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565

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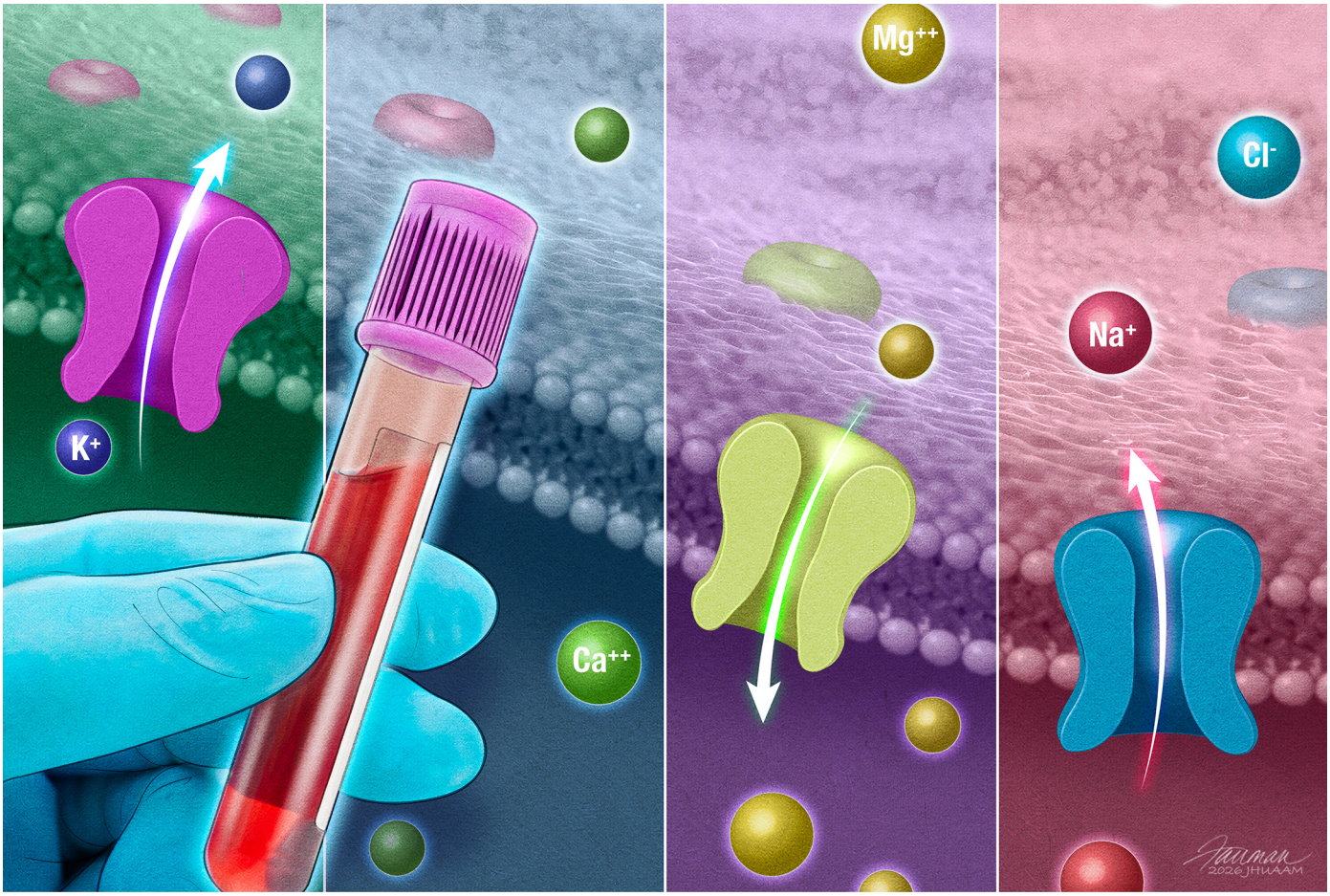
Acid-Base and Electrolyte Disorders



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Acid-Base and Electrolyte Disorders

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Foreword

Whether it was during my medical training, leading group Knowledge Self-Assessments, or treating patients, few topics were met with a greater abundance of blank stares or groans than acid-base disorders. Unless you treat critically ill patients on a regular basis, the process of ordering the proper testing, applying the appropriate equations, reaching the correct differential diagnosis, and treating the causes of these disorders feels overwhelming to many.

While the concepts can seem complicated, they are often necessary for the management of patients even in the outpatient setting. As I reviewed this monograph, I thought of my 90-year-old patient who recently was hospitalized after developing hyponatremia. She lives in the community with the support of family and is generally very active. She has a long-standing history of hypertension, and it was no longer being controlled with amlodipine, ramipril, and hydrochlorothiazide. I added spironolactone to her medication regimen, which achieved control of her blood pressure. However, on blood work a week later, her sodium level was less than 130 mEq/L and she was experiencing significant fatigue, so she was admitted to the hospital for a few days for intravenous fluid therapy. She is now back home and off diuretics, has a normal sodium level, and is feeling much better.

Sections One and Two of this monograph review electrolyte disorders of sodium and potassium. They discuss the importance of normal electrolyte levels for cellular function, and the clinical manifestations of and evaluations and treatments for abnormalities. Section Three explores acid-base disorders, with a focus on how family physicians can correctly interpret laboratory values to determine which acid-base disturbance is affecting their patient. Section Four reviews calcium disorders and includes the clinical presentation, diagnosis, and treatment of hypocalcemia and hypercalcemia.

The authors have done a fabulous job of explaining the complicated topics of acid-base and electrolyte disorders in ways that make them easy to understand, even if you do not deal with them every day. If you are not sure about the next steps in the management of your patient with these complex disorders, the many algorithms in this monograph simplify evaluation and treatment.

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Editorial Mission

The mission of *FP Essentials* is to provide practicing family physicians, family medicine residents, and other clinicians and trainees with high-quality, cost-effective educational content that emphasizes new advances in clinical practice.

CME Objectives

1. Apply learned concepts to the diagnosis, screening, and treatment of clinical conditions managed by family physicians.
2. Identify the strengths and weaknesses of diagnostic and treatment strategies.
3. Determine the most effective treatment strategy based on best available evidence in the literature.
4. Differentiate and implement practice recommendations from evidence-based guidelines and consensus guidelines rather than personal opinion.

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Key Practice Recommendations

These key learning points summarize the consensus- and evidence-based recommendations included in this edition. The sources listed here for each statement recommend that physicians perform or implement these actions directly in a clinical setting. A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the Strength of Recommendation Taxonomy (SORT) evidence rating system, go to https://www.aafp.org/afp/2004/0201/p548.

1. For patients with chronic hyponatremia, correct the sodium level at a rate of no more than 8 to 10 mEq/L (8-10 mmol/L) in 24 hours and 18 mEq/L (18 mmol/L) in 48 hours to prevent osmotic demyelination syndrome.
Evidence rating: SORT C
Sources: Section One, references 1 and 4

2. For patients with hyperkalemia who take renin-angiotensin-aldosterone system inhibitor medications (eg, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists) for mortality benefits (eg, heart failure), consider addition of a diuretic or potassium binder to usual treatment.
Evidence rating: SORT A
Sources: Section Two, references 3, 11, 29, and 35

3. For all patients with a suspected acid-base disorder, calculate an initial anion gap, as use of only the serum bicarbonate or pH could result in missing a serious diagnosis.
Evidence rating: SORT C
Source: Section Three, reference 14

4. For patients with asymptomatic primary hyperparathyroidism who do not meet surgical criteria, consider monitoring due to low risk of progression and minimal benefit from parathyroidectomy. Monitoring should include serum calcium and creatinine measurement annually and bone mineral density assessment every 1 to 2 years.
Evidence rating: SORT B
Source: Section Four, references 27 and 29

CME Quiz Questions

FP Essentials subscribers may complete the posttest at https://www.aafp.org/assessment/listing/9 to earn 4 AAFP Prescribed CME credits. Credit may be claimed for 2 years from the date of this edition. Each question has only one correct answer. An explanation for each correct answer is provided at the end.

1. You are evaluating a 57-year-old patient with multiple medical conditions for admission to the intensive care unit. His serum sodium level is 162 mEq/L (162 mmol/L) and urine osmolality is 500 mOsm/kg (500 mmol/kg). Which one of the following is the most likely cause of hypernatremia in this patient?

☐ A. Burns.
☐ B. Inadequate water intake.
☐ C. Loop diuretic.
☐ D. Total parenteral nutrition.

2. You see an 54-year-old patient in the emergency department for fatigue and confusion. She appears to be euvolemic. Laboratory tests show a serum sodium of 126 mEq/L (126 mmol/L) and plasma osmolality of 274 mOsm/kg (274 mmol/kg). Urine osmolality is 85 mOsm/kg (85 mmol/kg). Which one of the following conditions is the most likely cause of hyponatremia in this patient?

☐ A. Acute kidney injury.
☐ B. Primary polydipsia.
☐ C. Pseudohyponatremia.
☐ D. Renal sodium loss.

3. You are reviewing the laboratory test results of a 71-year-old patient who is establishing care. You note an elevated serum sodium level of 150 mEq/L (150 mmol/L). A chart review shows that his sodium has been at this level for the past 2 years. Which one of the following outcomes is associated with acute and chronic hypernatremia?

☐ A. Seizures.
☐ B. Coma.
☐ C. Death.
☐ D. Rhabdomyolysis.

4. A 73-year-old patient is brought to the emergency department with sudden onset of lethargy and confusion. He has a history of lung cancer. His blood pressure is 100/60 mm Hg, and he has a normal pulse. On physical examination, he is minimally responsive and his mucous membranes are dry. A bolus of 1 L of normal saline is started and administered over 2 hours. Ten minutes later, his serum sodium level is 110 mEq/L (110 mmol/L), creatinine level is 1.9 mg/dL (168 µmol/L), and glucose level is 65 mg/dL (3.61 mmol/L). He is still minimally responsive. Which one of the following is the most appropriate next step?

☐ A. Stop normal saline and begin closely monitored fluid restriction.
☐ B. Change the fluid to lactated Ringer solution.
☐ C. Administer hypertonic (3%) saline.
☐ D. Administer a vasopressin receptor agonist.

5. You are treating a 69-year-old patient with pneumonia on the medical floor of the hospital. He has a history of hypertension and takes hydrochlorothiazide. On admission, his potassium level was 2.9 mEq/L (2.9 mmol/L). Over the past 24 hours, he has received 160 mEq (160 mmol) of potassium without significant improvement in his potassium level. If deficient, replacement of which one of the following will make it easier to correct the potassium level?

☐ A. Calcium.
☐ B. Chloride.
☐ C. Magnesium.
☐ D. Sodium.

6. A 45-year-old patient with acute-on-chronic kidney failure is brought to the emergency department. Her serum potassium level is 6.6 mEq/L (6.6 mmol/L). An electrocardiogram shows peaked T waves. Which one of the following medications should be the initial treatment?

☐ A. Inhaled albuterol.
☐ B. Insulin.
☐ C. Intravenous calcium gluconate.
☐ D. Potassium binder.

7. A 54-year-old patient who weighs 80 kg (176 lb) is admitted to the hospital due to dehydration from an acute gastrointestinal illness. His serum potassium level is 2.5 mEq/L (2.5 mmol/L). If the goal potassium level is 4.0 mEq/L (4.0 mmol/L), which one of the following is the approximate total body potassium deficit?

☐ A. 300 mEq (300 mmol).
☐ B. 375 mEq (375 mmol).
☐ C. 500 mEq (500 mmol).
☐ D. 620 mEq (620 mmol).

8. After routine laboratory testing, a 76-year-old patient is found to have a serum potassium level of 5.9 mEq/L (5.9 mmol/L). He is asymptomatic, and 2 weeks ago his potassium level was normal.

He reports that he is taking no new medications. You suspect pseudohyperkalemia. Which one of the following findings is a possible cause of this condition?

☐ A. Hypoglycemia due to having laboratory testing after his morning insulin.
☐ B. Hypomagnesemia due to inadequate dietary intake.
☐ C. Leukocytosis due to chronic lymphocytic leukemia.
☐ D. Thrombocytopenia due to iron deficiency.

9. You are evaluating a patient with a suspected acid-base disorder in the emergency department. Results of an arterial blood gas measurement show a low pH and elevated bicarbonate and carbon dioxide levels. Which one of the following primary acid-base disorders is the likely diagnosis?

☐ A. Metabolic acidosis.
☐ B. Metabolic alkalosis.
☐ C. Respiratory acidosis.
☐ D. Respiratory alkalosis.

10. You are assessing a critically ill patient with a blood pressure of 178/108 mm Hg in the emergency department. Arterial blood gas measurement shows a pH of 7.59, bicarbonate level of 36 mEq/L (36 mmol/L), Pco_2 of 49 mm Hg (6.52 kPa), and urine chloride level of 30 mEq/L (30 mmol/L). Which one of the following is the most likely cause of metabolic alkalosis in this patient?

☐ A. Vomiting and diarrhea.
☐ B. Cushing syndrome.
☐ C. Diuretic use.
☐ D. Guillain-Barré syndrome.

11. A 36-year-old patient is admitted with fatigue, headache, and acute mental status changes. Initial laboratory test results reveal a high anion gap metabolic acidosis. Which one of the following is a common cause of high anion gap metabolic acidosis?

☐ A. Diabetic ketoacidosis.
☐ B. Stroke.
☐ C. Sedative use.
☐ D. Obesity hypoventilation syndrome.

12. Which one of the following conditions is associated with chronic respiratory alkalosis?

☐ A. Chronic obstructive pulmonary disease.
☐ B. Pregnancy.
☐ C. Obstructive sleep apnea.
☐ D. Amyotrophic lateral sclerosis.

13. Results of routine laboratory tests and monitoring show that your otherwise healthy 35-year-old patient has an increased serum calcium level of 11.9 mg/dL (2.98 mmol/L). You obtain a parathyroid hormone level, and it is mildly increased at 72 pg/mL (72 ng/L). Which one of the following is the most likely cause of his hypercalcemia?

☐ A. Bone metastases.
☐ B. Hyperthyroidism.
☐ C. Primary hyperparathyroidism.
☐ D. Sarcoidosis.

14. You see a 50-year-old patient with recently diagnosed hypercalcemia. Her serum calcium is 12.4 mg/dL (3.1 mmol/L). Laboratory test results show low parathyroid hormone (8 pg/mL [8 ng/L]), low parathyroid hormone–related peptide (0.8 pmol/L), normal 1,25-dihydroxyvitamin D (34 pg/mL [81.6 pmol/L]), and normal 25-dihydroxyvitamin D (42 ng/mL [104.8 nmol/L]). Urine calcium levels are 150 mg/day. Which one of the following is the most likely cause of her hypercalcemia?

☐ A. Familial hypocalciuric hypercalcemia.
☐ B. Humoral hypercalcemia of malignancy.
☐ C. Hyperthyroidism.
☐ D. Primary hyperparathyroidism.

15. A 54-year-old patient presents with muscle cramps, fatigue, and perioral tingling for the past few days. He is seeing a nephrologist for stage 4 chronic kidney disease due to hypertension. On physical examination, he has involuntary contraction of the ipsilateral facial muscles when you tap on the facial nerve anterior to the ear. Based on this finding, which one of the following is the most likely electrolyte abnormality in this patient?

☐ A. Hypocalcemia.
☐ B. Hypercalcemia.
☐ C. Hyperkalemia.
☐ D. Hypermagnesemia.

16. A 43-year-old patient undergoes a thyroidectomy for localized thyroid cancer. On routine postoperative monitoring, her serum calcium level is 7.5 mg/dL (1.88 mmol/L). Which one of the following statements about hypocalcemia in postsurgical patients is correct?

☐ A. Most patients who undergo neck surgery develop hypocalcemia.
☐ B. Postsurgical hypocalcemia is usually lifelong.
☐ C. The serum parathyroid hormone level may be normal or decreased.
☐ D. Serum vitamin D levels are typically suppressed.

