/L/s]), plasma aldoste-

rone concentration was 35 ng/dL (0.97 nmol/L; reference range, 4-31 ng/dL [0.11-0.86 nmol/L]), and plasma magnesium level was 1.8 mEq/L (0.9 mmol/L; reference range, 1.3-2.1 mEq/L [0.65-1.05 mmol/L]). Urine electrolytes showed the following values: sodium, 83 mEq/L (83 mmol/L); potassium, 40 mEq/L (40 mmol/L); and chloride, <10 mEq/L (<10 mmol/L).

### Diagnosis

Surreptitious vomiting.

### Clinical Follow-up

The laboratory test results were discussed with the patient. She admitted to behavior consistent with surreptitious vomiting and was referred for counseling.

## DISCUSSION

Assessment of urinary potassium excretion allows one to determine whether hypokalemia is due to renal or extrarenal causes. Renal potassium handling can be assessed using a 24-hour urine collection or spot urine sample determining potassium-creatinine ratio. Twenty-four-hour urinary potassium excretion <20 mEq or a spot urine potassium-creatinine ratio <1 suggests an extrarenal cause of hypokalemia. The transtubular potassium gradient (TTKG) has been proposed as a useful tool to assess renal potassium handling because the equation takes into consideration the effect of renal water handling on urine potassium concentration:

$$\text{TTKG} = [\text{K}_{\text{urine}}^+ / (\text{Osm}_{\text{urine}} / \text{Osm}_{\text{serum}})] / \text{K}_{\text{serum}}^+$$

where  $\text{K}_{\text{urine}}^+$  is urine potassium concentration,  $\text{Osm}_{\text{urine}}$  is urine osmolality,  $\text{Osm}_{\text{serum}}$  is serum osmolality, and  $\text{K}_{\text{serum}}^+$  is serum potassium concentration. In an otherwise healthy individual ingesting a typical Western diet, TTKG ranges from 8-9 and will increase to >11 with increased potassium intake. In patients with hypokalemia caused by extrarenal potassium losses, TTKG should decrease to <3. Although the TTKG is of interest, in most settings, a spot urine potassium concentration and the clinical setting will be sufficient to determine the cause of potassium disturbances. Calculation of the TTKG may prove useful in patients in whom the cause of a dyskalemia remains in doubt.

Extreme dietary restriction of potassium alone potentially can lead to hypokalemia over time. Although the kidney can elaborate urine virtually free of sodium in response to dietary sodium

restriction, it can decrease urinary potassium excretion to only approximately 15 mEq/d in response to a potassium-free diet. More commonly, dietary potassium restriction exacerbates hypokalemia from other causes. Clinical situations associated with extreme potassium-deficient diets include anorexia nervosa, crash diets, alcoholism, and intestinal malabsorption. Increased urinary potassium excretion due to magnesium deficiency (which often is present in these clinical situations) may contribute to the observed hypokalemia.<sup>1</sup> In this setting, hypokalemia can be refractory to treatment due to a persistent increase in urinary potassium excretion because intracellular magnesium normally inhibits potassium secretion through the ROMK (renal outer medullary  $\text{K}^+$  channel; encoded by the *KCNJ1* gene) channel in the distal nephron. As discussed next, this kaliuretic effect is exacerbated further under conditions of increased distal sodium delivery and increased aldosterone levels.

Total-body potassium content in a typical 70-kg individual is approximately 3,500 mEq. Of total-body potassium, 98% is located in the intracellular space, primarily in skeletal muscle, whereas 2% is found in the extracellular space. The kidney is responsible primarily for maintaining total-body potassium content by matching potassium intake with potassium excretion. Because adjustments in urinary potassium excretion can take several hours, changes in extracellular potassium concentration initially are buffered by the movement of potassium into or out of skeletal muscle (Box 1). After a meal, postprandial release of insulin functions not only to regulate serum glucose concentration, but also to shift dietary potassium into cells until the kidney excretes the potassium load, re-establishing normal total-body potassium content. During exercise, the release of catecholamines through  $\beta_2$  stimulation limits the increase in extracellular potassium concentration that otherwise would occur as a result of normal potassium release by contracting muscle.

