

Approach to Fluid and Electrolyte Disorders and Acid-Base Problems

Biff F. Palmer, MD

Department of Internal Medicine, Division of Nephrology, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390, USA

Employing a systematic approach to the interpretation of serum chemistries is the most effective way to ensure abnormalities are detected and correctly interpreted. This article reviews a series of steps that can be used in both the outpatient and inpatient settings. These steps will help to ensure the clinician not only identifies overt abnormalities but also subtle disturbances that may lay hidden in a routine set of serum chemistry values.

Steps to interpreting a set of chemistry values

- Step 1: First check serum sodium [Na] and work up tonicity disorders if abnormal
- Step 2: Check serum chloride [Cl]
- Step 3: Calculate anion gap
- Step 4: If anion gap \uparrow , determine whether measured serum bicarbonate $[\text{HCO}_3]$ is equal to predicted $[\text{HCO}_3]$
- Step 5: Analyze arterial blood gas
- Step 6: Check potassium

First step: examine the serum sodium concentration

Hyponatremia

Is the hyponatremia representative of a hypoosmolar state?

There are two general causes of hyponatremia in which it is not associated with a hypoosmolar state. The first of these is pseudohyponatremia, which involves an abnormal measurement of the serum sodium (Na). This

occurs in patients with hyperglobulinemia or hypertriglyceridemia, in whom plasma water relative to plasma solids is decreased in blood, leading to less sodium in a given volume of blood. In general, hyperglobulinemia sufficient to cause pseudohyponatremia is rare and occurs only in Waldenstrom's macroglobulinemia. Triglycerides must be in the thousands to cause this condition and are most commonly seen in diabetics. In general, this problem is becoming less prevalent, as many laboratories are using sodium electrodes without diluting the blood such that the plasma sodium measurement becomes independent of plasma water and solid contents.

The other cause of hyponatremia in the absence of a hypoosmolar state involves true hyponatremia, but with elevations in the concentration of another osmole. Clinical examples include hyperglycemia as seen in uncontrolled diabetes or, rarely, hypertonic infusion of mannitol used in the treatment of cerebral edema. The increases in plasma glucose raise serum osmolality, which pulls water out of cells and dilutes the serum Na. For every 100 mg/dL rise in glucose or mannitol, the serum Na will quickly fall by 1.6 mEq/L. The increased tonicity will also stimulate thirst and arginine vasopressin (AVP) secretion, both of which contribute to further water retention. As the plasma osmolality returns toward normal, the decline in serum Na will be 2.8 mEq/L for every 100 mg/dL rise in glucose. The net result is a normal plasma osmolality but a low serum sodium.

Is the kidney's ability to dilute the urine intact?

The presence of hypotonic hyponatremia implies that water intake exceeds the ability of the kidney to excrete water. In unusual circumstances, this can occur when the kidney's ability to excrete free water is intact. However, because a normal kidney can excrete 20 L to 30 L of water per day, the presence of hyponatremia with normal renal water excretion implies that the patient is drinking more than 20 L to 30 L of water per day. This condition is referred to as primary polydipsia. These patients should have a urine osmolality less than 100 mOsm/L. While primary polydipsia is a common condition that leads to polyuria and polydipsia, it is uncommon as a sole cause of hyponatremia.

In the absence of primary polydipsia, hyponatremia is associated with decreased renal water excretion and urine that is inappropriately concentrated. It is important to note that in the presence of hyponatremia, urine should be maximally dilute and a urine osmolality higher than this (greater than 100 mOsm/L) is inappropriate. An inappropriately concentrated urine implies a defect in renal water excretion (Fig. 1).

Excretion of water by the kidney is dependent on three factors. First, there must be adequate delivery of filtrate to the tip of the loop of Henle. Second, solute absorption in the ascending limb and the distal nephron must be normal so that the tubular fluid will be diluted. Lastly, AVP levels must be low in the plasma. Of these three requirements for water excretion, the one which is probably most important in the genesis of hyponatremia is

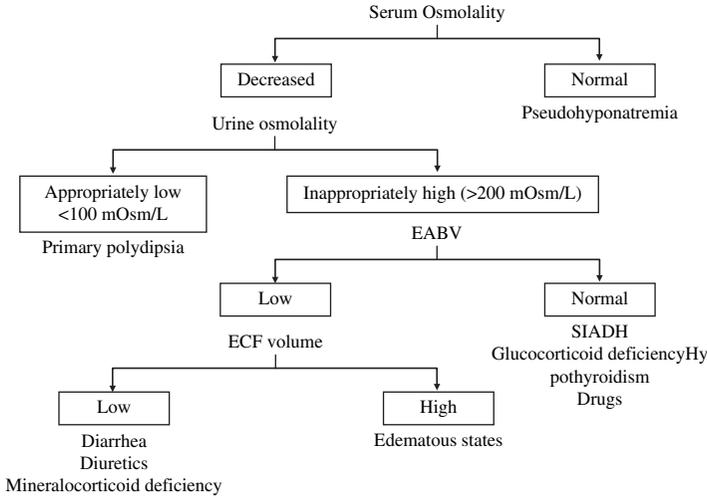


Fig. 1. Approach to the hyponatremic patient. *Abbreviations:* EABV, effective arterial blood volume; ECF, extracellular fluid; SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

the failure to maximally suppress AVP levels. In many conditions, decreased delivery of filtrate to the tip of the loop of Henle also contributes. Defective solute absorption in the ascending limb and distal nephron is probably only relevant to hyponatremia seen with chloruretic diuretics.