SECTION ONE

Sodium Disorders

Sodium disorders are commonly encountered in clinical practice and are frequently misunderstood. Abnormal serum sodium levels are due to an imbalance in free water. Hyponatremia and hypernatremia can be asymptomatic if mild and chronic; however, acute and severe changes in sodium levels may cause substantial symptoms. In acute mild hyponatremia, symptoms can include confusion, vomiting, and weakness. In severe cases, seizures can occur. Determining the patient's volume status helps to determine the underlying etiology and appropriate treatment strategy. Euvolemic hyponatremia is the most common presentation due to the prevalence of syndrome of inappropriate antidiuretic hormone. Depending on severity, hyponatremia can be managed in the outpatient or inpatient setting. Management is directed at treating underlying causes and relieving severe symptoms while decreasing the risk of serious adverse effects from treatment. In patients with chronic hyponatremia without severe symptoms, rapid correction of serum sodium should be avoided to minimize the risk of osmotic demyelination syndrome. Hypernatremia is caused by a loss of free water, inadequate water intake, or salt overload. Patients with acute hypernatremia may present with fatigue, signs of dehydration, and weakness. Symptomatic acute and severe hypernatremia require inpatient admission and management of free water deficit with intravenous hypotonic fluids.

Olson A. Acid-Base and Electrolyte Disorders: Sodium Disorders. FP Essent. *2026;565:7-13.*

Case 1. LT is a 63-year-old woman admitted to the hospital for acute shortness of breath. During the physical examination, you note bilateral inspiratory crackles at the lung bases and lower extremity edema. A chest radiograph shows pulmonary congestion. You receive a call from her nurse that the serum sodium is low at 125 mEq/L (125 mmol/L).

Physiology

Sodium disorders are commonly encountered in clinical practice and are frequently misunderstood. They differ from other electrolyte disorders in that abnormal serum sodium levels are not due to a sodium imbalance but to an imbalance of free water. Osmolality and tonicity are important concepts for understanding fluid balance, and sodium is the major contributor to both.

Plasma osmolality is a measure of solute-water balance and is expressed in milliosmoles per kilogram of plasma water (ie, mOsm/kg). Tonicity is the concentration of functional osmoles (ie, osmoles that do not freely cross cell membranes), but it is not easily measured, so osmolality is used as a surrogate measure.

Osmolality can be estimated by calculation or measured directly. A difference of more than 10 mOsm/kg (10 mmol/kg) between estimated and measured values indicates the presence of unmeasured osmoles.[1] Normal serum sodium ranges from 135 to 145 mEq/L (135-145 mmol/L).

Tonicity is primarily regulated by vasopressin (ie, antidiuretic hormone), which is produced in the hypothalamus, stored in the pituitary gland, and secreted when hypertonicity triggers hypothalamic osmoreceptors. Vasopressin release is also stimulated by decreased perfusion of carotid baroreceptors due to hypotension, hypovolemia, or conditions with low effective arterial circulation (eg, heart failure, cirrhosis). Vasopressin increases renal reabsorption of water in the collecting ducts, thereby concentrating urine and diluting plasma. Factors such as pain, nausea, and certain malignancies can stimulate vasopressin release, leading to syndrome of inappropriate antidiuretic hormone (SIADH).[1]

Urine osmolality is an indirect marker of vasopressin activity. The range of urine osmolality achievable with normal renal function is 50 to 1,200 mOsm/kg (50-1,200 mmol/kg).[1] Therefore, unless free water intake exceeds maximum urine free water volume, an average adult is able to avoid becoming hyponatremic by excreting more than 10 L of urine per day. Thirst is important for maintaining tonicity and fluid volume when vasopressin is inadequate, such as in hypotension and severe volume depletion.

Hyponatremia

Hyponatremia occurs in 15% to 30% of hospitalized patients and 5% of ambulatory patients.[2,3] It is defined as a serum sodium level less than 135 mEq/L.[1] Acute

hyponatremia is defined as occurring within 48 hours, and chronic hyponatremia as lasting 48 hours or longer.[4] Acute hyponatremia is associated with severe morbidity and mortality, and rapid overcorrection of chronic hyponatremia can lead to serious, long-term neurologic outcomes.[5-7]

Risk factors for hyponatremia include conditions associated with hypovolemia, hypervolemia, and SIADH, which occur with cirrhosis, glucocorticoid deficiency, heart failure, hypothyroidism, and kidney failure. The kidneys require solute to excrete free water, thus those with low solute intake (eg, patients 65 years and older, those with alcohol use disorder) are at increased risk of hyponatremia.[3,7]

Medications associated with hyponatremia include nonsteroidal anti-inflammatory drugs, opioids, proton pump inhibitors, selective serotonin reuptake inhibitors, thiazide diuretics, tricyclic antidepressants, and some antipsychotics and anticonvulsants. Use of intravenous hypotonic fluids also increases risk. The American Academy of Pediatrics recommends administration of isotonic maintenance fluids rather than hypotonic solutions in patients ages 28 days to 18 years to decrease the risk of hyponatremia, with a number needed to treat of 8.[3,8]

CLINICAL PRESENTATION

The clinical presentation of hyponatremia varies with rate of onset and severity. When it develops slowly, the body compensates by decreasing intracellular solutes. Patients with chronic hyponatremia often lack overt symptoms. However, even patients with mild chronic cases may have subtle impairments on neurocognitive testing.[9] Chronic hyponatremia is associated with unstable gait and falls.[10]

If hyponatremia develops rapidly, compensation may be inadequate, leading to cerebral edema and brain herniation due to excess water entering cells. When present, the most common signs and symptoms of acute mild hyponatremia are confusion, vomiting, and weakness.[7] Moderate hyponatremia presents similarly but with a higher likelihood of symptoms. With severe hyponatremia, seizures and Glasgow Coma Scale scores of less than 12 can occur.[7]

DIAGNOSIS

A history should be taken and a physical examination performed, with particular attention given to the patient's volume status and medication list[12,13] (Figure 1[4,11]). Laboratory tests should include blood urea nitrogen (BUN), creatinine, serum electrolytes, serum glucose, serum and urine osmolality, urine sodium, and potentially serum cortisol level, liver function tests, and thyrotropin. Initial classification of hyponatremia is based on serum osmolality.

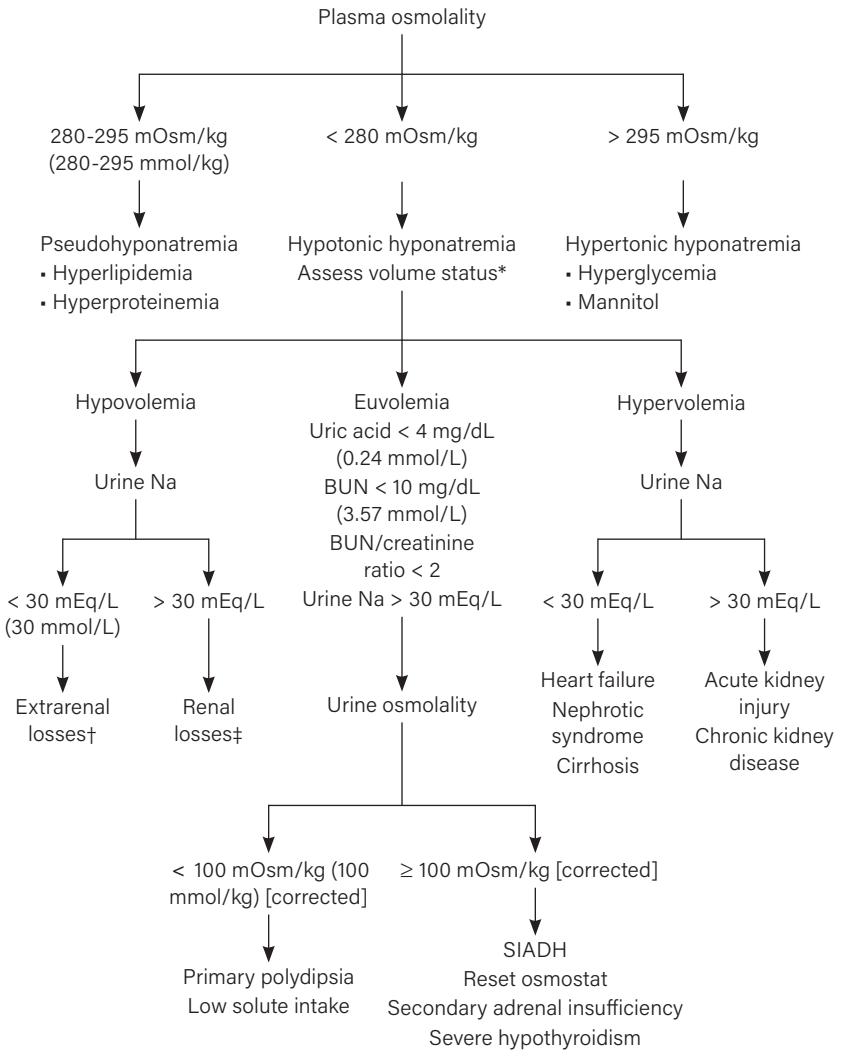
Pseudohyponatremia. The laboratory artifact of a low serum sodium level associated with a normal serum osmolality occurs when hyperlipidemia or hyperproteinemia is present. This is most commonly related to hypertriglyceridemia, but also can occur with obstructive jaundice and myeloma.[12] On certain analyzers, this leads to a decreased sodium measurement while the clinically relevant concentration of sodium per liter of serum water is normal. Measurement of sodium by direct potentiometry (used in point-of-care analyzers) is not subject to this limitation.

Hypertonic hyponatremia. Hyperglycemia and mannitol infusion can cause osmotic shifts, pulling water out of cells into the plasma and lowering the serum sodium level. In hyperglycemia, the corrected sodium can be estimated using the following equation: sodium + 2 × [(glucose – 100 mg/dL)/100].[14] If the corrected sodium is abnormal, further evaluation is required.

Hypotonic hyponatremia. Once hyponatremia is determined to be hypotonic, the next step in evaluation is determining volume status. Hypovolemia and hypervolemia are often clinically evident. Urine sodium should be low in response to hypovolemia or low effective blood volume (with heart failure and cirrhosis) as the kidneys attempt to retain sodium and volume.[11] However, urine sodium can be elevated with diuretic use and in patients with chronic kidney disease and impaired sodium reabsorption. With vomiting, urine chloride may be low and is a better marker of volume depletion than urine sodium. While exercise-induced hyponatremia has traditionally been described as hypovolemic, it may be due to excessive hypotonic fluid intake.[15]

Euvolemic hyponatremia is the most common presentation of hypotonic hyponatremia due to the prevalence of SIADH.[2,7] Urine sodium can help determine volume status when it is difficult to determine otherwise. It is usually more than 30 mEq/L (30 mmol/L) in patients with SIADH but may be low in those with a very low-sodium diet.

Clues to hypovolemia include increased BUN, creatinine, BUN-creatinine ratio, and serum uric acid. A fractional excretion of uric acid greater than 12% has the highest sensitivity and specificity of a single test for SIADH, although the sensitivity is only 66% and the specificity is 77%. A fractional excretion of urea greater than 55% has a specificity of 96% for SIADH.[16] If the volume status remains uncertain, a trial of infusion of 0.5 to 1 L of isotonic saline will improve hyponatremia in hypovolemic patients, but is ineffective or may worsen hyponatremia in those with SIADH.[13] Adrenal insufficiency should be excluded before diagnosing SIADH. Cortisol suppresses vasopressin, and low-cortisol states can cause euvolemic hyponatremia.



BUN = blood urea nitrogen; Na = sodium; SIADH = syndrome of inappropriate antidiuretic hormone.

*—If volume status is unclear, urine Na can differentiate. Hypovolemia is likely with urine Na < 20 mEq/L (20 mmol/L), whereas euvolemia is likely with urine Na > 30 mEq/L. Diuretic use can result in variable urine Na. [corrected]

†—Extrarenal losses include acute blood loss, diarrhea, skin loss (eg, extreme exercise, burns), and third spacing (eg, pancreatitis, small bowel obstruction).

‡—Renal losses include Bartter syndrome, cerebral salt wasting, congenital adrenal hyperplasia, Gitelman syndrome, primary adrenal insufficiency, and osmotic diuresis.

Figure 1. Differential diagnosis of hyponatremia.

Information from references 4 and 11.

Urine osmolality can help to distinguish SIADH and primary polydipsia. In primary polydipsia, excessive free water intake exceeds urinary diluting capacity. Urine osmolality is low in primary polydipsia (less than 100 mOsm/kg [100 mmol/kg]) and elevated in SIADH (greater than or equal to 100 mOsm/kg]). [corrected] Patients with a reset osmostat have a lower serum sodium that suppresses vasopressin, so that serum sodium does not decrease lower than approximately 125 mEq/L.[4,13]

TREATMENT

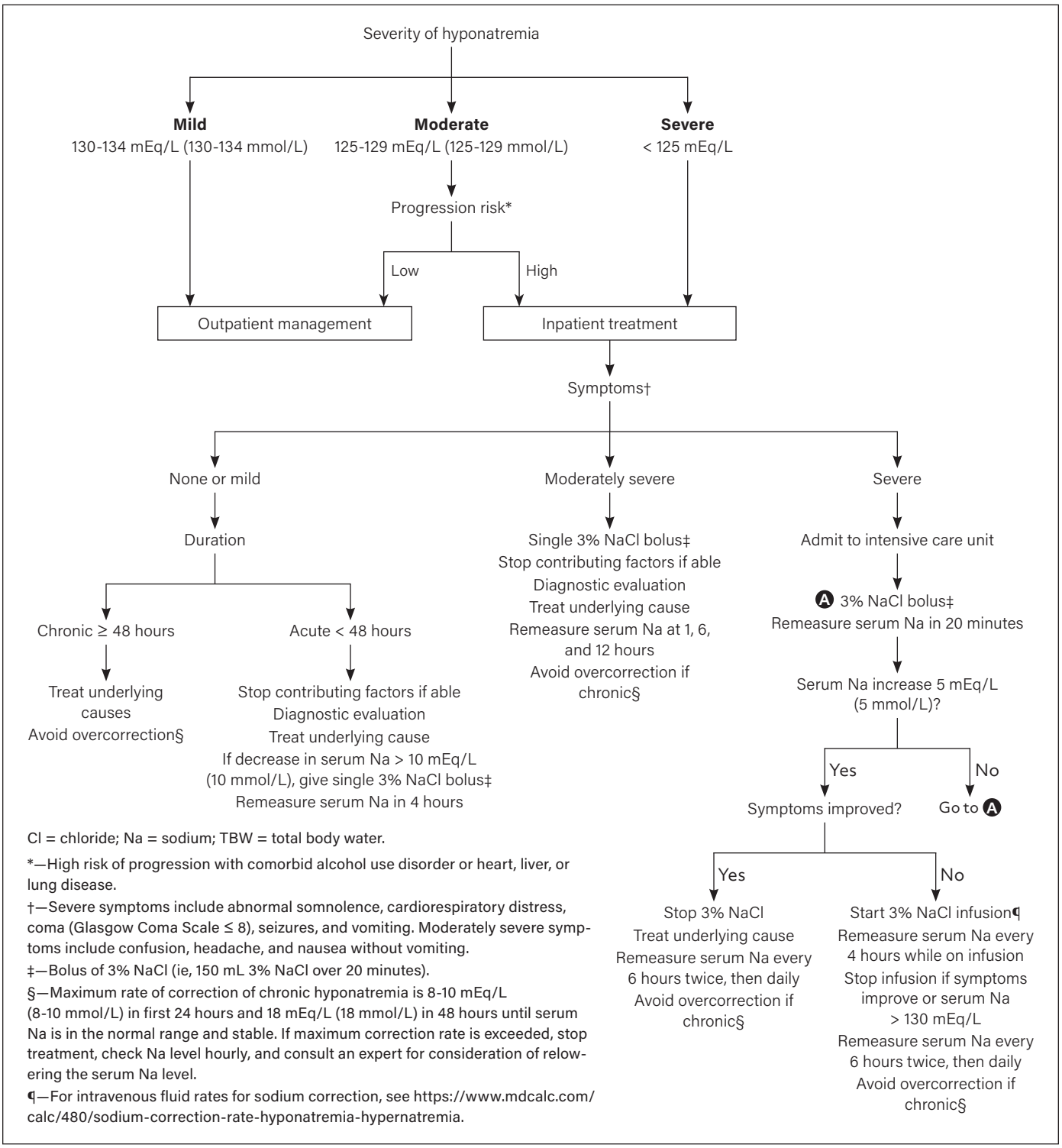
Treatment of hyponatremia is based on the etiology, duration, and severity of symptoms (Figure 2[4,11]). Acute or severely symptomatic hyponatremia is a medical emergency and requires rapid correction of the sodium level with hypertonic (3%) saline.[11] Chronic hyponatremia requires a slower correction rate after severe symptoms have resolved.