Pathologic stimulation of  $\beta_2$  receptors can result in symptomatic hypokalemia. For example, hypokalemia is a potential complication of the hyperadrenergic state that often accompanies alcohol withdrawal syndromes or myocardial infarction. Clenbuterol is a  $\beta_2$ -adrenergic

**Box 1.** Causes of Hypokalemia Due to Internal Cellular Shift

- Alkalosis (effect is trivial)
- Insulin administration
- $\beta_2$ -Adrenergic stimulation
  - ◊ Stress-induced epinephrine release
  - ◊ Drugs: theophylline intoxication, ritodrine, terbutaline, albuterol, clenbuterol
- Anabolism
  - ◊ Treatment of pernicious anemia
  - ◊ Rapidly growing leukemias and lymphomas
- Hypokalemic periodic paralysis
  - ◊ Acquired in association with hyperthyroid state
  - ◊ Familial
- Drugs/toxins/herbs
  - ◊ Barium intoxication
  - ◊ Chloroquine intoxication
  - ◊ Cesium salts (reported in herbal preparations marketed as antitumor agent)

agonist with a rapid onset and long duration of action approved for limited use in veterinary medicine.<sup>2,3</sup> The drug has been used illicitly as an alternative to anabolic steroids because of its effects to increase muscle mass. Hypokalemia as a result of clenbuterol toxicity has now been reported in users of heroin adulterated with clenbuterol.

Hypokalemic periodic paralysis is a rare disorder characterized by muscle weakness or paralysis caused by the sudden movement of potassium into cells.<sup>4</sup> The attacks are precipitated by rest after exercise, stress, high-carbohydrate meals, and events accompanied by increased release of catecholamines or insulin. The acquired form of the disease typically occurs in hyperthyroid men of either Asian or Mexican descent. The disorder is cured when the patient is rendered euthyroid.

The familial form of hypokalemic periodic paralysis is inherited as an autosomal dominant disorder and has clinical features similar to the acquired form. Notable differences include younger age at presentation (usually <20 years), equal male-female distribution, and most occurrence in whites. The familial disorder most commonly is caused by mutations in the muscle calcium channel  $\alpha$ -1 subunit gene (*CACNA1S*) on chromosome 1q3132.

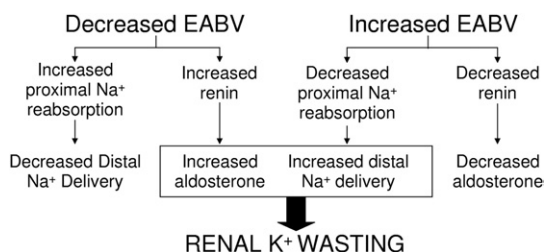
Hypokalemia in the setting of decreased total-body potassium can be the result of extrarenal or renal losses. Cutaneous loss of potassium sufficient to cause hypokalemia is uncommon, but may occur in the setting of intense exercise in a

hot humid environment. Under these conditions, large volumes of sweat can be lost each day, and potassium depletion may result. Gastrointestinal syndromes are the most common clinical disorders of extrarenal potassium losses.<sup>5</sup> Diarrhea leads to fecal potassium wastage and is associated with normal anion gap metabolic acidosis. Although usually associated with low urinary potassium concentration, acidosis can lead to some degree of urinary potassium wasting through increased distal delivery of sodium.<sup>6</sup> In addition, the acidosis will result in potassium redistribution out of cells, leading to a degree of hypokalemia that underestimates the degree of total-body potassium depletion.

Potassium is filtered freely by the glomerulus, but is reabsorbed extensively by the proximal tubule and loop of Henle, so that approximately 10% of the filtered load reaches the distal nephron.<sup>7</sup> The distal nephron secretes potassium into the tubular fluid, which will be excreted.<sup>8</sup> Two of the most important physiologic determinants of urinary potassium excretion in this segment are mineralocorticoid secretion and distal sodium delivery.

Under normal circumstances, there is a balanced reciprocal relationship between distal sodium delivery and circulating aldosterone that serves to maintain potassium balance during normal volume regulation. It is only under pathophysiologic conditions that distal sodium delivery and aldosterone become coupled.<sup>9</sup> In this setting, urinary potassium wasting will occur (Fig 1). When evaluating a patient who is hypokalemic because of urinary potassium wasting, one must determine whether the primary disorder is an increase in mineralocorticoid activity or in distal sodium delivery.