Assess the patient's volume status

In patients with hypotonic hyponatremia with an inappropriately concentrated urine, one needs to define whether effective arterial volume is decreased. Most of the causes of hyponatremia result from a decrease in effective arterial volume, which causes baroreceptor stimulation of AVP secretion and leads to decreased distal delivery of filtrate to the tip of the loop of Henle. If effective arterial volume is low, extracellular fluid volume can be low in the volume-depleted patient (hypovolemic hyponatremia) or can be high in the edematous patient (hypervolemic hyponatremia). If effective arterial volume is normal, one is dealing with the euvolemic causes of hyponatremia (isovolemic hyponatremia).

The clinical determination of effective arterial volume is usually straightforward. On physical examination, the best index of effective arterial volume is the pulse and blood pressure. Urinary electrolytes are also extremely useful in the assessment of effective arterial volume. Patients with a low effective arterial volume will tend to have low urinary sodium, low urinary chloride, and low fractional excretions of sodium and chloride in the urine. Patients with euvolemic hyponatremia, however, will be in balance and will excrete sodium and chloride at rates that reflect dietary intake of sodium

and chloride. Thus, generally they have urinary sodium and chlorides greater than 20 mEq/L and fractional excretions of these electrolytes more than 1%.

Plasma composition can also be used to assess effective arterial volume. The blood urea nitrogen (BUN) is particularly sensitive to effective arterial volume. In patients with normal serum creatinines, a high BUN suggests a low effective arterial volume and a low BUN suggests a high effective arterial volume. The plasma uric acid can also be used as a sensitive index of effective arterial volume. In comparing patients with SIADH and other causes of hyponatremia, patients with low effective arterial volume tend to have an elevated serum uric acid. In patients with SIADH, serum urate is not only not elevated, but is actually depressed. This is because of the fact that these patients are volume expanded, although it is clinically difficult to detect the degree of volume expansion.

Hypernatremia

Why is the patient not drinking?

The initial approach to any patient with hypernatremia is to determine why there has been inadequate intake of water. Hypernatremia is rare in conscious patients who have free access to water because of the extreme sensitivity of the thirst mechanism. Inadequate water intake may result from conditions in which there is a specific lesion of the thirst center. More commonly, there is an alteration in the level of consciousness so that patients become unaware of thirst or cannot adequately communicate the need for water. In some instances, thirst is adequately sensed but water is unavailable or there is restricted access to water because patients are restrained. Reduced sensation of thirst also occurs in otherwise normal individuals as a feature of increasing age, rendering the elderly particularly susceptible to the development of hypernatremia.

Has there been accelerated water loss or increased sodium gain?

The next step in the evaluation of hypernatremia is to search for the presence of accelerated water loss or increased sodium gain, both of which will increase the likelihood of a patient developing hypernatremia. This best can be accomplished by clinically assessing the patient's extracellular fluid status.

Hypovolemic hypernatremia. Hypernatremia in the setting of hypovolemia results from fluid losses in which the sodium concentration is less than the plasma concentration. Extrarenal losses of salt and water from the gastrointestinal tract or from profuse sweating or renal losses because of osmotic diuresis are the major causes. Diuretics can also predispose to the development of hypernatremia, because these agents are associated with renal salt and water loss but water loss to a greater extent. It should

be emphasized, however, that hypernatremia will only develop if there is an associated impairment in water intake. Urine sodium concentration should be low with extrarenal fluid losses, while the concentration is typically high with an osmotic diuresis or during the administration of a diuretic.

Hypervolemic hypernatremia. Hypernatremia in the setting of hypervolemia can be caused by iatrogenic administration of hypertonic sodium chloride (NaCl) or hypertonic sodium bicarbonate or mineralocorticoid excess. Administration of hypertonic fluids is usually evident from the clinical setting and is associated with a high urine sodium concentration. Mineralocorticoid excess is suggested by the presence of hypertension and hypokalemic metabolic alkalosis. Urine sodium concentration will vary according to dietary intake.

Isovolemic hypernatremia. Pure water loss, whether from mucocutaneous routes or from the kidneys, causes isovolemic hypernatremia. Because two thirds of pure water loss is sustained from within cells, patients will not become clinically volume-depleted unless the water deficit becomes substantial. Insensible losses from the respiratory tract or skin results in a concentrated urine. Inappropriate water loss by the kidney, whether from central or nephrogenic diabetes insipidus, results in a dilute urine. Although renal water loss can lead to hypernatremia in patients with impaired thirst or access to water, most patients with diabetes insipidus have neither of these defects, and typically a patient presents with polyuria and polydipsia and a normal serum sodium concentration. As a result, the initial clue to the presence of diabetes insipidus usually comes not from the detection of hypernatremia but rather during the evaluation of the polyuric patient.

Step 2: Examine the serum chloride concentration

One should always examine the serum chloride concentration with respect to the serum sodium concentration. As the serum sodium concentration either increases or decreases because of disorders in tonicity, the serum chloride concentration will change in parallel and to the same extent. Whenever the serum chloride concentration moves in a direction opposite or changes disproportionately to the change in serum sodium concentration, an acid-base disorder is suggested.