Patients with a serum sodium level less than 120 mEq/L (120 mmol/L) are at risk of osmotic demyelination syndrome due to cerebral adaptation of osmolality. With a rapid increase in sodium, fluid can shift from the intracellular space to plasma, causing cell shrinkage and potentially devastating neurologic dysfunction.[13]

Treatment guidelines for chronic hyponatremia, which are based on observational evidence and expert opinion, recommend a rate of increase of no more than 8 to 10 mEq/L (8-10 mmol/L) in 24 hours and 18 mEq/L (18 mmol/L) in 48 hours.[1,4] Recent evidence suggests that a more rapid rate of correction is associated with lower all-cause mortality without increasing the rate of osmotic demyelination syndrome, but additional studies are needed.[6,17] Risk factors for developing this syndrome are an initial sodium level of less than 105 mEq/L (105 mmol/L), alcohol use disorder, cirrhosis, hypokalemia on admission, and malnutrition.[6,11]

Chronic hyponatremia often corrects with treatment of the underlying cause. Contributing medications should be discontinued, volume status corrected, and potassium replaced.

For SIADH related to a nonmodifiable cause (eg, lung cancer), fluid restriction is the first-line treatment. Daily fluid intake should be 500 mL below total daily urine output.[13] Patients should be advised to drink only when eating or thirsty.



Cl = chloride; Na = sodium; TBW = total body water.

*—High risk of progression with comorbid alcohol use disorder or heart, liver, or lung disease.

†—Severe symptoms include abnormal somnolence, cardiorespiratory distress, coma (Glasgow Coma Scale ≤ 8), seizures, and vomiting. Moderately severe symptoms include confusion, headache, and nausea without vomiting.

‡—Bolus of 3% NaCl (ie, 150 mL 3% NaCl over 20 minutes).

§—Maximum rate of correction of chronic hyponatremia is 8-10 mEq/L (8-10 mmol/L) in first 24 hours and 18 mEq/L (18 mmol/L) in 48 hours until serum Na is in the normal range and stable. If maximum correction rate is exceeded, stop treatment, check Na level hourly, and consult an expert for consideration of relowering the serum Na level.

¶—For intravenous fluid rates for sodium correction, see https://www.mdcalc.com/calc/480/sodium-correction-rate-hyponatremia-hypernatremia.

Figure 2. Treatment of hypotonic hyponatremia.

Information from references 4 and 11.

Guidelines on second-line treatments for patients with SIADH vary. European guidelines recommend use of urea or loop diuretics with sodium chloride tablets, and avoiding lithium, demeclocycline, or vasopressin receptor antagonists.[4] US guidelines include demeclocycline and vasopressin receptor antagonists as options.[13] The duration of vasopressin receptor antagonist therapy is generally limited to 30 days due to potential liver toxicity.[1,18] For patients with primary polydipsia and low solute intake, sodium chloride tablets may also be effective.

Hypernatremia

Hypernatremia most often occurs in the inpatient setting, affecting up to 10% of patients in intensive care units.[19] It is defined as a serum sodium level greater than 145 mEq/L. It typically is caused by a lack of free water (due to impaired thirst, limited ability to access water, or increased water loss) or salt overload (Table 1[1,20]).

Most patients, even those with a predisposing condition, will not become hypernatremic if they have adequate water intake. Decreased thirst may be due to hypothalamic lesions or neurocognitive conditions. Very old or young individuals who depend on others for access to free water are at increased risk of hypernatremia.[3] Impaired urinary concentrating ability, which leads to renal free water loss, may result from arginine vasopressin (AVP) disorders, chronic kidney disease, medications (eg, lithium, diuretics, vasopressin receptor antagonists), or osmotic diuresis. Excess salt intake without free water (eg, hypertonic fluid administration, salt poisoning) can also be a cause.

CLINICAL PRESENTATION

Acute hypernatremia can be severe and life-threatening. Symptoms usually do not occur until serum sodium is greater than 158 mEq/L (158 mmol/L).[21] Patients may present with fatigue, signs of dehydration, and weakness, then progress to seizures, rhabdomyolysis, and coma. Severe neurologic sequalae from rapid osmolar shifts of fluid from the intracellular space include cerebral hemorrhage and osmotic demyelination syndrome.[22,23]

Hospital-acquired hypernatremia is associated with a higher risk of inpatient mortality.[24] Chronic hypernatremia is often asymptomatic and discovered on routine laboratory testing. However, it is associated with an increased risk of mortality, cardiovascular events, and infection.[25] Symptoms are usually related to increased thirst with polyuria and polydipsia.

DIAGNOSIS

The presence of hypernatremia indicates hypertonic, hyperosmolar plasma. The underlying etiology is often clear from the patient history, but if uncertainty remains, urine osmolality can help differentiate among causes.

Inadequate fluid intake and extrarenal loss (eg, voluminous diarrhea) are associated with a urine osmolality greater than 600 mOsm/kg (600 mmol/kg).[1,20] Renal losses are usually due to renal concentrating defects. In both AVP deficiency (ie, central diabetes insipidus) and resistance (ie, nephrogenic diabetes insipidus), urine osmolality will usually be less than 300 mOsm/kg (300 mmol/kg). Hypokalemia and hypercalcemia cause transient AVP resistance.[1]

A water deprivation test can be used to differentiate AVP deficiency and resistance. During a period of water deprivation, patients with both AVP deficiency and resistance will continue to have dilute urine. Desmopressin administration will result in an increase in urine osmolality in AVP deficiency but not in complete AVP resistance.[1]

Copeptin is a surrogate marker of vasopressin and is produced from the same prohormone, but is more stable

TABLE 1
Hypernatremia Causes

Mechanism	Causes (examples)
Free water loss, extrarenal*	Burns
	Gastrointestinal loss (nasogastric suction, osmotic diarrhea, vomiting)
	Increased metabolic demand (fever)
	Perspiration (environmental exposure, extreme exercise)
	Pulmonary loss (hyperventilation, tachypnea)
Free water loss, renal†	Arginine vasopressin disorders:
	Deficiency or resistance (urine osmolality < 300 mOsm/kg [300 mmol/kg] water)
	Chronic kidney disease
	Medications: lithium, loop diuretics (isosthenuria), vasopressin receptor antagonists
	Osmotic diuresis (acute tubular necrosis recovery, glucosuria, urea-induced)
Inadequate water intake*	Decreased thirst (patients 65 years and older, hypothalamic lesions, neurocognitive conditions)
	Lack of access to water (altered mental status, intensive care unit patients with inadequate fluid administration, use of restraints)
Salt overload*	Hypertonic fluid administration (concentrated enteral feeds, concentrated infant formula, hypertonic saline, sodium bicarbonate, total parenteral nutrition)

*—Associated with urine osmolality ≥ 600 mOsm/kg (600 mmol/kg) water.

†—Associated with urine osmolality < 600 mOsm/kg water.

Information from references 1 and 20.

and easier to measure. Copeptin levels are low in AVP deficiency and high in AVP resistance.[26]

Measuring urine sodium concentration can also help distinguish between causes. Renal losses with loop diuretics and excess salt intake are associated with a urine sodium greater than 20 mEq/L (20 mmol/L), whereas extrarenal losses, such as diarrhea, often result in a urine sodium less than 20 mEq/L.[20]

TREATMENT

Hypernatremia can be classified by serum sodium concentration as mild (146-150 mEq/L [146-150 mmol/L]), moderate (151-155 mEq/L [151-155 mmol/L]), or severe (greater than 155 mEq/L [155 mmol/L]).[20] The distinction between acute and chronic is important for management, with acute being present for less than 48 hours and chronic being present for 48 hours or more.

Symptomatic hypernatremia should be managed in the hospital due to the likelihood of a serious underlying condition requiring inpatient treatment and monitoring. Patients with severe symptoms or significant clinical instability should be admitted to the intensive care unit. Symptomatic acute hypernatremia should be quickly corrected by calculating the free water deficit and replacing it at the appropriate rate or using a fixed rate of fluid administration, such as 5% dextrose in water at 1.35 mL/kg per hour. Several formulas are available, and one approach is outlined in Table 2.[1,20,27]

Unlike in hyponatremia, rapid correction of hypernatremia is not associated with neurologic complications in adults.[28] Correction rates greater than 0.5 mEq/L (0.5 mmol/L) per hour in children appear safe.[27] However, in neonates, cerebral edema and seizures may occur with correction rates greater than 0.5 mEq/L per hour.[29] There is evidence that a delay in correction for more than 72 hours increases mortality.

The sodium level typically should be corrected to a goal of 145 mEq/L (145 mmol/L) over 48 hours.[30] If a patient is hypovolemic, isotonic fluids may be required in addition to free water. This may be provided as a separate infusion, or the hypotonic fluids may be adjusted (ie, 5% dextrose, changed to half-normal saline, and rate adjusted per calculation).

In asymptomatic patients with normal renal function, treating the underlying cause will resolve hypernatremia in most cases. Patients who received a large sodium load will usually be hypervolemic, so loop diuretics may be given in addition to free water replacement. Patients with AVP deficiency may require desmopressin. Cessation of thiazide diuretics or lithium may improve AVP resistance.

Case 1, continued. The serum osmolality for LT is less than 280 mOsm/kg (280 mmol/kg), urine osmolality is 320 mOsm/kg (320 mmol/kg), and urine sodium is less

TABLE 2
Approach to Severe Hypernatremia Management

1. Fluid resuscitation with isotonic fluid if needed to restore hemodynamic stability
2. Address underlying cause:
   - Arginine vasopressin deficiency: administer desmopressin
   - Arginine vasopressin resistance: stop associated medications
   - Febrile illness: control fever
   - Gastrointestinal losses: symptomatic management, stop losses if able
   - Hypercalcemia: correct
   - Hyperglycemia: administer insulin
   - Hypertonic fluids: stop hypertonic intravenous fluids, correct mixing of infant formula, etc
   - Hypokalemia: replace potassium
3. Calculate free water deficit (L) = TBW* × ([measured serum Na/goal serum Na] – 1)
   - Goal serum Na is 145 mEq/L (145 mmol/L) if acute hypernatremia or no more than a 10 mEq/L (10 mmol/L) decrease per 24 hours if chronic hypernatremia
4. Choose correction fluid
   - For adults and children, use enteral water if able or intravenous 5% dextrose in water
5. Determine rate of fluid administration
   - Desired free water replacement in 24 hours = free water deficit (mL)/24 = mL/hour
   - Account for ongoing losses and adjust
   - Measure serum Na during correction and adjust rate
   - If feasible, measure gastrointestinal or renal free water losses and add to rate

Na = sodium; TBW = total body water.

*—TBW = men and children ≤ 12 years = weight in kg x 0.6; women and elderly men = weight in kg x 0.5; elderly women = weight in kg x 0.45.

Information from references 1, 20, and 27.

than 30 mEq/L, consistent with hypervolemic hypotonic hyponatremia. Laboratory tests show normal kidney and liver function. An echocardiogram reveals decreased cardiac ejection fraction. You treat her for acute decompensated heart failure with an intravenous loop diuretic. The hypervolemia resolves and the sodium level slowly increases to 138 mEq/L (138 mmol/L) before discharge.

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SECTION TWO

Potassium Disorders

A normal serum potassium level of 3.5 to 5.0 mEq/L is maintained via potassium ingestion, excretion, and distribution between intra- and extracellular fluid. Potassium balance is essential for maintenance of normal resting cell membrane potential in excitatory tissues. Abnormalities in serum potassium, whether low or high, can cause life-threatening complications due to cardiac, respiratory, or neurologic compromise. Hypokalemia results from renal or gastrointestinal losses, or transcellular shifts. In the absence of an identified cause, evaluation of urinary potassium excretion and acid-base status can help determine the etiology. Patients with severe (ie, serum potassium less than 2.5 mEq/L) or symptomatic hypokalemia should be admitted to the hospital for intravenous potassium replacement and cardiac monitoring. Patients with mild to moderate hypokalemia are often asymptomatic and can be treated with oral potassium while the underlying cause is addressed. Hyperkalemia is usually due to low urinary excretion, and less often to cellular release and transcellular shifts. Patients with acute hyperkalemia with associated electrocardiography findings and those with potassium levels 6.5 mEq/L or greater require inpatient treatment with calcium gluconate and other measures. Asymptomatic patients with chronic mild to moderate hyperkalemia can be managed as outpatients with dietary modification, diuretics, and medication adjustments.

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Case 2. CP is a 45-year-old patient with hypertension who is taking amlodipine 10 mg daily. His home blood pressure measurements have been higher than 150/90 mm Hg, so your colleague prescribed lisinopril 20 mg daily in addition to his current regimen. One month after starting lisinopril, CP returns to your clinic with a blood pressure of 126/84 mm Hg. Routine laboratory tests show an elevated serum potassium of 6.2 mEq/L (6.2 mmol/L).

Physiology

A normal serum potassium level of 3.5 to 5.0 mEq/L (3.5-5.0 mmol/L) is maintained via potassium ingestion, excretion, and distribution between intra- and extracellular fluid.[1] Approximately 2% of potassium in the body is extracellular, whereas 98% is intracellular. This gradient is maintained by the sodium-potassium pumps that move three sodium ions out of the cell and two potassium ions into the cell.[2]

In excitatory tissues, the potassium concentration gradient across the cell membrane sets the resting membrane potential and allows for generation of the action potential required for normal neural and musculoskeletal function. Abnormalities in serum potassium, whether low or high, can cause devastating clinical manifestations.

Aldosterone and kidney function play key roles in potassium homeostasis. Approximately 90% of potassium intake is excreted in the urine and 10% by the gastrointestinal tract.[1,3]

After ingestion of potassium, cellular uptake is stimulated via insulin and beta-2 adrenergic receptors in the muscle and liver. A mild increase in serum potassium stimulates aldosterone release, which increases potassium excretion in the principal cells of the distal nephron by stimulating sodium channels.

This increases sodium uptake into the principal cells, creating a negative charge in the lumen, which then draws in potassium to be excreted. Thus, sodium and water delivery are required for adequate sodium uptake into the principal cells of the distal nephron, and for potassium excretion. Increased serum potassium also stimulates apical potassium secretory channels in the principal cells, causing more potassium to flow into the lumen for excretion.[1-3]

Potassium adaptation refers to the ability of the kidneys to excrete potassium more efficiently over time with increased potassium loads, so that excretion matches intake.[2] Therefore, even with ingestion of large amounts of potassium, hyperkalemia will not result unless excretion is impaired. Also, the kidneys are extremely efficient at reabsorbing potassium, with the ability to excrete as little as 5 mEq daily.[4]

Hypokalemia

Hypokalemia, defined as a serum potassium level less than 3.5 mEq/L, results from renal or gastrointestinal losses, or transcellular shifts.[1] Decreased potassium intake is rarely

the sole cause due to efficient renal potassium reabsorption. The most common cause of hypokalemia is renal loss from diuretic use.[5] Inappropriate renal losses also result from increased mineralocorticoid activity, kidney disorders, and hypomagnesemia (Table 1[2]). Gastrointestinal losses are often due to diarrhea, and skin losses may occur with severe exertion in hot climates or in individuals with cystic fibrosis.[1,6] Large or rapid transcellular shifts can cause transient hypokalemia, such as in hypokalemic periodic paralysis or alkalemia.