A primary increase in mineralocorticoid activity can be caused by primary increases in renin secretion, primary increases in aldosterone secretion, or increases in a nonaldosterone mineralocorticoid or increased mineralocorticoid-like effect. In all these conditions, extracellular fluid volume is expanded and hypertension typically is present. Workup of these patients is extremely important because these disorders represent the most common causes of curable hypertension. The differential diagnosis for a patient with hypertension, hypokalemia, and metabolic alkalosis rests on measurement of plasma renin activity



**Figure 1.** Under normal circumstances, delivery of sodium ( $\text{Na}^+$ ) to the distal nephron is associated inversely with serum aldosterone levels. For this reason, urinary potassium ( $\text{K}^+$ ) excretion is kept independent of changes in extracellular fluid volume. Hypokalemia due to renal potassium wasting can be explained by pathophysiologic changes that lead to coupling of increased distal sodium delivery and aldosterone or aldosterone-like effects. When evaluating a patient who has hypokalemia caused by urinary potassium wasting, one must determine whether the primary disorder is an increase in mineralocorticoid activity or in distal sodium delivery. Abbreviation: EABV, effective arterial blood volume.

and plasma aldosterone concentration (Fig 2). The reader is referred to recent reviews of the specific disorders that are in this category.<sup>10,11</sup>

Conditions that give rise to primary increases in distal sodium delivery are characterized by normal or low extracellular fluid volume. Blood pressure typically is normal. Increases in distal sodium delivery most frequently are caused by diuretics, which act proximal to the cortical collecting duct.<sup>12</sup> Increased delivery also can be the result of nonreabsorbed anions, such as bicarbonate, as with active vomiting or proximal renal tubular acidosis. Ketoanions and sodium salts of penicillins are other examples. The inability to reabsorb these anions in the proximal tubule results in increased delivery of sodium to the distal nephron. Because these anions also escape reabsorption in the distal nephron, a more lumen-negative voltage develops and the driving force for potassium excretion into the tubular fluid is enhanced.

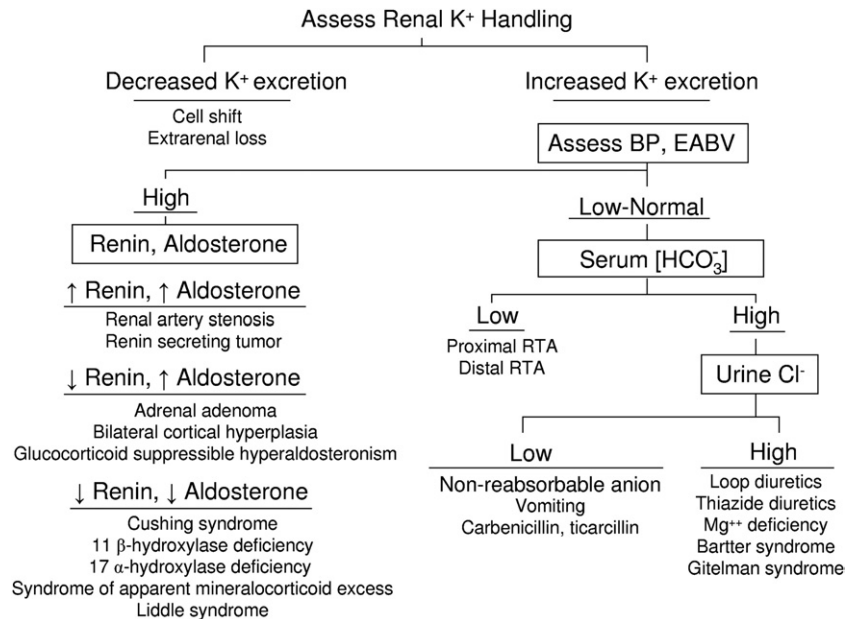
Disorders of hypokalemia caused by primary increases in distal sodium delivery can be categorized best according to the presence of metabolic acidosis or metabolic alkalosis (Fig 2). In the category of metabolic acidosis are disorders that cause renal tubular acidosis. In proximal renal tubular acidosis, the threshold for bicarbonate reabsorption is decreased, resulting in self-limited bicarbonaturia. The loss of sodium bicarbonate in urine leads to volume depletion, which

in turn activates the renin-angiotensin-aldosterone system. The coupling of increased aldosterone levels with increased distal sodium delivery results in urinary potassium wasting. In the steady state, when virtually all filtered bicarbonate is reabsorbed in the proximal and distal nephron, urinary potassium wasting is minimal and the degree of hypokalemia tends to be mild. In contrast, treatment of metabolic acidosis with bicarbonate improves the acidosis, but worsens the degree of hypokalemia.