The chloride concentration is decreased with respect to the serum sodium concentration

Whenever the chloride concentration is decreased with respect to the serum sodium concentration, one should suspect the presence of either an acute or chronic respiratory acidosis or a metabolic alkalosis. The fall in

chloride concentration will be accompanied by an increase in the serum bicarbonate concentration in these conditions.

Acute and chronic respiratory acidosis

Acute hypercapnia is associated with several effects that lead to an immediate small decrease in the chloride concentration and rise in the serum bicarbonate (HCO_3^-) concentration. First, the decrease in pH that accompanies acute respiratory acidosis increases hydrogen (H^+) binding to albumin. This effect will cause a fall in the anion gap and a slight rise in the serum HCO_3^- concentration. Second, a small amount of H^+ enters parenchymal cells in exchange for Na^+ and potassium (K^+), also contributing to a small increase in extracellular HCO_3^- concentration. Third, the high carbon dioxide (CO_2) tension is immediately transmitted into red blood cells, where in the presence of carbonic anhydrase (H_2CO_3) is generated. This acid dissociates and the H^+ binds to hemoglobin, leaving HCO_3^- in the cytoplasm of the red cell. Hemoglobin can bind a considerable amount of H^+ because of the rich histidine content of the molecule. As the HCO_3^- concentration rises, it exits from the cell in exchange for plasma chloride (Cl^-), a process termed the red cell HCO_3^- - Cl^- shift. The net effect of these changes is that in acute respiratory acidosis, the plasma HCO_3^- concentration increases by 1 mEq/L for each 10 mm Hg elevation in partial pressure of carbon dioxide (PaCO_2) (Box 1).

Box 1. Compensation in acid-base disorders

- Acute respiratory acidosis
For every 10 mm Hg, rise in PaCO_2 the HCO_3^- increases by 1 mEq/L
- Chronic respiratory acidosis
For every 10 mm Hg, rise in PaCO_2 the HCO_3^- increases by 3.5 mEq/L
- Acute respiratory alkalosis
For every 10 mm Hg, fall in PaCO_2 the HCO_3^- decreases by 2 mEq/L
- Chronic respiratory alkalosis
For every 10 mm Hg, decrease in PaCO_2 the HCO_3^- decreases by 5 mEq/L
- Metabolic acidosis
1.2 mm Hg decrease in PaCO_2 for each 1 mEq/L fall in HCO_3^-
 $\text{PaCO}_2 = \text{HCO}_3^- + 15$
 $\text{PaCO}_2 =$ last two digits of pH
- Metabolic alkalosis
 PaCO_2 increases by 0.7 for each mEq/L HCO_3^-

In chronic respiratory acidosis, the increase in plasma HCO_3^- concentration is higher because of compensatory renal mechanisms. The chronic elevation in CO_2 leads to intracellular acidosis in proximal tubular cells, increasing H^+ secretion and resulting in accelerated HCO_3^- reabsorption. The retention of NaHCO_3 leads to slight expansion of the extracellular fluid compartment and causes increased renal excretion of NaCl , so as to return volume back to normal. The net effect is an increase in serum HCO_3^- and decreased Cl^- concentration. In chronic respiratory acidosis there is a 3.5 mEq/L increase in HCO_3^- for each 10 mm Hg elevation in PaCO_2 . Higher or lower plasma HCO_3^- concentrations suggest the presence of mixed respiratory and metabolic acid-base disorders.

The chloride concentration is increased with respect to the serum sodium concentration

Whenever the chloride concentration is increased with respect to the serum sodium concentration, one should suspect the presence of either an acute or chronic respiratory alkalosis or a normal gap hyperchloremic metabolic acidosis. The rise in chloride concentration will be accompanied by a fall in the serum bicarbonate concentration in these conditions.

Acute and chronic respiratory alkalosis

An acute fall in PaCO_2 causes plasma and red blood cell CO_2 tensions to fall. In response, albumin and other non- HCO_3^- buffers release H^+ to decrease the plasma HCO_3^- concentration. Within red cells, the fall in PaCO_2 causes hemoglobin to release H^+ and red blood cell HCO_3^- concentration also falls. Plasma HCO_3^- will enter the red cell in exchange for Cl^- . This $\text{HCO}_3^-/\text{Cl}^-$ shift accounts for the small initial compensatory response in acute respiratory alkalosis in which the HCO_3^- concentration falls by 2 mEq/L for every 10-mm Hg decrease in PaCO_2 .

In chronic respiratory alkalosis the renal HCO_3^- reabsorptive capacity decreases and there is a transient NaHCO_3 diuresis. This process takes 2 to 3 days to become fully manifest. Once a new steady state is achieved, the HCO_3^- concentration will have decreased by 5 mEq/L for each 10-mm Hg fall in PaCO_2 . A higher or lower value for the plasma HCO_3^- concentration suggests the presence of an additional metabolic disorder.

While the urinary loss of NaHCO_3 does not increase total body Cl^- , it causes a decrease in total body Na^+ and total body HCO_3^- , leading to contraction of extracellular fluid volume and a hypotonic state. The response to these changes is increased renal reabsorption of NaCl and suppression of antidiuretic hormone secretion. The increase in renal water excretion returns the Na^+ concentration to normal and leads to a high Cl^- concentration. The final result is a decrease in the HCO_3^- concentration and an increase in the Cl^- concentration.