CLINICAL PRESENTATION

Symptoms generally manifest with severe hypokalemia (ie, serum potassium less than 2.5 mEq/L [2.5 mmol/L]),

TABLE 1
Hypokalemia Causes and Associated Findings

Cause	Laboratory findings: Urine potassium excretion	Laboratory findings: Serum sodium bicarbonate concentration and pH	Other findings
Renal loss			
Thiazide diuretic	↑	↑	↑ Urine chloride
Loop diuretic	↑	↑	↑ Urine chloride
Hypomagnesemia	↑	NA	↑ Urine chloride
Cushing syndrome	↑	↑	↑ Blood pressure, decreased renin and aldosterone levels
Bartter syndrome	↑	↑	↑ Urine calcium and chloride
Gitelman syndrome	↑	↑	↓ Urine calcium, increased urine chloride, hypomagnesemia
Liddle syndrome (pseudo-hyperaldosteronism)	↑	↑	↓ Renin and aldosterone levels, impaired renal sodium excretion
Renal tubular acidosis, types 1 and 2	↑	↓	Associated autoimmune disorder or multiple myeloma
Primary hyperaldosteronism	↑	↑	↑ Blood pressure and renin to aldosterone ratio
Gastrointestinal loss			
Vomiting or nasogastric tube suction	↓	↑	Dehydration
Diarrhea or laxative abuse	↓	↓	Dehydration
Malabsorption	↓	↓	NA
Transcellular shift			
Insulin use	↓	Normal or ↓	NA
Beta agonist use	↓	Normal or ↓	NA
Other			
Skin loss (cystic fibrosis, excessive sweating in extreme climates)	↓	Normal or ↓	NA

NA = not applicable.

Information from reference 2.

but may occur at higher concentrations with acute onset, such as with hypokalemic periodic paralysis. Patients may experience muscle cramps, weakness, or paralysis in an ascending pattern, similar to Guillain-Barré syndrome.[6] Nausea, vomiting, and ileus may result from smooth muscle weakness. Rarely, respiratory depression can occur.

Cardiac manifestations include changes on electrocardiography (ECG), arrythmias, and cardiac arrest (Table 2[7]). ECG findings correlate inconsistently with serum potassium levels. However, when present, they are associated with a twofold increased risk of ventricular arrythmias.[8]

DIAGNOSIS

ECG should be considered for all patients with hypokalemia, especially those with a severe case or acute onset. Laboratory tests should include a basic metabolic panel and serum magnesium. The underlying cause is often obvious from the patient history (eg, diarrhea, diuretic medications, vomiting). Patients treated with thiazide diuretics have an 11-fold increased risk of hypokalemia.[9]

In the absence of an identified cause, evaluation of urinary potassium excretion (to distinguish renal vs extrarenal causes) and assessment of acid-base status should clarify the etiology. A 24-hour urine potassium of greater than 30 mEq/L (30 mmol/L) or a spot urine potassium to creatinine ratio greater than 13 mEq/g suggests renal potassium wasting.[1] While a 24-hour urine potassium is more accurate, a spot urine potassium to creatinine ratio is more practical in patients with severe hypokalemia who need rapid potassium replacement.[10] Abnormalities in serum bicarbonate level often indicate metabolic acidosis or alkalosis.

TREATMENT

All patients with a serum potassium level less than 2.5 mEq/L or clinical manifestations require inpatient treatment and intravenous (IV) potassium replacement with continuous cardiac monitoring and serial ECGs.[1] For patients with life-threatening signs or symptoms, 5 to 10 mEq (5-10 mmol) of potassium chloride can be rapidly infused through central venous access over 15 to 30 minutes with cardiac monitoring.

After life-threatening manifestations are addressed, potassium can be infused with non-glucose-containing IV fluids through central venous access at up to 20 mEq (20 mmol) per hour. If IV fluids are administered through peripheral access, the rate should not be more than 10 mEq (10 mmol) per hour due to risk of venous sclerosis. Patients with renal impairment are at risk of hyperkalemia with potassium replacement, so consultation with a nephrologist should be considered.

Serum potassium levels should be reassessed every 2 to 4 hours until concentrations are greater than 3.5 mEq/L and symptoms resolve. For prevention of arrhythmias, expert consensus recommends maintaining a serum potassium level 4.0 mEq/L (4.0 mmol/L) or greater in patients with acute myocardial infarction or heart failure.[11-13]

Magnesium deficiency is seen in more than 50% of patients with clinically significant hypokalemia, usually in those receiving loop or thiazide diuretic therapy.[1] When serum magnesium decreases below 1.2 mg/dL (0.49 mmol/L), hypokalemia is often refractory to treatment and magnesium must be replaced.[14]

Due to potassium distribution in intra- and extracellular spaces, every 0.3 mEq/L (0.3 mmol/L) decrease in serum potassium represents a total body potassium loss of approximately 100 mEq (100 mmol). Losses may be more profound in chronic hypokalemia.[15] After life-threatening complications are averted, the potassium deficit can be replaced over days to weeks.

For patients requiring large amounts of potassium, oral potassium may be used in addition to initial IV replacement. Potassium chloride is the most effective oral formulation because only 40% as much potassium is absorbed from other forms (ie, potassium phosphate or citrate).[16,17] Potassium chloride dosing is 40 to 120 mEq given in two to four divided doses not to exceed 200 mEq in 24 hours.[1,6,7] IV potassium phosphate can be given if the patient also has hypophosphatemia, and potassium citrate or bicarbonate can be considered if the patient is acidotic.

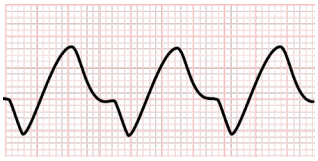
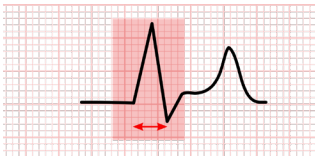
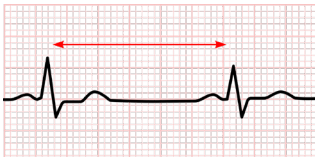
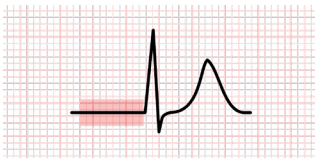
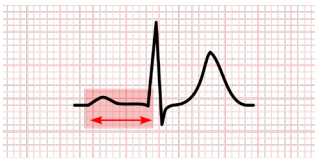
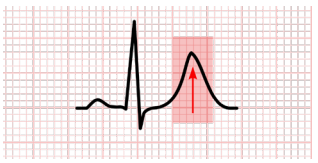
Hyperkalemia is a risk of treatment in patients with a low serum potassium concentration due to transcellular shifts, such as in correction of acute acidosis. Even small changes in pH or fluid status can cause large shifts in serum potassium levels.[1] If a transcellular shift is the suspected etiology of hypokalemia, the underlying cause should be treated and replacement avoided unless hypokalemia is life-threatening.

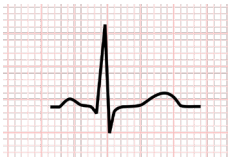
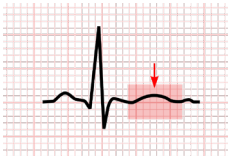
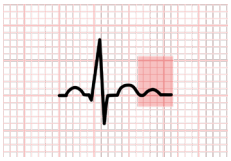
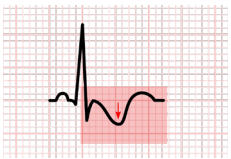
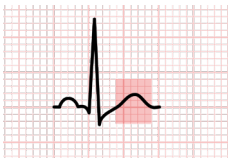
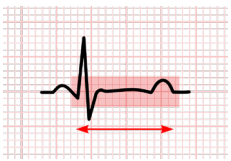
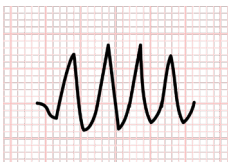
Patients with moderate to mild hypokalemia (serum potassium 2.5-3.4 mEq/L [2.5-3.4 mmol/L]) are often asymptomatic, particularly if the hypokalemia is chronic.[1] These patients can be treated as outpatients with oral potassium replacement and close follow-up.

Although a potassium-rich diet is associated with lower blood pressure and other health benefits, most dietary potassium is in the form of potassium phosphate. Therefore, the effect of diet as the sole treatment for hypokalemia is limited.[7,17]

As the deficit is corrected, any underlying causes should be evaluated and addressed to minimize ongoing losses. A thiazide or loop diuretic may be changed to a

TABLE 2
Electrocardiogram Changes Associated With Potassium Derangements

Serum potassium (mEq/L and mmol/L)	Name of waveform change	Electrocardiogram waveform
> 9.0	Sinusoidal wave pattern	
> 5.5 to ≤ 9.0	Wide QRS duration*	
	Bradyarrhythmias*	
	Loss of P wave, junctional rhythms*	
	Prolonged PR interval	
> 5.5	Peaked T wave	

Serum potassium (mEq/L and mmol/L)	Name of waveform change	Electrocardiogram waveform
3.5 to 5.0 (normal range)	Normal sinus rhythm	
	Decreased amplitude of T wave	
	U waves, best seen in leads V_2 and V_3	
≥ 2.0 to < 3.5	ST-segment depression, T wave inversion, prominent U wave	
	T and U wave fusion	
	Prolonged QT interval	
< 2.0	Ventricular tachycardia, torsades de pointes	

Note: Serum potassium concentrations do not reliably correlate to a specific finding on electrocardiogram. Changes on electrocardiogram are more indicative of the rapidity of serum potassium derangement from the baseline.

*—Most likely to result in an adverse event.

Adapted with permission from Kim MJ, Valerio C, Knobloch GK. Potassium disorders: hypokalemia and hyperkalemia. *Am Fam Physician.* 2023;107(1):70A.

potassium-sparing diuretic or, if needed for hypertension, a potassium-sparing medication, such as an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB). Bicarbonate supplementation in distal (type 1) renal tubular acidosis will prevent renal losses of potassium, and treatment of chronic diarrhea can limit gastrointestinal loss.

Hyperkalemia

Hyperkalemia is generally defined as a serum potassium level greater than 5.0 mEq/L, and is found in approximately 3% of the general population and 10% of hospitalized patients.[18] Hyperkalemia is usually due to low urinary excretion, and less often to cellular release and transcellular shifts (Table 3[19,20]).

Decreased potassium excretion may be due to aldosterone resistance, lack of aldosterone, or decreased delivery of sodium and water to the distal nephron. Kidney disease or medications such as potassium-sparing diuretics may increase resistance to aldosterone, while low aldosterone levels may be attributable to medications (eg, ACEIs, ARBs) or adrenal insufficiency.

Increased potassium intake alone is unlikely to cause hyperkalemia but may contribute when other risk factors are present. The risk of developing hyperkalemia is significantly increased in patients with cardiovascular disease, chronic kidney disease, and diabetes, with a prevalence of up to 20%.[21]

CLINICAL PRESENTATION

Signs and symptoms of hyperkalemia, including weakness and cardiac complications, are similar to those of hypokalemia. They generally occur in patients with a serum potassium 6.5 mEq/L (6.5 mmol/L) or greater, but may develop at lower concentrations when there is a rapid increase in potassium level.[6]

ECG changes are associated with an increased risk of adverse cardiac events and can evolve rapidly and unpredictably (Table 2[7]). These changes are more common with rapid increases in potassium concentration and concurrent hypocalcemia, hyponatremia, and acidemia, but have low sensitivity for diagnosing hyperkalemia.[6,18,22-24] With increasing severity of hyperkalemia, conduction delays, arrythmias, and cardiac arrest may occur.

DIAGNOSIS

Pseudohyperkalemia is a common finding, most often with a hemolyzed blood sample.[7,25,26] This can be a result of a traumatic blood draw, use of a tourniquet during a blood draw, or repeated fist clenching by the patient during a blood draw. It may also be seen in patients with chronic leukemias or thrombocytosis. Pseudohyperkalemia should be suspected in asymptomatic patients without risk factors and repeat sampling should be performed without fist clenching or tourniquet use.

After obtaining a history, performing a physical examination, and evaluating for underlying causes and clinical manifestations, an ECG should be considered in patients with an acute increase in potassium concentration to 5.0 to 5.9 mEq/L (5.0-5.9 mmol/L) and obtained in all patients with a potassium level 6 mEq/L (6 mmol/L) or greater.[6,7] A basic metabolic panel and additional laboratory tests to evaluate for chronic kidney disease (eg, urinalysis, urine protein-to-creatinine ratio) may be helpful. If hypoaldosteronism is suspected, then renin, aldosterone, and early morning cortisol levels are useful tests.

TREATMENT

Due to the risk of mortality, severe hyperkalemia with a potassium level 6.0 to 6.4 mEq/L (6.0-6.4 mmol/L) associated with clinical symptoms or ECG findings, or a potassium level 6.5 mEq/L or greater are medical emergencies.[6,27] All patients with ECG changes, symptoms, or serum potassium 6.0 mEq/L or greater should be treated in an inpatient setting and monitored closely with continuous telemetry. Early identification and correction are associated with lower risk of mortality.[28]

IV calcium gluconate (1-3 g) is given initially to stabilize cardiac cell membranes, but it does not lower serum potassium (Table 4[6,19,29]). Calcium gluconate is recommended for patients with ECG changes or a serum potassium level 6.5 mEq/L or greater.[6] ECG should be repeated 5 minutes after calcium administration, and if ECG changes have not resolved, treatment should be repeated.[11] Calcium gluconate is preferred over calcium chloride, which requires central access. In patients with hyperkalemia who take digoxin, calcium should be given if indicated. However, it should be administered as a slow infusion to prevent hypercalcemia, which can precipitate digoxin toxicity.[30]

Next, insulin and beta agonists are given together to drive extracellular potassium into the cells, as their effects are synergistic. For patients with a blood glucose level less than 250 mg/dL (13.88 mmol/L), insulin should be given with IV dextrose.[11,31,32] Blood glucose should be measured hourly for up to 6 hours following insulin administration to monitor for hypoglycemia. High-dose inhaled albuterol (four to eight times the usual bronchodilator dose) is given with insulin. Beta agonists alone have a minimal effect.[19]

Sodium bicarbonate is only effective for shifting potassium intracellularly when metabolic acidosis is present. It should be considered if acidosis is severe, and a nephrologist should be consulted.

TABLE 3
Hyperkalemia Causes, Mechanisms, and Additional Findings

Cause	Mechanism	Additional findings
Pseudohyperkalemia	Cell trauma or breakdown with potassium release, commonly in vitro	Also seen with chronic lymphocytic leukemia and thrombocytosis
Trimethoprim	Direct inhibition of the epithelial sodium channel in the distal nephron thereby limiting potassium excretion	Trimethoprim-sulfamethoxazole is a common cause of acute hyperkalemia, especially in patients with chronic kidney disease
Renin-angiotensin-aldosterone system inhibitory drugs (eg, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers)	Decreased aldosterone activity	NA
Mineralocorticoid receptor antagonists (eg, spironolactone, finerenone)	Antagonize aldosterone receptors in the distal convoluted tubule	NA
Nonsteroidal anti-inflammatory drugs	Decreased renin and aldosterone synthesis	NA
Potassium-sparing diuretics (eg, amiloride, triamterene)	Inhibit sodium reabsorption in the distal kidney thereby limiting potassium excretion	NA
Acute kidney injury, chronic kidney disease	Aldosterone resistance, oliguria	NA
Urinary obstruction	Aldosterone resistance from associated acute kidney injury	NA
Low effective arterial circulation	Aldosterone resistance, decreased kidney function	Heart failure, cirrhosis, sepsis
Decreased flow to distal convoluted tubule	Decrease in distal nephron sodium and water delivery limits potassium excretion	Hypovolemia
Digoxin toxicity	Inhibits sodium-potassium pumps in cell membranes, especially in cardiac myocytes	NA
Tissue breakdown	Cellular release of potassium	Trauma, intravascular hemolysis, rhabdomyolysis thrombocytosis, tumor lysis syndrome
Acidosis, hyperglycemia	Transcellular shift	NA
Beta blockers	Transcellular shift	NA
Low-insulin state	Transcellular shift, with acidosis	NA

NA = not applicable.

Information from references 19 and 20.