The development of hypokalemia in distal renal tubular acidosis (dRTA) can be caused by several mechanisms.<sup>13</sup> First, systemic acidosis by itself can lead to urinary potassium wasting. Metabolic acidosis is associated with decreased net proximal sodium reabsorption.<sup>6</sup> The subsequent increase in distal delivery leads to volume contraction and activation of the renin-angiotensin-aldosterone system. These changes lead to increased renal potassium excretion. Second, dRTA that might be caused by a defect in the adenosine triphosphatase proton-potassium pump ( $\text{H}^+ - \text{K}^+ - \text{ATPase}$ ) will increase renal potassium excretion by directly impairing potassium reabsorption in the distal nephron. Third, potassium wasting can be the result of leakage into the tubular lumen as a result of an ionophoric effect, as seen in the gradient type of dRTA caused by administration of amphotericin B.

In the category of hypokalemia and metabolic alkalosis are the use of loop diuretics and Bartter syndrome. Bartter syndrome is a hereditary disorder characterized by renal salt wasting and hypokalemic metabolic alkalosis resembling the features of ongoing loop diuretic therapy. Hypokalemia can be severe and result in complications, such as rhabdomyolysis and periodic paralysis. This disease results from gene defects that lead to decreased sodium chloride reabsorption in the thick ascending limb of the loop of Henle. Dysfunction within this segment leads to significant salt wasting, inability to maximally concentrate urine, and increased 24-hour urinary calcium excretion. An acquired form of the disorder can occur in association with administration of aminoglycoside antibiotics.<sup>14</sup>

Gitelman syndrome is an inherited disorder with clinical manifestations that mimic the ongoing use of a thiazide diuretic.<sup>15</sup> This disease is caused by an inactivating mutation in the gene



**Figure 2.** Approach to a patient with hypokalemia. Renal potassium (K<sup>+</sup>) excretion can be assessed using a 24-hour urine collection, spot urine potassium-creatinine ratio, or determination of the transtubular potassium gradient along with the clinical setting (see text for a more detailed discussion). Urine sodium excretion is increased in disorders caused by a primary increase in distal sodium delivery accompanied by metabolic alkalosis and high urinary chloride (Cl<sup>-</sup>) excretion. Remote use of loop and thiazide diuretics before correction of extracellular fluid volume is characterized by low urinary sodium, chloride, and potassium excretion. In patients with a history of vomiting that has stopped, but who are still volume contracted, urinary sodium, chloride, and potassium excretion are low. In this setting, generation of new bicarbonate has ceased and equilibrium has been established in which the filtered load of bicarbonate is more completely reabsorbed, such that distal delivery of sodium now is low. Urinary potassium loss is far less compared with urine loss with active vomiting. With chronic diarrhea, urine sodium and potassium excretion are low, whereas urine chloride excretion is increased because of increased urinary excretion of ammonium chloride. Abbreviations: BP, blood pressure; EABV, effective arterial blood volume; [HCO<sub>3</sub><sup>-</sup>], bicarbonate concentration; Mg<sup>++</sup>, magnesium; RTA, renal tubular acidosis.

(*SLC12A3*) for the thiazide-sensitive apical sodium-chloride (Na<sup>+</sup>-Cl<sup>-</sup>) co-transporter (NCCT) in the distal convoluted tubule. In contrast to Bartter syndrome, these patients more commonly have hypomagnesemia, have less severe salt wasting, have decreased urinary calcium excretion, and retain the ability to concentrate urine.