Another characteristic finding in chronic respiratory alkalosis is an increase of 3 mEq/L to 5 mEq/L in the serum anion gap. The increase in gap is the result of an increase in the number of anionic sites on albumin as protons disassociate in response to the increased blood pH. The circulating levels of lactate are also increased in this setting. Lactate production is increased because of a stimulatory effect of high pH on phosphofructokinase, the rate-limiting step in the glycolytic pathway.

Step 3: Calculate the anion gap

Calculation of the anion gap should be a routine part of the examination of every set of electrolytes, no matter how normal the individual values may appear. The anion gap is equal to the difference between the plasma concentrations of the major cation (Na^+) and the major measured anions ($\text{Cl}^- + \text{HCO}_3^-$).

$$\text{Anion gap} = (\text{Na}^+) - (\text{Cl}^-) - (\text{HCO}_3^-)$$

The normal value of the anion gap is approximately 12 plus or minus 2. Most of the unmeasured anions consists of albumin, and therefore the normal anion gap changes in the setting of hypoalbuminemia (normal anion gap is approximately three times the serum albumin in g/dL). Because the total number of cations must equal the total number of anions, a fall in the serum HCO_3^- concentration must be offset by a rise in the concentration of other anions. If the anion accompanying excess H^+ is Cl^- , then the fall in the serum HCO_3^- concentration is matched by an equal rise in the serum Cl^- concentration. The acidosis is classified as a normal gap or hyperchloremic metabolic acidosis. By contrast, if excess H^+ is accompanied by an anion other than Cl^- , then the fall in HCO_3^- is balanced by a rise in the concentration of the unmeasured anion. The Cl^- concentration remains the same. In this setting, the acidosis is said to be a high anion gap metabolic acidosis. An increase in the anion gap can occur whenever there is an increase in unmeasured anions (increased valency of albumin, hyperphosphatemia) or a decrease in the unmeasured cations (hypocalcemia, hypomagnesemia). However, the most common cause of an increase in the anion gap is the generation of a metabolic acidosis by addition of a non-Cl acid.

Classification of metabolic acidosis

Hyperchloremic normal gap acidosis

Renal origin

Proximal renal tubular acidosis (Type II RTA)

Hypokalemic distal renal tubular acidosis (Type I RTA)

Hyperkalemic distal renal tubular acidosis (Type IV RTA)

Renal tubular acidosis of renal insufficiency (glomerular filtration rate or GFR usually > 15 mL/min– 20 mL/min)

Extrarenal origin

Diarrhea

Gastrointestinal ureteral connections

External loss of pancreatic or biliary secretions

Anion gap metabolic acidosis

Renal origin

Uremic acidosis (GFR usually < 15 mL/min– 20 mL/min)

Extrarenal origin

Lactic acidosis

Diabetic ketoacidosis

Starvation ketoacidosis

Alcoholic ketoacidosis

Poisoning (ethylene glycol, methanol, salicylate)

Pyroglutamic acidosis

The patient with metabolic acidosis and an increased anion gap should be worked up aggressively because of the numerous life-threatening conditions that can cause this disorder. Measurement of the BUN or creatinine will disclose the presence of an acidosis of renal insufficiency. Blood lactate levels and ketoacids can be measured in the plasma and urine using the nitroprusside test. The presence of a significant osmolar gap, calcium oxalate crystals in the urine, abnormal vision, coexistent respiratory alkalosis, or tinnitus may suggest an overdose. The clinical setting is often helpful. The patient may be in shock, the patient may be a known diabetic, or the patient may have a known history of suicide attempts.

Step 4: Is the measured HCO_3^- concentration equal to the predicted HCO_3^- ?

In the setting of an increased anion gap, one needs to determine whether the measured serum HCO_3^- is equal to the predicted serum HCO_3^- . In general, the serum HCO_3^- concentration will fall by an amount equal to the increase in the anion gap. Sometimes an increased anion gap may be the only clue to a metabolic acidosis. For instance, consider a patient with a measured plasma HCO_3^- concentration of 22 mEq/L in the setting of an anion gap of 22. In this instance the anion gap has increased by 10, assuming the normal anion gap is 12. One would predict the serum HCO_3^- should be approximately 14 mEq/L, assuming a normal value of 24 mEq/L ($24 - 10 = 14$). To explain the near normal serum HCO_3^- in this setting, one concludes a metabolic alkalosis is also present. Thus, the patient has two acid-base processes: an anion gap metabolic acidosis and a metabolic alkalosis. If one did not calculate the anion gap one might mistakenly call this patient's acid-base status normal.

Consider a patient with a measured serum HCO_3^- concentration of 6 mEq/L in the setting of an anion gap of 22. Once again, the predicted HCO_3^- concentration based on an increase in anion gap of 10 would be 14 mEq/L. To explain the lower measured value, one concludes there is also a normal gap hyperchloremic metabolic acidosis. Thus, this patient has two acid-base disturbances: an anion gap metabolic acidosis and a normal gap hyperchloremic metabolic acidosis.

Step 5: Interpret the arterial blood gas

Before one can approach a patient with an acid-base disorder, it is important to distinguish the suffixes “-emia” and “-osis.” The suffix, “-emia” refers to the concentration in the blood. Thus, acidemia means excess acid in the blood (low blood pH), and alkalemia means excess alkali in the blood (high blood pH). The suffix “-osis” refers to a process. Thus, acidosis refers to a process that adds acid to the blood, while alkalosis refers to a process that adds alkali to the blood. A patient could have a metabolic acidosis and a respiratory alkalosis, and these could result in a normal blood pH, a high blood pH (alkalemia) or a low blood pH (acidemia).