Insulin and beta agonists provide a temporizing effect lasting 2 to 6 hours while measures to eliminate potassium are initiated. If the patient is not hypervolemic or anuric, loop diuretics are administered with IV fluids to increase delivery of sodium and water to the distal tubule for enhanced urinary potassium excretion.[33,34]

Potassium binders (eg, sodium zirconium cyclosilicate [Lokelma], patiromer [Veltassa]) bind potassium

TABLE 4
Medications for Hyperkalemia Management

General agent, class, or medication	Specific agent or medication (dose)	Onset	Duration	Comments
Calcium	Calcium gluconate (1-3 g IV, preferred) Calcium chloride (1 g IV, via central venous access)	Immediate	2 hours	Calcium stabilizes cell membranes with little or no effect on potassium level
Insulin	Regular insulin (10 units IV)	30-60 minutes	4-6 hours	Monitor blood glucose hourly for up to 6 hours Administer with IV dextrose in patients with blood glucose level less than 250 mg/dL (13.88 mmol/L)
Beta agonists	Albuterol (10-20 mg nebulized)	30-120 minutes	2-4 hours	4- to 8-fold normal dose of albuterol used only with insulin for synergistic effect
Sodium bicarbonate	Isotonic IV infusion (850 mL sterile water or 5% dextrose in water) with 150 mL sodium bicarbonate over 2-4 hours	Dependent on pH correction	Dependent on pH correction	Administer if patient has metabolic acidosis, seek nephrologist consultation
Loop diuretics	Dose determined by clinical situation (eg, furosemide 40 mg IV every 6-12 hours)	2-6 hours	6-12 hours	Administer with IV fluids in acute setting if patient is not hypervolemic or anuric
Potassium binders	Patiromer (Veltassa; initially 8.4 g daily to maximum of 25.2 g daily)	7 hours	24 hours	7.2% of patients experience gastrointestinal disturbances
	Sodium zirconium cyclosilicate (Lokelma; initially 10 mg three times per day for 2 days; maintenance dose 5-15 mg daily)	1-2 hours	Sustained with continued use	Often administered to patients with kidney failure on nondialysis days May be beneficial in acute hyperkalemia treatment
	Sodium polystyrene sulfonate (oral suspension 15-60 g daily or rectal enema 30-60 g daily)	1-24 hours	Hours to days	FDA boxed warning for use with sorbitol due to risk of gastrointestinal complications Still used in select situations but newer compounds are preferred

IV = intravenous.

Information from references 6, 19, and 29.

in the intestinal tract for excretion in the stool. With sodium zirconium cyclosilicate, potassium levels decrease within 1 hour, with an average decrease of 0.37 mEq/L (0.37 mmol/L) in 4 hours and 1 mEq/L (1 mmol/L) in 24 hours.[29,35]

Patiromer works more slowly, within 7 hours. Due to risk of colonic necrosis, sodium polystyrene sulfonate is no longer a preferred treatment but may be used if newer binders are not available.[29,35]

Hemodialysis is the most effective and rapid intervention for hyperkalemia.[7] It is indicated for severe and refractory hyperkalemia in the presence of life-threatening cardiac conduction abnormalities, and may be the only option in patients with acute or chronic kidney failure.[36]

Early nephrology consultation is recommended in patients with hyperkalemia and severe kidney dysfunction.

Patients with chronic mild to moderate hyperkalemia (5.0-5.9 mEq) are often asymptomatic, and the potassium level may be slowly decreased over days to weeks with dietary modification, diuretics, and adjustments to contributing medications. A low-potassium diet and avoidance of salt substitutes containing potassium may be necessary for patients with chronic kidney disease. Causative medications (eg, nonsteroidal anti-inflammatory drugs, nonselective beta blockers) should be discontinued.

Among patients with heart or kidney disease, renin-angiotensin-aldosterone system inhibitor medications, such as ACEIs, ARBs, or mineralocorticoid receptor antagonists, may be lifesaving, so use of a diuretic or potassium binder should be considered because it may allow these patients to continue using these medications.[3,11,29,35]

Case 2, continued. When you are notified that the serum potassium level for CP is 6.2 mEq/L, you call him. He denies any new symptoms, but due to the degree of hyperkalemia, you instruct him to go to the emergency department for evaluation. Repeat laboratory tests in the emergency department confirm a potassium level of 6.3 mEq/L (6.3 mmol/L), blood glucose level of 298 mg/dL (16.54 mmol/L), and creatinine of 1.4 mg/dL (106.75 µmol/L). ECG shows peaked T waves.

CP is treated rapidly with 1 g IV calcium gluconate, 20 mg nebulized albuterol, and 10 units of IV insulin. ECG abnormalities resolve within 10 minutes of treatment. His potassium level is 5.4 mEq/L (5.4 mmol/L) after 2 hours. He is admitted and treated with 40 mg IV furosemide every 12 hours and infusion of normal saline.

The following morning, the potassium concentration for CP is 5.1 mEq/L (5.1 mmol/L). You learn from his history that he was using a potassium-based salt substitute. He is discharged with a follow-up visit scheduled in 3 days. Amlodipine is discontinued, lisinopril (20 mg daily) is continued, and hydrochlorothiazide (25 mg daily) is initiated. You follow his electrolyte levels and kidney function over the next 2 months. CP is subsequently found to have an A1C of 7.2% and is treated for newly diagnosed type 2 diabetes. With this medication regimen, his potassium levels remain stable at 4.2 mEq/L (4.2 mmol/L).

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SECTION THREE

Acid-Base Disorders

Maintaining a normal physiologic acid-base balance is essential for the functioning of every organ system in the body. The renal and pulmonary systems are the primary regulators of acid-base balance. There are four principal acid-base disorders: metabolic acidosis, metabolic alkalosis, respiratory acidosis, and respiratory alkalosis. A systematic approach to evaluation is critical to identify potential etiologies. A history, physical examination, metabolic profile, and arterial blood gas measurement provide a full assessment of acid-base status. However, availability of arterial blood gas measurements is usually limited outside of inpatient and emergency department settings. Calculation of an anion gap is a crucial first step for evaluating laboratory test results. Changes in serum pH, P_{CO_2}, serum bicarbonate concentration, and anion gap suggest the primary disorder, and predictable compensatory changes indicate whether a secondary acid-base disturbance is present. Mixed acid-base disorders involving the renal and pulmonary systems can occur, underscoring the importance of a systematic approach to evaluation. In the outpatient setting, primary care physicians play a vital role in identifying and treating these disorders based on initial evaluation. Prompt recognition and management of acid-base disorders can help prevent morbidity and mortality.

Regehr J. Acid-Base and Electrolyte Disorders: Acid-Base Disorders. FP Essent. *2026;565:23-29.*

Case 3. CR is a 22-year-old patient with type 1 diabetes. She has had gastroenteritis for the past few days, with frequent episodes of vomiting and decreased oral intake. CR says she reduced the basal rate on her insulin pump because she was afraid of hypoglycemia. You take a careful history and perform a physical examination. CR appears lethargic and her breath has a fruity smell. You obtain blood samples for a metabolic profile and urinalysis to be performed at the office. Urinalysis results show 3+ ketones.

Physiology

Every organ system in the body relies on the physiologic maintenance of normal acid-base status to function.[1,2] Serum pH is controlled within a tight range, and any deviation can have potentially fatal adverse effects.[1]

The renal and pulmonary systems regulate this process via the bicarbonate buffer system in the blood. Carbon dioxide is produced by normal cellular metabolism and a portion of it is eliminated via alveolar ventilation in the lungs.[1] Carbon dioxide can be exhaled or retained to maintain a normal serum pH.[3] In addition, the body produces a large amount of acid daily, which the kidneys excrete and buffer via ammonia production.[4] The kidneys also produce, filter, and reabsorb bicarbonate to help maintain a normal serum pH.[1]

There are four principal acid-base disorders: metabolic acidosis, metabolic alkalosis, respiratory acidosis, and respiratory alkalosis.[5] Acidosis refers to an increase in hydrogen ion concentration, while alkalosis refers to a decrease.

Acidemia refers to a low serum pH (ie, less than 7.35) and alkalemia a high serum pH (ie, greater than 7.45).[2] Any disruption that results in a serum pH outside the normal range prompts a predictable compensatory response that does not usually return the serum pH to normal.[2] However, the serum pH can be normal when a mixed acid-base disorder is present.[6]

Initial Evaluation

Evaluation of an acid-base disorder begins with a history and physical examination, which can provide clues to the underlying cause.[2] Patient medications should be reviewed carefully because diuretics, laxatives, metformin, and salicylates can cause abnormalities in acid-base balance.[7]

Patients who present with acute acid-base disturbances are often more systemically ill than patients with chronic acid-base abnormalities. This is due in part to a greater deviation from physiologic pH in patients with acute disorders.[2] Patients with signs of intoxication, vomiting, or hypovolemia are more likely to have acute acid-base disorders. Underlying liver, kidney, or lung pathology predisposes patients to chronic acid-base disturbances, though superimposed acute disorders can occur.[5,8,9]

If an acid-base disorder is suspected after initial evaluation, the next step is laboratory testing. In the outpatient

setting, physicians should order a metabolic profile that includes serum electrolytes, bicarbonate, renal function, and anion gap.[5] A full assessment would ideally include arterial blood gas measurement, but this is not usually available in the outpatient setting.

For inpatients, an initial arterial blood gas is preferred but can be difficult to acquire. A venous blood gas may be considered but has limitations. Venous pH is an average of 0.03 units lower than arterial pH, and venous P_{CO_2} is 4 to 6.5 mm Hg higher than arterial P_{CO_2}. In critically ill patients, these differences can be fourfold greater.[10] Venous blood gas may be used for monitoring.

Stable patients with history, physical examination, and laboratory test findings indicating the same cause may not need arterial blood gas measurement.[5] For example, a patient with acute decompensated heart failure who has a metabolic alkalosis due to volume contraction from high-dose intravenous diuretics.[11]

A systematic approach to evaluation will help identify the underlying cause and guide treatment. Changes in serum pH, P_{CO_2}, serum bicarbonate concentration, and anion gap suggest the primary disorder, and predictable compensatory changes indicate whether a secondary acid-base disturbance is present (Table 1[12]). In metabolic disturbances, the serum bicarbonate and P_{CO_2} follow the pH. In respiratory disturbances, bicarbonate and P_{CO_2} move in the opposite direction from the pH.[1,3,13] An initial anion gap should be calculated for all patients with a suspected acid-base disorder.[14]

Metabolic Disorders

METABOLIC ACIDOSIS

Metabolic acidosis occurs when a primary pathophysiologic disturbance causes the serum bicarbonate level to decrease below the normal range.[13] Acute metabolic acidosis is often due to overproduction of organic acids, whereas chronic metabolic acidosis commonly results from bicarbonate wasting by the renal or gastrointestinal system.[15]

When evaluating patients for metabolic acidosis, the anion gap should be calculated.[16] This is the sodium concentration minus the chloride level minus the serum bicarbonate level. A normal anion gap is 10 mEq/L (10 mmol/L) or less[12] (Table 2[12], Figure 1[2,12]).

Many approaches to assessing for acid-base disorders start with a serum pH, but in the case of mixed acid-base disturbances, a normal serum pH, normal serum bicarbonate, or both may be present.[6,17] Starting with calculation of the anion gap can prevent missing the diagnosis of potentially fatal conditions.

An increased anion gap indicates strong acid has accumulated in the blood and a high anion gap metabolic acidosis is present.[12,13] A mnemonic to recall the most common causes is KULOST (ketoacidosis [due to diabetes or alcohol use with starvation], uremia [attributable to kidney failure], lactic acidosis [caused by inadequate tissue oxidation or defects in cellular metabolism], osmolar gap etiologies [methanol, ethylene glycol, or propylene glycol ingestion], salicylates or acetaminophen, and toxins) (Table 3[2,3,5,7,12,16,18-20]). The most common causes are the first three items listed.

The osmolar gap should also be assessed[21] (Table 2[12]). An osmolar gap greater than 10 mOsm/kg suggests that an unmeasured serum anion (eg, methanol, ethylene glycol, propylene glycol) is present in the serum. Small osmolar gaps can occur in ketoacidosis and lactic acidosis.[2]

Urgent treatment is required for the specific etiology of high anion gap metabolic acidosis. Bicarbonate therapy is usually reserved for patients with severe acidosis (pH less than 7.1).[22]

If a high anion gap is present, the next step is to calculate the delta gap, which is the difference in the anion gap from a baseline of 10 mEq/L. This change should correspond to an equal decrease in serum bicarbonate.[13] If not,

TABLE 1
Primary Acid-Base Disorders and Expected Biochemical Changes

Primary disorder	pH	HCO_3	P_{CO_2}	Expected compensation
Metabolic acidosis	↓	↓	↓	$P_{CO_2} = 1.5 \times HCO_3 + 8 \pm 2$
Metabolic alkalosis	↑	↑	↑	$P_{CO_2} = 0.7 \times HCO_3 + 20 \pm 5$
Respiratory acidosis	↓	↑	↑	Acute: $HCO_3 = 24 + [1 \times (P_{CO_2} - 40)/10]$ Chronic: $HCO_3 = 24 + [3.5 \times (P_{CO_2} - 40)/10]$
Respiratory alkalosis	↑	↓	↓	Acute: $HCO_3 = 24 - [2 \times (40 - P_{CO_2})/10]$ Chronic: $HCO_3 = 24 - [5 \times (40 - P_{CO_2})/10]$

HCO_3 = serum bicarbonate.

Information from reference 12.

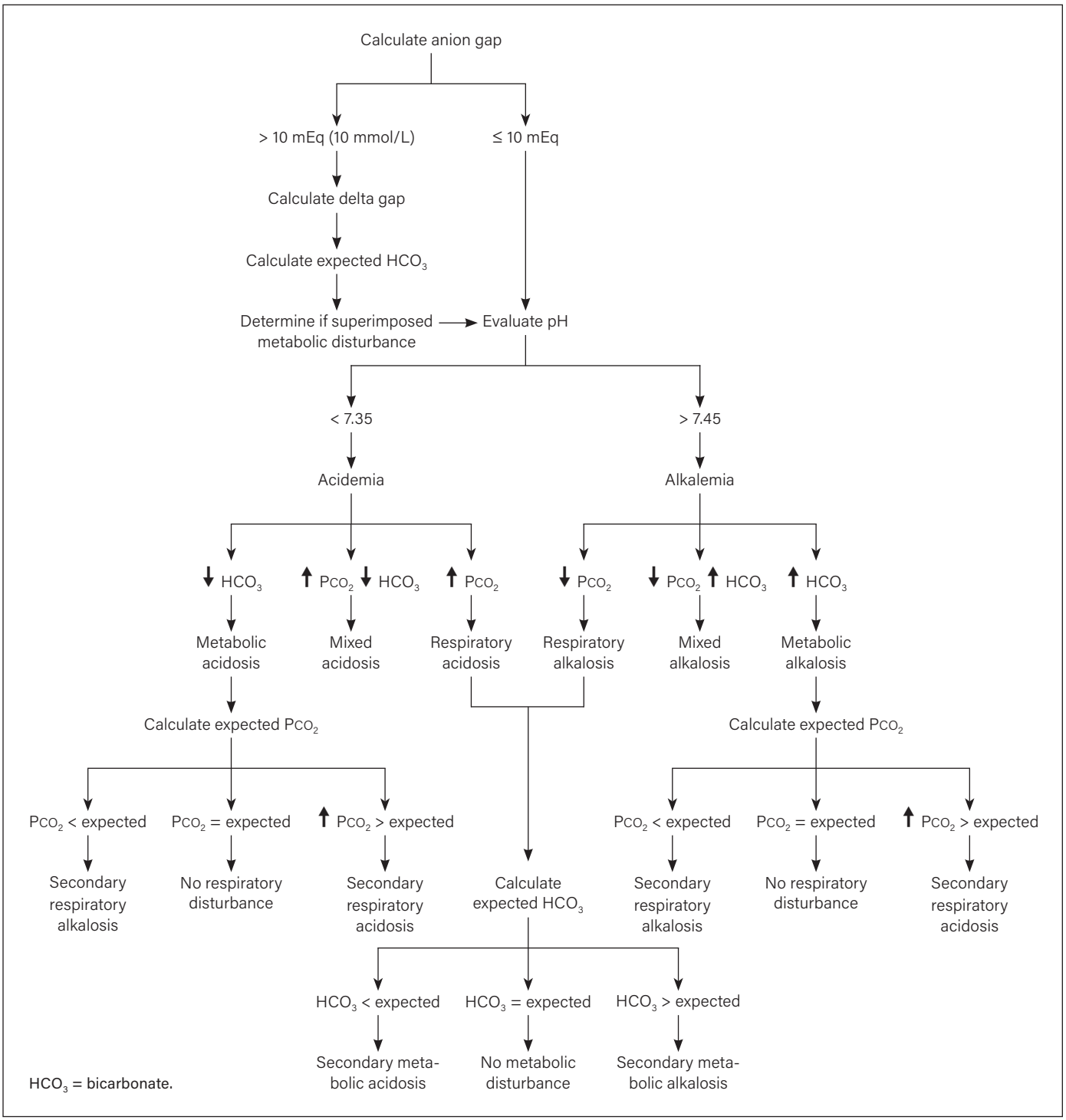

Figure 1. Approach to evaluation of acid-base disorders.