Gitelman and Bartter syndromes would be considerations in the differential diagnosis of the patient in the case report. Although hypokalemic metabolic alkalosis and normal blood pressure are typical of these syndromes, urine electrolytes are characterized by increased sodium, potassium, and chloride levels. In addition, most patients with Bartter syndrome and virtually all patients with Gitelman syndrome have hypomagnesemia. The low urinary chloride level in the setting of increased urinary sodium and potassium levels in the case report is most consistent with active vomiting. The increase in urinary

sodium relative to the urine chloride excretion in vomiting is caused by the nonreabsorbable anion effect of newly generated filtered bicarbonate.<sup>16</sup> Urinary potassium wasting results from the coupling of the increased distal delivery of sodium with increased aldosterone levels, the latter stimulated by contraction of extracellular fluid volume.

Hypokalemia can cause a variety of clinical manifestations because of alterations in the excitability of neuromuscular tissues. A decrease in extracellular potassium concentration leads to hyperpolarization of the cell membrane, causing the cell to become less sensitive to exciting stimuli. Clinically, this effect accounts for the association of hypokalemia and muscle weakness. Occasionally, muscle weakness can be severe enough to cause paralysis, as in patients with hypokalemic dRTA. Muscle paralysis in this disorder can begin insidiously with weakness evolving gradually during a 24- to 48-hour

period to complete flaccid quadriplegia. Attacks of flaccid paralysis in patients with dRTA have been referred to as “RTA crisis” by some investigators because this striking clinical manifestation may result in a clinician overlooking the underlying cause.<sup>17,18</sup>

Myopathy also may occur, which in its most severe form can lead to frank rhabdomyolysis and kidney failure. Hypokalemia also can lead to central nervous system changes, with confusion and affective disorders, and to smooth muscle dysfunction, including paralytic ileus.

Cardiac complications of hypokalemia also may be important. The typical electrocardiogram change is ST depression, T-wave flattening, and

an increase in amplitude of the U wave. This change, often misread as a widened QT, is non-specific, often absent, and of little clinical use. It is well known that patients on cardiac glycoside therapy have an increased incidence of premature ventricular contractions, and when hypokalemic, supraventricular and ventricular tachyarrhythmias.

Hypokalemia also causes a renal concentrating defect because of both a decrease in medullary gradient and resistance of the cortical collecting tubule to antidiuretic hormone (ADH). This leads to polyuria and polydipsia. Hypokalemic nephropathy, or “kaliopenic nephropathy,” is a chronic tubulointerstitial disease characterized by polyuria, proteinuria, development of renal cysts, and loss of kidney function.<sup>19,20</sup> Histologically, there is evidence of tubular atrophy, interstitial infiltration of macrophages, and interstitial fibrosis. Because insulin release is regulated partially by serum potassium, hypokalemia can lead to glucose intolerance. For every 1-mEq/L decrease in potassium level, there is an approximate 10-mg/dL (0.56-mmol/L) increase in glucose level.<sup>21</sup>

Hypokalemia is encountered commonly in clinical practice. By using a systematic approach to patients with this disorder, one can ensure that the underlying cause of the disturbance is accurately determined. Key teaching points are listed in Box 2.

#### Box 2. Key Teaching Points

- Transient causes of hypokalemia are due to cell shift, whereas sustained hypokalemia is caused by either inadequate intake or excessive potassium loss. Hypokalemia resulting from excessive potassium loss can be due to renal or extrarenal causes
- Administration of a carbohydrate load to malnourished patients can unmask total-body deficits of potassium, phosphate, and magnesium because of insulin-mediated shifts into the intracellular compartment
- Urinary potassium wasting is caused by pathophysiologic conditions that couple increased distal sodium delivery with increased plasma aldosterone levels or aldosterone-like effects
- Conditions associated with a primary increase in plasma aldosterone level or aldosterone-like effects are characterized by hypokalemia, metabolic alkalosis, and hypertension. These conditions are approached best by measuring plasma renin activity and plasma aldosterone levels
- Conditions that give rise to primary increases in distal sodium delivery are characterized by normal or low extracellular fluid volume and normal blood pressure. These disorders can be categorized best according to the presence of metabolic acidosis or metabolic alkalosis. Urinary chloride excretion can be used to further differentiate conditions characterized by metabolic alkalosis
- Mineral acidosis will result in potassium redistribution out of cells, leading to a degree of hypokalemia not as severe as the degree of total-body potassium depletion
- Hypokalemia can lead to adverse effects on skeletal and cardiac muscle, including severe muscle weakness, rhabdomyolysis, and cardiac arrhythmias
- Metabolic complications of hypokalemia include impaired urinary concentrating ability and decreased  $\beta$ -cell release of insulin, resulting in glucose intolerance
- Long-standing hypokalemia can lead to a chronic tubulointerstitial renal disease, referred to as kaliopenic nephropathy