Determine primary disorders

Once a patient is found to have an acid-base abnormality, the next step is to determine which abnormalities are primary disorders and which involve normal compensations. For instance, increased net acid production leads to a drop in serum HCO_3^- concentration in a primary metabolic acidosis. The drop in PaCO_2 , which occurs in response to this, is a normal respiratory compensation and is not a primary disorder. A primary metabolic acid-base disturbance refers to a primary increase or decrease in HCO_3^- concentration because of addition or loss of nonvolatile acids or alkali from the extracellular fluid. A primary respiratory acid-base disturbance refers to a primary change in PaCO_2 , reflecting a primary increase or decrease in alveolar ventilation relative to existing CO_2 production. In both of these cases, the word “primary” implies that the change is not because of a change in blood pH, and is thus not a secondary compensation. To determine which process is primary and which is secondary, one generally follows a three-step process, addressing three questions.

Step 1: What is blood pH?

Compensations generally do not return blood pH back to 7.4, such that a pH of 7.4 in the presence of an abnormal HCO_3^- concentration and PaCO_2 generally implies two simultaneous primary acid-base disorders: a metabolic and a respiratory one. If blood pH is low, then at least one primary abnormality is an acidosis and if blood pH is high at least one primary abnormality is an alkalosis.

Step 2: Has PaCO₂ or HCO₃⁻ concentration moved in the direction of the pH?

Taking the example of an acidemia, one would then look at the HCO₃⁻ concentration and the PaCO₂ to see which has moved in the acid direction. A drop in the HCO₃⁻ concentration or an increase in the PaCO₂ would both be a change in the acid direction. If either has moved in the acid direction, it must represent a primary disorder. If they have both moved in the acid direction, a mixed metabolic respiratory acidosis is present. If only one of them has moved in the acid direction, this is a cause of a primary acidosis.

Step 3: Are there one or more abnormalities?

The last question is whether the response of the other variable is appropriate (in which case it would simply be a normal compensation) or whether the response of the other variable is outside the acceptable limits implying, once again, two abnormalities or a mixed acid-base disorder. To answer the last question requires knowledge of the appropriate compensations in response to primary metabolic or respiratory acid-base changes. For this, one may merely refer to an “acid-base map.” The map plots the combinations of HCO₃⁻ concentration, PaCO₂, and pH that are seen in the various disorders, with 95% confidence limits. If one does not wish to carry such a map around with them, a few general rules can be remembered. As stated above, as a general rule pH should be returned toward and not to or past normal. In addition, there are some numbers that the physician can carry with him or memorize, which describe an average compensation. These are listed in **Box 1**.

Using these equations, one can calculate the appropriate compensatory response. If the response is far different from this, a second primary process (ie, a mixed acid-base disorder) is implied. For instance, if a patient has a primary metabolic acidosis with a decrease in his plasma HCO₃⁻ concentration to 14 mEq/L (a decrease of 10 mEq/L), the appropriate pulmonary response for a respiratory compensation is a decrease in the PaCO₂ to approximately 29 mm Hg. If the PaCO₂ only falls to 35, this would represent an inadequate respiratory response and the patient would be said to have a combined metabolic and respiratory acidosis. Conversely, if the PaCO₂ is 18 (a greater than normal response), then the patient would be said to have a combined metabolic acidosis and respiratory alkalosis.

Interpret the acid-base disorders in the context of the clinical presentation

The final step in evaluating acid-base disorders is to determine the etiology of the identified processes based on the clinical presentation of the patient. The evaluation of the laboratory data must fit with the clinical presentation of the patient. Consider the following set of laboratory values: pH 7.47, PaCO₂ 20, HCO₃ 14 mEq/L. These values are typical of a normal

pregnancy at 34 weeks gestation. The high progesterone levels during pregnancy exert a stimulatory effect on the respiratory center, causing the development of a chronic respiratory alkalosis. The decrease in HCO_3 of 10 mEq/L (from 24 to 14) is the expected compensatory change for a chronic decrease in PaCO_2 of 20 mm Hg.

However, the interpretation of these same values would differ if they were obtained from a 23-year-old man who 6 hours earlier ingested a large quantity of aspirin. First, the alkaline pH and low PaCO_2 are indicative of a respiratory alkalosis. However, based on the clinical history, the process is acute. In the setting of acute respiratory alkalosis the expected compensatory change in serum HCO_3 is a decline to 20 mEq/L (2 mEq/L for each 10-mm Hg decline in PaCO_2). The measured value of 14 mEq/L suggests an additional process is present. In this case one concludes there is a metabolic acidosis. Indeed, a combination of respiratory alkalosis and anion gap metabolic acidosis is typical of adults who present with aspirin intoxication.

Consider a second set of laboratory data: pH 7.53, PaCO_2 51, HCO_3 40. The pH is alkaline and the serum HCO_3 has moved in the alkaline direction, making metabolic alkalosis the primary disturbance. The increase in PaCO_2 to 53 mm Hg is an appropriate compensatory response for a simple metabolic alkalosis ($0.7 \times$ the increase in HCO_3 above the normal value of 24 mEq/L). These values are consistent with a 56-year-old man who presents with nausea and vomiting because of a gastric outlet obstruction.