Information from references 2 and 12.

the patient should be evaluated for a mixed metabolic disturbance, as a concomitant metabolic alkalosis or normal anion gap metabolic acidosis can also be present.[2]

If the anion gap is normal in the setting of metabolic acidosis, this indicates normal anion gap metabolic acidosis due to bicarbonate loss rather than acid production or retention. Diarrhea and renal tubular acidosis are common causes of bicarbonate loss.[23] In acute or chronic kidney dysfunction, the kidneys lose the ability to excrete acid, which may lead to normal anion gap metabolic acidosis.[9] Administration of normal saline can also be a cause, as the chloride ions in the saline react with the bicarbonate in

TABLE 2
Stepwise Approach to Evaluation of High Anion Gap Metabolic Acidosis

1. Calculate anion gap	
Anion gap = Na – ($Cl + HCO_3$) (normal range is 10-12 mEq/L [10-12 mmol/L])	If above normal reference range, strong acid has been added to the blood and high anion gap metabolic acidosis is present
Adjust for albumin: anion gap + 2.5 × [normal albumin – observed albumin]	
If anion gap is high, calculate osmolar gap: [(2 × Na) + (BUN/2.8) + (glucose/18) + (ethanol/3.7)] – serum osmolality	Osmolar gap > 10 mOsm/kg (10 mmol/kg) is abnormal; assess for methanol, ethylene glycol, and propylene glycol
2. Calculate delta gap	
Delta gap = anion gap – 10	Indicates how much extra acid is present in the blood
3. Calculate expected bicarbonate	
Expected bicarbonate = 24 – delta gap	Decrease in bicarbonate should be similar to the amount of strong acid added to the blood
4. Determine if superimposed metabolic disturbance is present	
Compare measured HCO_3 to expected HCO_3	If HCO_3 is less than expected, superimposed normal anion gap metabolic acidosis is present
	If HCO_3 is greater than expected, superimposed metabolic alkalosis is present
5. Evaluate pH to determine if acidemia or alkalemia is present	
Obtain pH from arterial blood gas	pH < 7.35 = acidemia
	pH > 7.45 = alkalemia
6. Calculate the expected P_{CO_2}	
For metabolic acidosis: expected $P_{CO_2} = 1.5 \times HCO_3 + 8 \pm 2$	Calculates expected physiologic respiratory response if no respiratory disturbance is present
For metabolic alkalosis: expected $P_{CO_2} = 0.7 \times HCO_3 + 20 \pm 5$	
7. Determine if respiratory disturbance present	
Compare measured P_{CO_2} to expected P_{CO_2}	If P_{CO_2} is greater than expected, respiratory acidosis is present
	If P_{CO_2} is less than expected, respiratory alkalosis is present

BUN = blood urea nitrogen; Cl = chloride; HCO_3 = bicarbonate; Na = sodium.

Information from reference 12.

the serum to buffer the pH, which leads to depletion of bicarbonate.[24]

The respiratory system responds quickly to metabolic acidosis, increasing ventilation to eliminate carbon dioxide and produce a decrease in P_{CO_2}. Compensation starts within 30 minutes and is complete within 24 hours.[1] A lack of compensation indicates underlying pulmonary or neuromuscular disease.

Maximum respiratory compensation occurs at a P_{CO_2} of 8 to 12 mm Hg (1.06-1.60 kPa), so this P_{CO_2} should be expected in a patient with a primary metabolic acidosis and a serum bicarbonate level of 5 mEq/L (5 mmol/L) or less.[13] Respiratory compensation for a severe metabolic acidosis cannot be maintained indefinitely, thus a secondary respiratory acidosis could be observed due to respiratory fatigue.

METABOLIC ALKALOSIS

Metabolic alkalosis is characterized by an increase in serum bicarbonate and is common in hospitalized patients.[12,18] It generally results from a net loss of acid through the gastrointestinal tract or an accumulation of

TABLE 3
Acid-Base Disorder Causes

Metabolic acidosis

High anion gap
- Ketoacidosis
- Lactic acidosis (including from metformin)
- Osmolar gap etiologies
- Oxoproline level increase
- Salicylates or acetaminophen
- Toxins (eg, toluene)
- Uremia

Normal anion gap
- Diarrhea
- Laxatives
- Normal saline infusion
- Renal tubular acidosis

Metabolic alkalosis

Urine chloride < 20 mEq/L (20 mmol/L)
- Gastrointestinal loss
  - Diarrhea
  - High-volume losses from ileostomy
  - Laxative overuse
  - Vomiting
- Renal loss
  - Bicarbonate infusion
  - Cystic fibrosis
  - Diuretics
  - Post-hypercapnic state

Urine chloride ≥ 20 mEq/L
- Blood pressure normal or decreased
  - Bartter syndrome
  - Diuretic use
  - Gitelman syndrome
- Blood pressure increased
  - Cushing syndrome
  - Hyperaldosteronism
  - Licorice ingestion
  - Liddle syndrome
  - Renal artery stenosis
  - Renin-producing tumor

Respiratory acidosis (hypoventilation)

- Central etiologies
  - Central or obstructive sleep apnea
  - Encephalitis
  - Myxedema coma
  - Obesity hypoventilation
  - Sedatives
  - Stroke
- Neuromuscular or thoracic cage abnormalities
  - Acute abdomen
  - Amyotrophic lateral sclerosis
  - Botulism
  - Flail chest
  - Guillain-Barré syndrome
  - Massive pleural effusion
  - Myasthenia gravis
  - Severe spinal anatomic abnormalities
  - Spinal cord disorders
- Overproduction of carbon dioxide
  - Extreme exercise
  - Fever
  - Sepsis
  - Thyrotoxicosis
- Pulmonary etiologies
  - Chronic obstructive pulmonary disease
  - Diffuse infection
  - Pulmonary edema or cardiogenic shock
  - Pulmonary embolism

Respiratory alkalosis (hyperventilation)

- Anxiety/anxiety-induced hyperventilation syndrome
- Cheyne-Stokes respirations
- Heart failure
- Hyperthyroidism
- Hypoxemia
- Liver disease
- Pain
- Pneumonia
- Pregnancy
- Salicylate toxicity
- Sepsis

Information from references 2, 3, 5, 7, 12, 16, and 18-20.

bicarbonate.[25] Nearly all cases involve an excessive amount of mineralocorticoids that are due to primary conditions involving overproduction or as a response to volume depletion.

The urine chloride level can help determine the underlying cause of metabolic alkalosis (Table 3[2,3,5,7,12,16,18-20]). A concentration less than 20 mEq/L (20 mmol/L) indicates volume contraction, and these etiologies are considered chloride-responsive. Volume expansion will generally resolve the metabolic alkalosis.[25] If the urine chloride is 20 mEq/L or greater, the condition is chloride-nonresponsive and patients should be evaluated for underlying renal or endocrine disorders.[18,25]

Respiratory Disorders

RESPIRATORY ACIDOSIS

Primary respiratory acidosis results from inability of the lungs to adequately exhale carbon dioxide. Common causes include primary lung disease (eg, acute exacerbation of chronic obstructive pulmonary disease, respiratory failure in severe pneumonia), but it can also occur due to central or neuromuscular etiologies.[26]

In the setting of an acute respiratory acidosis, rapid cellular shifts help maintain a normal pH.[27] After several hours, renal compensation occurs and bicarbonate will increase by 1 mEq/L (1 mmol/L) for every 10 mm Hg (1.33 kPa) increase in P_{CO_2}. Over the course of days, the kidneys reabsorb and produce more bicarbonate, with concentration increases of 3.5 mEq/L (3.5 mmol/L) for every 10 mm Hg increase in P_{CO_2}.[3] The patient history is critical for determining whether an acute or chronic respiratory acidosis is present, and the expected metabolic compensation.

The underlying cause of acute respiratory acidosis should be identified and treated. Initial measures should include provision of ventilation assistance. For conscious patients, noninvasive positive pressure ventilation is a standard initial strategy. Unconscious patients will likely require intubation. Treatment of the underlying disorder in patients with chronic respiratory acidosis rarely corrects the P_{CO_2} completely, thus the focus should be on appropriate oxygenation and maintenance of normal pH.[3]

RESPIRATORY ALKALOSIS

Acute respiratory alkalosis (ie, primary hypocapnia) is a common and serious condition in critically ill patients.[28] The increase in pH impairs the ability of hemoglobin to release oxygen in peripheral tissues, and the hypocapnia causes vasoconstriction exacerbating hypoperfusion.

There is a proportional relationship between the severity of alkalemia and mortality in patients in intensive care units.[3] Therefore, patients with acute respiratory alkalosis should be promptly evaluated and treated. Common causes include hypoxemia, salicylate toxicity, pneumonia, heart failure, and anxiety-induced hyperventilation syndrome (Table 3[2,3,5,7,12,16,18-20]). In contrast, patients with chronic respiratory alkalosis are generally stable and asymptomatic, with mild, compensated changes as seen with pregnancy or underlying liver disease.

Serum bicarbonate levels decrease by 2 mEq/L (2 mmol/L) with every 10 mm Hg lowering in P_{CO_2} in acute respiratory alkalosis.[3] This effect occurs quickly and is due to the increase in pH creating a favorable environment for bicarbonate to shift into cells.

In chronic respiratory alkalosis, the bicarbonate decrease is more than double that in acute respiratory alkalosis (ie, a 5 mEq/L [5 mmol/L] decrease for every 10 mm Hg reduction in P_{CO_2}) and is due to transient bicarbonate diuresis mediated by the kidneys over the course of a few days.

Mixed Acid-Base Disorders

Mixed acid-base disorders are common. Use of a systematic approach to their evaluation provides vital diagnostic information and guides timely treatment in critically ill patients (Figure 1[2,12]). Patients may have high anion gap metabolic acidosis with a second metabolic disturbance, either a normal anion gap metabolic acidosis or metabolic alkalosis. Additionally, a respiratory disorder can be present.[14]

For patients who present with primary metabolic disturbances, the expected P_{CO_2} should be calculated (Table 2[12]). If the measured P_{CO_2} is greater than the expected value, there is a concomitant respiratory acidosis. If it is less than expected, then a respiratory alkalosis is present.

For patients who present with primary respiratory disturbances, serum bicarbonate levels should be assessed. If the level is greater than expected based on the formulas, then a superimposed metabolic alkalosis is present. If the bicarbonate level is less than expected, a metabolic acidosis is present.

A normal, or near normal, serum bicarbonate level does not exclude metabolic acidosis. A triple acid-base disorder can occur in patients with methanol or ethylene glycol intoxication. These patients may present with an elevated anion gap with a relatively normal serum bicarbonate in the setting of vomiting and liver disease, with a secondary metabolic alkalosis and respiratory alkalosis in addition to high anion gap metabolic acidosis.

Use of only the serum bicarbonate or pH for initial evaluation of patients with suspected acid-base disorders could result in missing a serious diagnosis. Starting with calculation of the anion gap can prevent such missed diagnoses, and may be lifesaving.[14]

Case 3, continued. Metabolic panel results for CR show increased levels of: potassium 5.6 mEq/L (5.6 mmol/L), blood urea nitrogen 30 mg/dL (10.71 mmol/L), creatinine 2.0 mg/dL (176.8 mmol/L), and glucose 496 mg/dL (27.53 mmol/L). They also show normal levels of sodium 140 mEq/L (140 mmol/L) and bicarbonate 22 mEq/L (22 mmol/L), and decreased levels of chloride 90 mEq/L (90 mmol/L).

You are not able to obtain a blood gas measurement in the office. However, you calculate that the anion gap is 28 mEq/L (28 mmol/L) and expected bicarbonate is 6 mEq/L (6 mmol/L). The actual bicarbonate of 22 mEq/L (22 mmol/L) shows CR has a secondary metabolic alkalosis likely due to vomiting. Noting this, her increased urine ketones and blood glucose level, you admit her to the hospital for acute diabetic ketoacidosis.

On admission, an arterial blood gas measurement shows a pH of 7.22 and P_{CO_2} of 47 mm Hg (6.25 kPa). You calculate the expected P_{CO_2} to be 41 mm Hg (5.45 kPa), showing that she has a secondary respiratory acidosis, likely due to respiratory fatigue from her prolonged illness.

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SECTION FOUR

Calcium Disorders

Calcium is an essential element for normal physiologic function. Normal serum calcium is maintained within a close range of 8.4 to 10.4 mg/dL, and acute or severe changes can result in serious cardiac, musculoskeletal, and neurologic consequences. Normal calcium levels are maintained by interactions of parathyroid hormone and vitamin D. Parathyroid hormone regulates calcium levels via bone resorption, renal calcium reabsorption, and enhanced calcium absorption in the small intestine. Causes of hypocalcemia include hypoparathyroidism (often postsurgical), severe chronic kidney disease, and vitamin D deficiency. Laboratory testing for serum parathyroid hormone, kidney function, vitamin D metabolites, and serum phosphorus can help differentiate among causes. Acutely symptomatic patients require inpatient treatment with intravenous calcium gluconate, cardiac monitoring, and correction of hypomagnesemia. Hypercalcemia is most often due to primary hyperparathyroidism or malignancy. In the evaluation, hypercalcemia should first be confirmed by measurement of ionized calcium or repeat measurement of total serum calcium and correction for albumin. Obtaining a serum parathyroid hormone level is the next step. Asymptomatic, chronic mild hypercalcemia is often caused by primary hyperparathyroidism, which can be observed or treated surgically. Patients with severe hypercalcemia may have profound dehydration and require inpatient treatment with intravenous fluids, bisphosphonates, and calcitonin.

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Case 4. SG is a 56-year-old patient who has recently been treated for a third kidney stone in 2 years. You order a metabolic biochemistry panel and find that her calcium level is mildly increased at 12 mg/dL (3 mmol/L).

Physiology

Calcium is an essential element that plays a critical role in cardiac, hormonal, musculoskeletal, and neurologic functions. Precise control of serum calcium requires minute-to-minute adjustments to maintain homeostasis. Mild changes in the calcium level are relatively asymptomatic, but acute or severe changes can lead to serious consequences.

Normal calcium levels are maintained by interactions of parathyroid hormone (PTH) and vitamin D (Figure 1[1]). In the parathyroid glands, the calcium-sensing receptor detects changes in serum ionized calcium and either stimulates PTH release if there is hypocalcemia or downregulates PTH release with hypercalcemia.[2] PTH causes osteoclast-mediated bone resorption, increases renal calcium reabsorption, and enhances calcium absorption in the small intestine via increased renal secretion of 1,25-dihydroxyvitamin D (calcitriol), culminating in increased serum calcium. Decreased levels of PTH exert the opposite effects and lower serum calcium.