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#### REFERENCES

1. Huang C, Kuo E. Mechanism of hypokalemia in magnesium deficiency. *J Am Soc Nephrol.* 2007;18(10):2649-2652.
2. Hoffman R, Kirrane B, Marcus S; Clenbuterol Study Investigators. A descriptive study of an outbreak of clenbuterol-containing heroin. *Ann Emerg Med.* 2008;52(5):548-553.
3. Centers for Disease Control and Prevention (CDC). Atypical reactions associated with heroin use—five states, January-April 2005. *MMWR Morbid Mortal Wkly Rep.* 2005; 54(32):793-796.
4. Kung AW. Clinical review: thyrotoxic periodic paralysis: a diagnostic challenge. *J Clin Endocrinol Metab.* 2006; 91(7):2490-2495.
5. Agarwal R, Afzalpurkar R, Fordtran JS. Pathophysiology of potassium absorption and secretion by the human intestine. *Gastroenterology.* 1994;107(2):548-571.

6. Farouqi S, Sheriff S, Amlal H. Metabolic acidosis has dual effects on sodium handling by rat kidney. *Am J Physiol Renal Physiol*. 2006;291(2):F322-331.
7. Giebisch G, Krapf R, Wagner C. Renal and extrarenal regulation of potassium. *Kidney Int*. 2007;72(4):397-410.
8. Hebert SC, Desir G, Giebisch G, Wang W. Molecular diversity and regulation of renal potassium channels. *Physiol Rev*. 2005;85(1):319-371.
9. Palmer BF. Approach to fluid and electrolyte disorders and acid-base problems. *Prim Care*. 2008;35(2):195-213.
10. Palmer BF, Sterns R. Fluid, electrolyte and acid-base disturbances. *NephSAP*. 2009;8:70-165.
11. Mattsson C, Young WF Jr. Primary aldosteronism: diagnostic and treatment strategies. *Nat Clin Pract Nephrol*. 2006;2(4):198-208.
12. Palmer BF, Naderi AS. Metabolic complications associated with use of thiazide diuretics. *J Am Soc Hypertens*. 2007;1(6):381-392.
13. Battle D, Moorthi KM, Schlueter W, Kurtzman N. Distal renal tubular acidosis and the potassium enigma. *Semin Nephrol*. 2006;26(6):471-478.
14. Glassock RJ, Bargman JM, Palmer BF, Samaniego-Picota M, Fervenza FC. Nephrology quiz and questionnaire: 2009. *Clin J Am Soc Nephrol*. 2010;5(6):1141-1160.
15. Jang HR, Lee JW, Oh YK, et al. From bench to bedside: diagnosis of Gitelman's syndrome—defect of sodium-chloride cotransporter in renal tissue. *Kidney Int*. 2006;70(4):813-817.
16. Palmer BF, Alpern RJ. Metabolic alkalosis. *J Am Soc Nephrol*. 1997;8(9):1462-1469.
17. Bresolin NL, Grillo E, Fernandes VR, Carvalho FL, Goes JE, da Silva RJ. A case report and review of hypokalemic paralysis secondary to renal tubular acidosis. *Pediatr Nephrol*. 2005;20(6):818-820.
18. Soy M, Pamuk ON, Gerenli M, Celik Y. A primary Sjögren's syndrome patient with distal renal tubular acidosis, who presented with symptoms of hypokalemic periodic paralysis: report of a case study and review of the literature. *Rheumatol Int*. 2005;26(1):86-89.
19. Reungjui S, Roncal CA, Sato W, et al. Hypokalemic nephropathy is associated with impaired angiogenesis. *J Am Soc Nephrol*. 2008;19(1):125-134.
20. Reungjui S, Hu H, Mu W, et al. Thiazide-induced subtle renal injury not observed in states of equivalent hypokalemia. *Kidney Int*. 2007;72(12):1483-1492.
21. Zillich AJ, Garg J, Basu S, Bakris GL, Carter BL. Thiazide diuretics, potassium, and the development of diabetes: a quantitative review. *Hypertension*. 2006;48(2):219-224.