However, one would need to alter the interpretation of the values if obtained from a 63-year-old woman with severe chronic obstructive lung disease and cor pulmonale recently started on loop diuretics. In this setting, the expected acid base disturbance is a chronic respiratory acidosis. If the PaCO_2 is chronically 51 mm Hg, the expected renal compensation is for the serum HCO_3 concentration to be increased to approximately 28 mm Hg. In addition, the arterial pH should be less than 7.4. Given the alkaline pH, the higher than expected serum HCO_3 concentration of 40, and clinical history, one concludes the patient has chronic respiratory acidosis with diuretic induced metabolic alkalosis. The latter is now the dominant acid base disturbance.

Step 6: Examine serum potassium concentration

Hypokalemia

Is the hypokalemia due to a cell shift?

In the absence of physical and historical evidence of gastrointestinal or renal potassium (K) losses, either a redistribution of K at the cellular level or laboratory error will account for a low serum K. The regulation of K distribution between the intracellular and extracellular space is referred to as internal K balance. While the kidney is ultimately responsible for maintenance of total body K, factors that modulate internal balance are important in the disposal of acute K loads. Cell shifts are extremely important, in

that only 2% of total body potassium is located in the extracellular fluid. A large potassium meal could potentially double extracellular K, were it not for the rapid shift of the potassium load into cells. The kidney cannot excrete potassium rapidly enough in this setting to prevent life-threatening hyperkalemia. Thus, it is important that this excess K be rapidly shifted and stored in cells until the kidney has successfully excreted the K load. The major regulators of K shift into cells are insulin and catecholamines, with a lesser effect mediated by metabolic and respiratory alkalosis.

What is the cause of decreased total body potassium?

In the absence of cellular redistribution, a low serum K can result from inadequate dietary intake, extra-renal losses as in gastrointestinal or skin, or renal losses. It should be emphasized that there are overlaps among these groups. The urinary K concentration serves as a useful guide in discerning between these possibilities. A urine K concentration of less than 20 mEq/L is suggestive of extra-renal losses, whereas a urine concentration of greater than 20 mEq/L suggests renal K losses.

Inadequate dietary intake. Inadequate dietary intake is an unusual cause of hypokalemia. However, if patients go extended lengths of time without potassium ingestion, hypokalemia will develop. Clinical situations associated with extreme K-deficient diets include anorexia nervosa, crash diets, alcoholism, and intestinal malabsorption. Increased renal K excretion owing to magnesium deficiency (which is often present in these clinical situations) may contribute to the observed hypokalemia.

Extra-renal potassium losses. Sweat, with its low concentration of potassium, is an unusual cause of K depletion. However, during physical training sweat losses can become substantial and K depletion may result. Gastrointestinal syndromes are the most common clinical disorders of extra-renal K losses. Diarrhea truly leads to fecal K wastage and is associated with a normal anion gap acidosis. Although usually associated with a low urinary K concentration, the acidosis per se can lead to some degree of renal K wasting through increased distal delivery of sodium. As discussed below, the acidosis will result in K redistribution out of cells, leading to a degree of hypokalemia that is not as severe as the degree of K depletion.

Renal potassium losses. Potassium is freely filtered by the glomerulus but is extensively reabsorbed by the proximal tubule and loop of Henle, so that approximately 10% of the filtered load reaches the distal nephron. The distal nephron secretes K into the tubular fluid, which will be excreted. Under most physiologic and pathologic conditions, K delivery to the distal nephron remains small and does not vary, but rather the rate of secretion by the distal nephron varies. Thus, the rate of K secretion in the distal nephron will determine the rate of K excretion. Two of the most important

physiologic determinants of renal K excretion are mineralocorticoid secretion and distal sodium delivery.

Aldosterone is a major determinant of K secretion. Aldosterone-induced stimulation of sodium reabsorption in the collecting tubule makes the luminal potential more negative, which stimulates K secretion. In addition, mineralocorticoids directly stimulate K secretion in the distal nephron. Increased distal delivery of Na stimulates distal Na absorption, which makes the luminal potential more negative and thus increases K secretion. In addition, increased luminal flow rate lowers luminal K concentration, which secondarily stimulates K secretion.

The dependence of K secretion on distal delivery and aldosterone levels helps to make K excretion independent of volume status. When patients are volume overloaded, distal delivery is increased but aldosterone is suppressed. When patients are volume depleted, aldosterone is increased (secondary hyperaldosteronism), but distal delivery is decreased. In both of the above states K homeostasis is maintained. Disruption of this balance explains many of the renal forms of hypokalemia. The approach to the patient with hypokalemia is given in Fig. 2.