PTH also stimulates renal phosphorus excretion, maintaining normal serum phosphorus levels despite increased bone resorption. Magnesium is required for normal parathyroid function, and serum levels less than 1 mg/dL (0.41 mmol/L) are associated with PTH resistance and impaired secretion.[3]

Biologically active calcium is unbound (ie, free or ionized) and accounts for 50% of total serum calcium.[4] Approximately 40% of serum calcium is protein-bound, mostly to albumin, and 10% is complexed with anions. The normal range of total serum calcium is 8.4 to 10.4 mg/dL (2.1-2.6 mmol/L), compared with a normal ionized calcium range of 4.5 to 5.3 mg/dL (1.13-1.32 mmol/L).

When the albumin concentration is low, total serum calcium will also be decreased (ie, pseudohypocalcemia) but can be corrected using a standard formula. Similarly, total calcium can be corrected for high albumin. However, these formulas have variable accuracy, so direct measurement of ionized calcium concentration is optimal when possible, particularly for critically ill patients and those with acid-base disorders.[5,6]

Hypocalcemia

Even a minute decrease in serum calcium stimulates the calcium-sensing receptor to release PTH, increasing serum calcium to prevent the potentially harmful effects of hypocalcemia (eg, tetany, seizures). Hypocalcemia occurs when the effect of PTH is insufficient to raise serum calcium

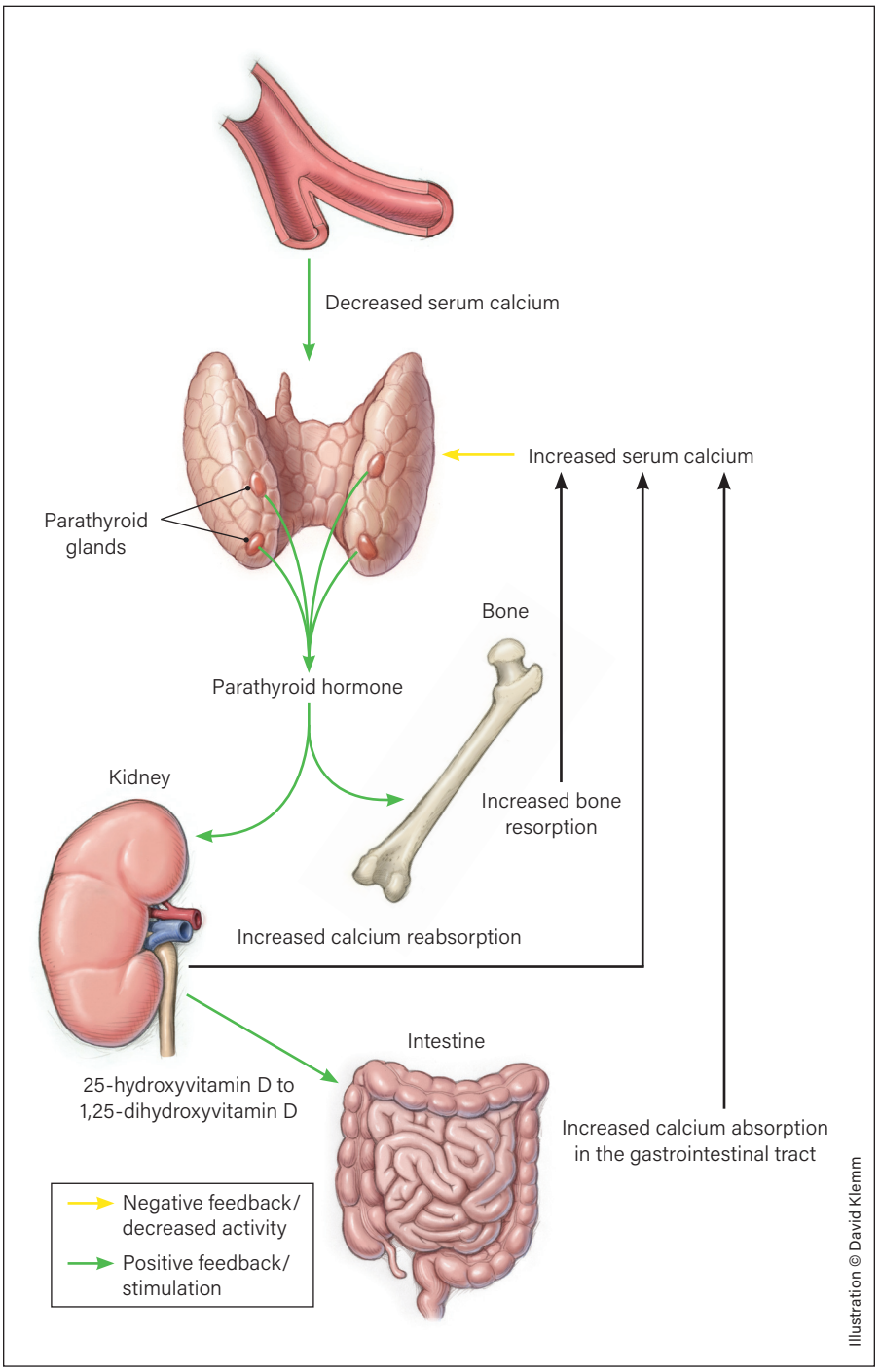


Figure 1. Calcium homeostasis.

Calcium-sensing receptors of parathyroid cells respond to serum calcium level and change with increased release (hypocalcemia) or suppression (hypercalcemia) of parathyroid hormone (PTH). PTH stimulates bone resorption, which increases serum calcium and phosphorus. In the kidney, PTH stimulates reabsorption of calcium and promotes phosphorus excretion. PTH also helps convert 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D in the kidneys, which then increases intestinal transport of calcium and phosphorus.

Illustration © David Klemm

Adapted with permission from Michels TC, Kelly KM. Parathyroid disorders. *Am Fam Physician.* 2013;88(4):250.

due to lack of PTH, resistance to PTH, vitamin D deficiency, or extravascular calcium deposition. Underlying causes include hypoparathyroidism and severe kidney failure.

Magnesium is also required for secretion and effect of PTH, therefore, hypomagnesemia may contribute to or be the sole cause of hypocalcemia. Large amounts of calcium deposition in tissues, which occurs with rhabdomyolysis or acute pancreatitis, can lead to transient hypocalcemia.

CLINICAL PRESENTATION

Hypocalcemia manifests with a range of presentations, from asymptomatic to life-threatening tetany, depending on the rate of onset and severity of decrease in serum calcium. An acute decrease to less than 7.0 to 7.5 mg/dL (1.75-1.88 mmol/L) can cause neuromuscular irritability.[7] Patients may experience paresthesia (eg, circumorally, in extremities) and muscle cramps. Tetany may be elicited with the Chvostek sign (ie, contraction of the ipsilateral facial muscles when the facial nerve anterior to the ear is tapped), or more commonly with the Trousseau sign (ie, carpal spasm after inflation of a sphygmomanometer cuff above systolic blood pressure for 3 minutes).[8]

Laryngospasm and bronchospasm can lead to respiratory arrest. Cardiac effects include prolonged QT interval and decreased cardiac contractility, which can contribute to heart failure and hypotension. Seizures may be generalized tonic-clonic, generalized absence, or focal.[9] Neurocognitive changes can include depression, anxiety, fatigue, and, less commonly, delirium or psychosis.[10]

Chronic, mild hypocalcemia (8.0 to less than 8.4 mg/dL [2.0-2.1 mmol/L]) is usually asymptomatic.[11] However, different etiologies can cause different complications. Chronic hypoparathyroidism is associated with decreased bone mineral density, cataracts, and

basal ganglia calcification.[7] Long-term vitamin D deficiency can present as rickets in children or osteomalacia in adults.

DIAGNOSIS

The first step in diagnosis is to confirm hypocalcemia and exclude pseudohypocalcemia. Review of previous laboratory test results to determine chronicity can be helpful. The etiology may be evident from the patient history (eg, chronic hypocalcemia due to chronic kidney disease [CKD], acute hypocalcemia with rhabdomyolysis). If the cause is unclear, obtaining a serum PTH concentration can assist in differentiating among causes (Table 1[2,7,12]).

In the presence of hypocalcemia, PTH should be increased. If PTH is low, then hypoparathyroidism is likely present. Normal levels of PTH are also considered inappropriately normal and often indicate hypoparathyroidism. More than 75% of hypoparathyroidism is postsurgical, and it occurs in 20% to 25% of patients who have undergone neck surgeries such as thyroidectomy or parathyroidectomy.[13] Most cases are transient and resolve within 2 months, but up to 5% may develop chronic hypoparathyroidism.[13,14] Hypomagnesemia and autosomal dominant hypocalcemia can also be associated with low PTH levels.[3]

If PTH is increased, then severe CKD (estimated glomerular filtration rate less than 15 mL/min/1.73 m^2 or dependence on dialysis) or vitamin D deficiency may be the cause. In severe CKD, impaired kidney function

TABLE 1
Hypocalcemia Causes and Associated Biochemical Findings

Cause	Parathyroid hormone	25-Hydroxy-vitamin D	Phosphorus	Additional findings
Postsurgical hypoparathyroidism	↓ or —	—	↑	History of thyroidectomy, parathyroidectomy, or radical surgery for head or neck cancer
Autoimmune hypoparathyroidism	↓	—	↑	Candidiasis and adrenal insufficiency suggest polyglandular autoimmune syndrome type 1
Hungry bone syndrome	↓	—	↓	Postparathyroidectomy Hypomagnesemia and hyperkalemia may be present
Autosomal dominant hypocalcemia	— or ↓	—	↑	Asymptomatic activating sequence variant in *CASR* lowers calcium set-point for parathyroid hormone secretion
Hypomagnesemia	— or ↓	—	—	Magnesium < 1.0 mg/dL (0.41 mmol/L) Hypocalcemia resolves within minutes to hours of magnesium replacement
Vitamin D deficiency	↑	↓	↓ or —	Low urine calcium
Chronic kidney disease	↑	—*	↑	Increased creatinine, decreased 1,25-dihydroxyvitamin D
Extravascular calcium deposition	↑	—	↑ or ↓	Rhabdomyolysis, tumor lysis syndrome, acute pancreatitis, or osteoblastic metastasis
Pseudohypoparathyroidism (*GNAS* gene sequence variant)	↑	—	↑	Presents in childhood, parathyroid hormone resistance

*—May be decreased if concurrent vitamin D deficiency.

Information from references 2, 7, and 12.

leads to increased phosphorus and decreased calcitriol levels. With vitamin D deficiency, 25-hydroxyvitamin D and phosphorous are low because vitamin D aids gastrointestinal absorption of phosphorus while increased PTH increases urinary phosphorus excretion.

TREATMENT

Acutely symptomatic patients require inpatient treatment with intravenous (IV) calcium gluconate and cardiac monitoring.[7] Calcium gluconate (1-2 g IV) should be initially given over 10 to 20 minutes to prevent cardiac dysfunction associated with more rapid infusion rates. This will quickly resolve symptoms, and additional IV calcium may be administered after 10 to 60 minutes if needed. If hypocalcemia persists, as in hypoparathyroidism or acute pancreatitis, a continuous infusion of calcium gluconate may be initiated.

Hypomagnesemia should be corrected with a goal concentration greater than 1 mg/dL. Calcium levels should be monitored every 4 to 6 hours until corrected, then oral calcium and vitamin D supplements started. Unless severely symptomatic, patients with transient hypocalcemia due to extravascular deposition should not receive IV calcium because the serum calcium level will normalize as the underlying cause resolves.

For patients with chronic, mild hypocalcemia, calcium can be replaced orally with 1 to 4 g of elemental calcium daily in two to three divided doses. Calcium carbonate is 40% elemental calcium, therefore 1,250 mg has 500 mg of elemental calcium. Information about elemental calcium content is usually provided on the supplement label. Calcium carbonate should be taken with meals to improve absorption. If patients take acid-blocking medications, calcium citrate is preferred because it does not require an acidic environment for absorption.[7] Calcium supplements also bind phosphate and may be used in patients with CKD to address concurrent hyperphosphatemia.[12]

Patients with hypoparathyroidism require lifelong calcium and calcitriol replacement, and those with refractory hypocalcemia may require recombinant PTH.[7,15] Patients with severe vitamin D deficiency (25-hydroxyvitamin D less than 10 ng/mL [24.96 nmol/L]) require vitamin D_2 or D_3 (ie, 50,000 IU weekly for 6 to 8 weeks and 800 to 1,000 IU daily thereafter).[16,17] In patients with other causes of hypocalcemia, the underlying etiology should be addressed. Patients with severe CKD may require calcitriol if hyperparathyroidism persists after vitamin D deficiency and hyperphosphatemia are corrected.[12] Patients with ongoing gastrointestinal or renal losses of magnesium, such as with Bartter syndrome, may require daily oral magnesium supplements.

Hypercalcemia

Hypercalcemia is commonly encountered in clinical practice, occurring in approximately 1% of the general population.[18] Primary hyperparathyroidism and malignancy account for up to 90% of cases, but there are many other causes[19] (Table 2[2,4,19-21]).

Humoral hypercalcemia of malignancy occurs with solid tumors that produce PTH-related peptide, a homologue of PTH that induces similar physiologic effects. Bone metastases and multiple myeloma stimulate osteoclast activity and increase bone resorption. Hematologic malignancies (eg, lymphoma) can ectopically produce calcitriol.

TABLE 2
Hypercalcemia Causes

PTH-mediated	Non–PTH-mediated
Familial hypocalciuric hypercalcemia	Endocrine disorders: adrenal insufficiency, hyperthyroidism, pheochromocytoma
Medications: lithium, teriparatide	Granulomatous disease: fungal infection (eg, coccidioidomycosis), sarcoidosis, tuberculosis
Primary hyperparathyroidism*: familial isolated hyperparathyroidism, multiple endocrine neoplasia, parathyroid adenoma or carcinoma	Immobilization
Tertiary hyperparathyroidism†	Malignancy*: bone metastases, ectopic calcitriol (eg, lymphoma), humoral hypercalcemia of malignancy, multiple myeloma
	Medications: levothyroxine (iatrogenic hyperthyroidism), sodium-glucose cotransporter-2 inhibitors, thiazide diuretics, vitamin A or D intoxication
	Milk-alkali syndrome

PTH = parathyroid hormone.

*—These causes account for more than 90% of hypercalcemic cases.

†—This condition occurs in patients with kidney failure who, after long-standing hypocalcemia and subsequent secondary hyperparathyroidism, develop parathyroid hyperplasia and PTH production that is no longer suppressed by increased calcium levels.

Information from references 2, 4, and 19-21.

Thiazide diuretics increase renal calcium reabsorption, leading to mild hypercalcemia.[20] Vitamin D intoxication generally occurs at levels greater than 100 to 150 ng/mL (249.6-374.4 nmol/L).[21] Large amounts of calcium carbonate intake may lead to milk-alkali syndrome, a triad of hypercalcemia, metabolic alkalosis, and acute kidney failure.

Granulomatous diseases, such as sarcoidosis, increase calcitriol and thus calcium absorbed from the intestinal tract. Familial hypocalciuric hypercalcemia is an autosomal-dominant inactivating sequence variation in the calcium-sensing receptor gene that requires a higher serum calcium level to downregulate PTH.

CLINICAL PRESENTATION

Like hypocalcemia, hypercalcemia manifests on a clinical spectrum ranging from relatively asymptomatic to severe, with debilitating dehydration and obtundation. The variation in symptoms is determined by the severity and rate of serum calcium increase.

Mild cases of hypercalcemia (ie, serum calcium less than 12 mg/dL [3.0 mmol/L) are often asymptomatic and detected on routine laboratory tests.[22] Patients may describe vague symptoms of constipation, depression, and fatigue.