Primary mineralocorticoid excess

In primary mineralocorticoid excess, mineralocorticoid levels are increased. The increase in mineralocorticoid is referred to as primary because it is not in response to a change in volume status or a result of hyperkalemia. An example of this would be an aldosterone-secreting tumor. Increased

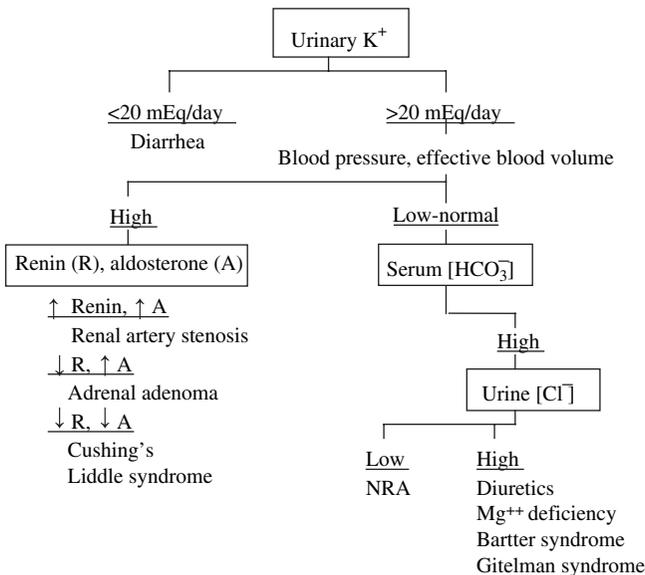


Fig. 2. Approach to the hypokalemic patient. NRA, non-reabsorbable anion.

mineralocorticoid activity causes renal Na^+ retention, which leads to volume expansion, which then leads to increased distal delivery. The net result is increased mineralocorticoid activity and increased distal delivery. The combination of these causes renal K^+ loss and hypokalemia. An increase in mineralocorticoids in the absence of volume contraction leads to a high incidence of hypertension, but edema is unusual. A so-called “escape” occurs before sufficient salt is retained for edema formation.

Primary increase in distal delivery

A primary increase in distal delivery of Na^+ , as would be seen with a diuretic, leads to an increase in urinary Na^+ excretion and volume depletion. This leads to secondary increases in aldosterone secretion. The combination of increased mineralocorticoid activity and increased distal delivery again leads to renal K^+ loss and hypokalemia. This group of disorders is different from the previous group in that elevated aldosterone levels are appropriate for the mildly decreased extracellular fluid volume.

The most common cause of renal K wasting is diuretic ingestion. As is obvious from the above discussion, any diuretic which acts proximal to the cortical collecting tubule will increase renal K excretion. This includes diuretics that act in the proximal tubule, (such as acetazolamide), diuretics that act in the loop of Henle (such as furosemide and ethacrynic acid), and diuretics that work in the early distal tubule (such as the thiazides). Osmotic diuresis will also lead to K wasting by this mechanism. Osmotic diuresis occurs in poorly controlled diabetes mellitus when serum glucose rises to higher levels than the proximal tubule can absorb. In addition, osmotic diuretics are used therapeutically in some conditions.

Bartter syndrome is a rare condition in which there appears to be a primary defect in the loop of Henle salt absorption. This leads to chronic increases in distal delivery and a chronic state of mild volume contraction. Patients are hypokalemic, with very high renin and aldosterone levels.

In certain conditions, Na is delivered distally with a nonreabsorbable anion. This will increase the lumen negative potential difference and lead to K wasting. All penicillins are nonreabsorbable anions, but only a few are given in sufficient quantities to lead to significant K wasting; carbenicillin is an example of one of these. Ketoacids will act as nonreabsorbable anions in patients with ketoacidosis because of diabetes, alcoholism, or starvation. Bicarbonate can function as a nonreabsorbable anion if it is delivered to the distal nephron in greater amounts than can be reabsorbed proximally. This occurs in active vomiting, proximal renal tubular acidosis, and with acetazolamide administration.

Hyperkalemia

Like the hypokalemic disorders, a high serum K can occur in the setting of normal or altered body stores of K. The body has a marked ability to

protect against hyperkalemia. This includes regulatory mechanisms that will excrete excess K quickly and mechanisms that will redistribute excess K into cells until it is excreted. All causes of hyperkalemia, therefore, involve abnormalities in these mechanisms. The causes of hyperkalemia are listed in **Box 2**.

Does the patient have pseudohyperkalemia?

In approaching a patient with a high measured serum K concentration, it is important to remember that not all of these patients have “true hyperkalemia.” Because cell K concentrations are large and plasma K concentrations are small, small leaks of K out of blood cells can have large effects on measured serum K. Normally, when blood is allowed to clot before centrifugation, enough K is released from platelets to raise serum K by approximately 0.5 mEq/L. This is accounted for within normal limits. However, excessive errors can occur in the presence of marked thrombocytosis, marked leukocytosis, or hemolysis on obtaining blood samples. These conditions are referred to as “pseudohyperkalemia.”

Is the hyperkalemia the result of a cellular shift?

Cellular redistribution is a more important cause of hyperkalemia than hypokalemia. One should realize that as little as a 2% shift of intracellular K to the extracellular fluid will result in a serum K of 8 mEq/L. Metabolic acidosis promotes K exit from cells dependent upon the type of acid present. Mineral acidosis (NH₄Cl or HCl), by virtue of the relative impermeability of the chloride anion, results in the greatest efflux of K from cells, while organic acidosis (ie, lactic, β -hydroxybutyric, or methylmalonic acid) result in no significant efflux of K. Acute respiratory acidosis also results in a small shift of K out of cells.

Box 2. Causes of hyperkalemia

- Pseudohyperkalemia
- Cellular redistribution
 - Mineral acidosis
 - Cell shrinkage (hypertonicity)
 - Deficiency of insulin
 - β -Blockers
 - Hyperkalemic periodic paralysis
 - Cell injury
- Excess intake (very rare)
- Decreased renal excretion
 - Decreased distal delivery of Na (oliguric renal failure)
 - Mineralocorticoid deficiency
 - Defect of cortical collecting tubule

Beta-adrenergic blocking agents can interfere with the disposal of acute K loads. Other drugs that can result in hyperkalemia include the depolarizing muscle relaxant succinylcholine and severe digitalis poisoning. Hyperkalemic periodic paralysis is a rare autosomal dominant disorder characterized by repeated bouts of paralysis associated with hyperkalemia.

As 98% of body potassium is located within cells, cell death can result in substantial endogenous loads of K. Muscle breakdown from crush injury or rhabdomyolysis can be associated with a substantial increase in serum K concentration. Cell death as seen in tumor lysis syndromes can also be as source of substantial K loads. These syndromes are often associated with compromised renal function.

Although redistribution of K can result in hyperkalemia, the rise in K is generally mild and nonsustained. Prolonged and severe hyperkalemia implies the presence of concomitant decreases in renal K excretion. After excluding pseudohyperkalemia and a cell shift, one has to consider a disorder in renal potassium excretion.

Why does the patient have a disturbance in renal potassium excretion?

Decreased renal excretion of K can be caused by one or more of three abnormalities: decreased distal delivery of Na, mineralocorticoid deficiency, and abnormal cortical collecting tubule function.

Decreased distal delivery of sodium. As discussed previously, most of filtered K is reabsorbed before the distal tubule. K excretion is then determined by the rate at which K is secreted in the distal nephron. Acute decreases in GFR, as occur in acute renal failure, would therefore not be expected to have a marked effect on K excretion. Acute decreases in GFR may, however, lead to marked decreases in distal delivery of salt and water, which may secondarily decrease distal K secretion. Thus, when acute renal failure is oliguric, hyperkalemia is a frequent problem; when acute renal failure is nonoliguric, distal delivery is usually sufficient and hyperkalemia is unusual.

Chronic renal failure is more complicated than acute renal failure. In addition to the decreased GFR and secondary decrease in distal delivery, there is nephron dropout and less collecting tubule mass to secrete K. However, this is counterbalanced by a K adaptation, in which the remaining nephrons develop an increased ability to excrete K. In addition, these patients possess two other defenses against hyperkalemia. First, in response to a K load they will redistribute the K into cells faster than normal people. Second, they have a markedly increased rate of K excretion in their stool. Thus, although patients with chronic renal failure do not excrete a K load as fast as normal people, hyperkalemia is unusual until chronic renal failure has progressed to GFRs less than 5 mL per minute. The occurrence of hyperkalemia with a GFR of greater than 10 mL per minute should raise the question of decreased mineralocorticoid activity or a specific lesion of the cortical collecting tubule.

Decreased mineralocorticoid activity. Aldosterone deficiency can occur alone or in combination with decreased cortisol levels. Addison's disease is the deficiency of aldosterone and cortisol because of destruction of the adrenal glands. Certain enzyme defects can result in either isolated deficiency of aldosterone or adrenogenital syndromes associated with decreased mineralocorticoid activity. Heparin administration is associated with decreased adrenal secretion of aldosterone.

Angiotensin converting enzyme inhibitors will lead to hyperkalemia by decreasing angiotensin II levels, a critical mediator of aldosterone secretion. Renin levels are high and aldosterone levels are low in all of these conditions. The syndrome of hyporeninemic hypoaldosteronism accounts for the majority of unexplained hyperkalemia in patients where the GFR and K intake would not be expected to result in hyperkalemia. Diabetic nephropathy and interstitial renal disease are the most common clinical entities associated with this syndrome. Other causes of renal disease associated with hyporeninemic hypoaldosteronism include analgesic nephropathy, urinary tract obstruction, sickle cell disease, systemic lupus erythematosus, and amyloidosis. Nonsteroidal anti-inflammatory drugs are associated with decreased renin secretion. Additionally, these agents can cause hyperkalemia by decreasing GFR and reducing distal delivery of sodium. Cyclosporine administration is associated with the development of hyperkalemia in renal transplant patients. Although cyclosporine has a direct effect on the renal tubule, many patients taking this drug have low renin and aldosterone levels. These patients additionally may have a primary tubular defect at the level of the tubule independent of cyclosporine. Beta receptor blockade will also result in a hyporeninemic state.

Distal tubular defect. Certain interstitial renal diseases can affect the distal nephron specifically and lead to hyperkalemia in the presence of mild decreases in GFR and normal aldosterone levels. Many of these diseases are the same ones that can cause hyporeninemic hypoaldosteronism, and frequently the impaired renin release and defect in tubular secretion coexist. Examples include renal transplant patients, systemic lupus erythematosus, amyloidosis, urinary obstruction, and sickle cell disease.

The K sparing diuretics impair the ability of the cortical collecting tubule to secrete K. Amiloride and triamterene inhibit Na reabsorption, which abolishes the lumen negative potential and therefore inhibits K secretion. Other compounds that block the Na channel and that have been clinically associated with hyperkalemia include trimethoprim and pentamidine. Spirolactone competes with aldosterone and thus blocks the mineralocorticoid effect. Although the potassium sparing diuretics are useful in patients with a hypokalemic tendency, they weaken an important defense mechanism against hyperkalemia. They should therefore be avoided in patients with other defects that predispose to hyperkalemia, such as diabetes mellitus and chronic renal insufficiency.

Further readings

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