Moderate hypercalcemia (ie, 12-14 mg/dL [3.0-3.5 mmol/L) can be relatively asymptomatic and well-tolerated if chronic, but acute changes in serum calcium can result in polyuria, polydipsia, nausea, dehydration, weakness, and confusion.[18,22] The effect of calcium on smooth muscle may manifest as symptoms of constipation, nausea, and anorexia. Hypercalcemia-induced pancreatitis and peptic ulcer disease can contribute to abdominal pain.[23]

Musculoskeletal symptoms can include bone pain, weakness, and decreased deep tendon reflexes. Neurocognitive changes (eg, lethargy, confusion) are more common among patients older than 50 years.[4] With long-standing hypercalcemia, nephrocalcinosis and nephrolithiasis can result in CKD.[24]

Severe hypercalcemia (ie, greater than 14 mg/dL) is often a medical emergency.[22] Patients may be severely dehydrated and obtunded, and are at risk of cardiac arrhythmias from a shortened QT interval. Hypercalcemia can cause arginine vasopressin resistance (ie, diabetes insipidus) due to downregulation of aquaporin channels, leading to diuresis and dehydration.[25]

Hypercalcemia stimulates renal vasoconstriction, and hypovolemia from dehydration contributes to declining renal function. This results in a self-perpetuating cycle of worsening diuresis due to high calcium, hypovolemia, worsening renal function, and decreased urinary calcium excretion.

DIAGNOSIS

Hypercalcemia should first be confirmed by measurement of ionized calcium or repeat measurement of total serum calcium and correction for albumin, as indicated. High concentrations of globulins can cause pseudohypercalcemia. When multiple myeloma is suspected, an ionized calcium level should be obtained. If available, previous serum calcium levels should be reviewed to assess chronicity.

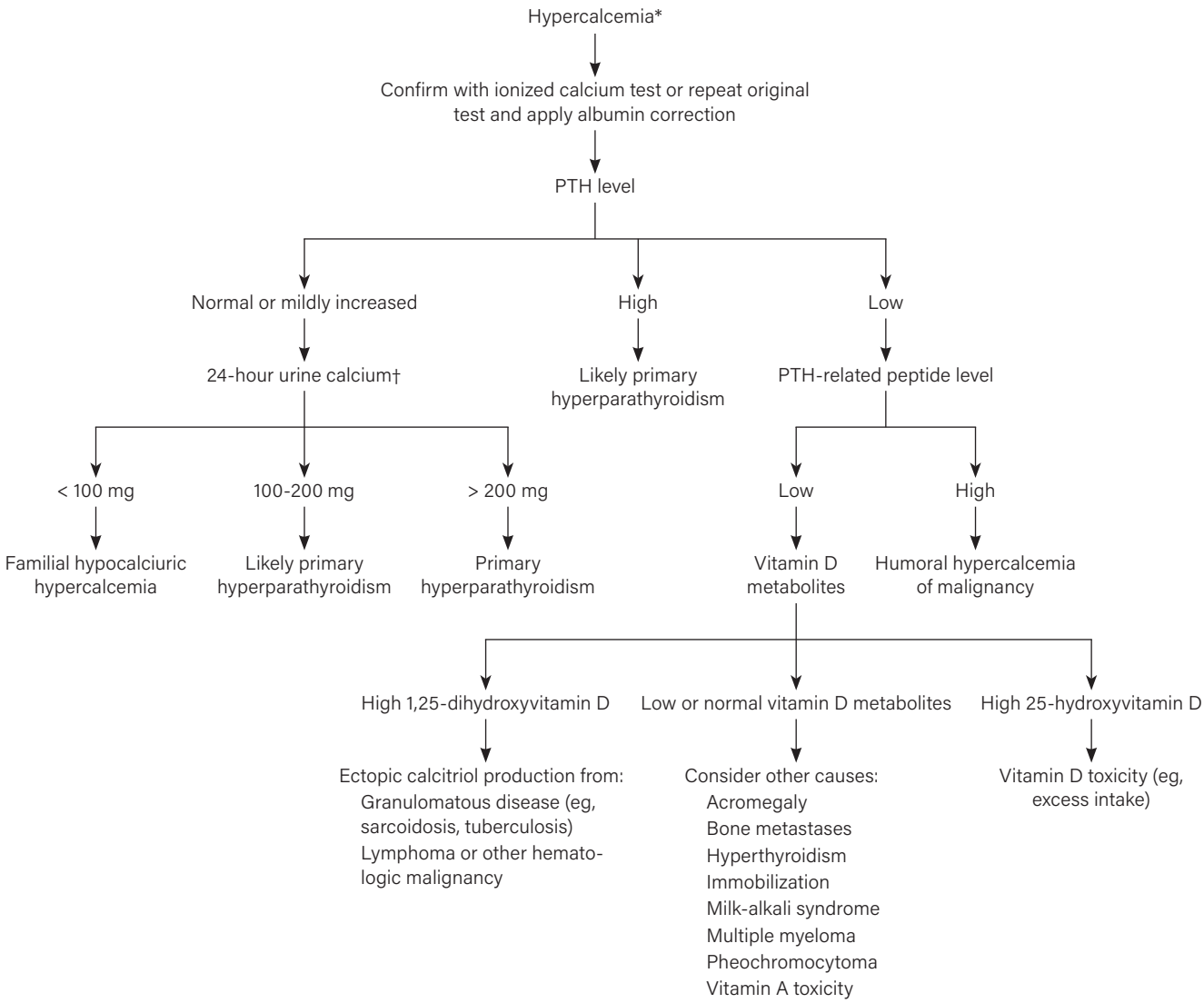
Long-standing, mild hypercalcemia suggests primary hyperparathyroidism. Severe or acutely symptomatic hypercalcemia is more likely due to malignancy.[19]

Patients with long-standing hypercalcemia may have a history of kidney stones or reduced bone mineral density on dual-energy X-ray absorptiometry screening.[26] Underlying causes can be identified on review of medications and supplements, including vitamin D and calcium. In healthy individuals, high dietary calcium intake alone will not cause hypercalcemia. A family history of hyperparathyroidism or multiple endocrine neoplasia, or a personal history of cancer may suggest the etiology.

Hypercalcemia is categorized as PTH-mediated and non–PTH-mediated. Thus, the next step in evaluation is to assess the serum PTH level (Figure 2). An increased PTH usually indicates primary hyperparathyroidism. In a patient with hypercalcemia, a normal PTH is still likely to indicate primary hyperparathyroidism, as an increased serum calcium should suppress PTH. However, mild hypercalcemia with a normal or mildly increased PTH level can occur in familial hypocalciuric hypercalcemia, which is asymptomatic, does not require treatment, and should be excluded before referral for parathyroidectomy.[27]

A 24-hour urine calcium test can help differentiate. Patients with primary hyperparathyroidism usually have a 24-hour urine calcium excretion greater than 200 mg/day. In patients with familial hypocalciuric hypercalcemia, it is often less than 100 mg/day. Patients with vitamin D deficiency may be hypocalciuric, so vitamin D should be replaced before evaluating calcium excretion. A fractional excretion of calcium can also be calculated using a 24-hour urine collection sample. Spot urine collections have not been validated. A fractional excretion of calcium less than 0.01 is highly suggestive of familial hypocalciuric hypercalcemia.[28]

In patients with a low PTH, malignancy is the most common cause of hypercalcemia.[19] Advanced cancer may be evident on presentation, but if uncertain, an increased level of PTH-related peptide indicates humoral hypercalcemia of malignancy. If PTH and PTH-related



PTH = parathyroid hormone.

*—If mild hypercalcemia (< 12 mg/dL [3.0 mmol/L]) and taking a thiazide diuretic, stop thiazide and reassess serum calcium in 1 month.

†—If 24-hour urine calcium is low, exclude low vitamin D (25-hydroxyvitamin D < 20 ng/mL [49.9 nmol/L]). If concomitant vitamin D deficiency, replace vitamin D and repeat 24-hour urine calcium measurement in 2 to 3 months.

Figure 2. Hypercalcemia evaluation.

peptide concentrations are both low, then measurement of vitamin D metabolites should be obtained. An elevated 25-hydroxyvitamin D level suggests excess intake, whereas increased calcitriol is consistent with ectopic production from granulomatous disease or malignancy. Chest radiography may show lymphadenopathy or pulmonary sarcoidosis.

If PTH, PTH-related peptide, and vitamin D metabolites are not increased, other causes to consider include bone metastases, immobilization, milk-alkali syndrome, multiple myeloma, hyperthyroidism, and vitamin A toxicity.

TREATMENT

Treatment depends on chronicity and severity of symptoms. For patients with chronic mild to moderate hypercalcemia and few symptoms, management includes avoidance of exacerbating factors and treatment of the cause. Contributing medications, such as thiazide diuretics, should be discontinued. Patients should maintain adequate hydration (ie, 64 oz of water daily), perform regular physical activity, and avoid excess intake of calcium (ie, 1,000 mg or less daily) and vitamin D (ie, 800 IU or less daily).

For patients with primary hyperparathyroidism, options include surgical parathyroidectomy or

TABLE 3
Indications for Parathyroidectomy in Asymptomatic Primary Hyperparathyroidism

Indication	Specific criteria
Age	< 50 years
Increased serum calcium	Serum calcium 1 mg/dL (0.25 mmol/L) greater than upper limit of normal
Renal involvement	Estimated glomerular filtration rate < 60 mL/min/1.73 m^2
	Nephrocalcinosis or nephrolithiasis noted on imaging
	Hypercalciuria (ie, women > 250 mg/day, men > 300 mg/day)
Skeletal involvement	Osteoporosis (ie, low bone mineral density, T-score ≤ –2.5 at any site on dual-energy x-ray absorptiometry)
	Vertebral fracture noted on imaging

Note: Patients with any one of the specific criteria meet guidelines for parathyroidectomy.
Information from reference 27.

observation. More than 85% of patients have a single adenoma and removal is curative.[29] Although all patients may be offered surgery, it is indicated for those with symptoms. Guidelines also recommend surgery for asymptomatic patients with a serum calcium level greater than 1 mg/dL (0.25 mmol/L) above the upper limit of normal, skeletal or renal involvement, or age younger than 50 years (Table 3[27]). Parathyroidectomy is associated with small improvements in bone mineral density, but not with lower risk of fracture or improved quality of life.[30,31]

Asymptomatic patients with hyperparathyroidism can be safely monitored for years without progression. A prospective cohort study found that over the course of 15 years, approximately two-thirds of asymptomatic patients did not meet criteria for parathyroidectomy.[32] Monitoring should include serum calcium and creatinine measurement annually and bone mineral density assessment every 1 to 2 years.[27] Cinacalcet, a calcimimetic, is an option for symptomatic patients who cannot undergo surgery. For patients with osteoporosis, a bisphosphonate should be offered.

Patients with severe hypercalcemia and acute symptoms (eg, severe dehydration, lethargy, stupor) require prompt inpatient admission to prevent life-threatening complications. Treatment includes hydration with IV fluids, bisphosphonates, and calcitonin to lower the serum calcium, with simultaneous evaluation for underlying causes. Normal saline should be administered at an initial rate of 200 to 300 mL/hour and adjusted to maintain a urine output of 100 to 150 mL/hour. Loop diuretics should be avoided unless hypervolemia occurs.[33]

Zoledronate, an IV bisphosphonate, has shown greater efficacy than and safety equivalent to that of pamidronate.[34] Zoledronate 4 mg has been shown to be as effective as 8 mg with less renal toxicity.[34] Bisphosphonates decrease serum calcium in 2 to 4 days. If rapid reduction is required, calcitonin may be added. Calcitonin lowers calcium within 1 hour by a maximum of 1 to 2 mg/dL (0.25-0.5 mmol/L) and is given intramuscularly or subcutaneously.[35] Due to the risk of tachyphylaxis, it is discontinued after 48 hours. In refractory cases and patients with severe renal impairment, denosumab is an alternative, but it is more likely to cause hypocalcemia.[36]

Hemodialysis is indicated for patients with serum calcium greater than 18 to 20 mg/dL (4.5-5.0 mmol/L), patients who cannot tolerate IV fluids (eg, with heart failure or end-stage renal disease), and refractory cases. For patients with granulomatous-associated hypercalcemia, glucocorticoids (eg, prednisone 20-40 mg daily) are preferred.[37]

Case 4, continued. You review SG's records and note a mildly increased serum calcium of 10.5 mg/dL (2.63 mmol/L) over the past 2 years. She has had constipation but denies other symptoms. You order a PTH level, which is at the upper end of the normal range. Her 25-hydroxyvitamin D level is 36 ng/mL (89.86 nmol/L), which is normal. You suspect primary hyperparathyroidism and order a 24-hour urine collection to exclude familial hypocalciuric hypercalcemia. Her 24-hour urine calcium level is elevated at 320 mg/day. You refer SG for a parathyroidectomy, and histopathologic evaluation reveals a single adenoma.

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CME Quiz Answers

Question 1: The correct answer is C.
Urine osmolality less than 600 mOsm/kg (600 mmol/kg) water is associated with renal free water loss, which may be due to arginine vasopressin deficiency or resistance, chronic kidney disease, loop diuretics, or osmotic diuresis. Urine osmolality greater than 600 mOsm/kg water typically is caused by extrarenal free water loss (eg, burns, gastrointestinal loss, increased metabolic demand, perspiration, pulmonary loss), inadequate water intake, or salt overload (resulting from administration of total parenteral nutrition). See Section One, Table 1.

Question 2: The correct answer is B.
Patients with hyponatremia due to primary polydipsia are euvolemic, and laboratory test results include plasma osmolality less than 280 mOsm/kg (280 mmol/kg) and urine osmolality less than 100 mOsm/kg (100 mmol/kg). In pseudohyponatremia, plasma osmolality is in the normal range, 280 to 295 mOsm/kg (280-295 mmol/kg). Patients with renal and extrarenal sodium losses tend to be hypovolemic and have plasma osmolality less than 280 mOsm/kg. Patients with hyponatremia related to acute or chronic kidney disease tend to be hypervolemic and have plasma osmolality less than 280 mOsm/kg. See Section One, Figure 1.

Question 3: The correct answer is C.
Chronic hypernatremia is often asymptomatic and discovered on routine laboratory testing. However, it is associated with increased risk of mortality, cardiovascular events, and infection. Acute hypernatremia can be severe and life-threatening. Symptoms usually do not occur until serum sodium is greater than 158 mEq/L (158 mmol/L). Patients may present with fatigue, signs of dehydration, and weakness, then progress to seizures, rhabdomyolysis, and coma. See page 11.

Question 4: The correct answer is C.
The preferred treatment of severe symptomatic hyponatremia is administration of hypertonic (3%) saline. Normal saline and lactated Ringer solution will not correct hypernatremia as quickly as hypertonic saline. It would be inappropriate to rely on fluid restriction to correct this patient's sodium level. See Section One, Figure 2.

Question 5: The correct answer is C.
Magnesium deficiency is seen in more than 50% of patients with clinically significant hypokalemia, usually in those receiving loop or thiazide diuretic therapy. When serum magnesium decreases below 1.2 mg/dL (0.49 mmol/L), hypokalemia is often refractory to treatment and magnesium must be replaced. Sodium, chloride, and calcium disturbances are other derangements that may co-occur with hypokalemia and should be investigated appropriately. See page 18.

Question 6: The correct answer is C.
In patients with acute hyperkalemia, intravenous calcium gluconate (1-3 g) is given initially to stabilize cardiac cell membranes. Calcium gluconate is recommended for patients with electrocardiography changes or a serum potassium level greater than 6.5 mEq/L. Next, insulin and beta agonists are given together to drive extracellular potassium into the cells, as their effects are synergistic. If the patient is not hypervolemic or anuric, loop diuretics are administered with intravenous fluids to increase delivery of sodium and water to the distal tubule for enhanced urinary potassium excretion. Potassium binders (eg, sodium zirconium cyclosilicate [Lokelma], patiromer [Veltassa]) bind potassium in the intestinal tract for excretion in the stool. The latter steps may be necessary, but the first step is to stabilize the cardiac cell membranes with calcium gluconate. See page 21.

Question 7: The correct answer is C.
Every 0.3 mEq/L (0.3 mmol/L) decrease in serum potassium represents a total body potassium loss of approximately 100 mEq (100 mmol) that needs to be replaced. Using 4.0 mEq/L (4 mmol/L) as the goal of treatment, this patient's serum potassium is decreased by 1.5 mEq/L (1.5 mmol/L) (ie, 5 x 0.3 mEq/L), the approximate total body potassium deficit is 5 x 100 mEq, or 500 mEq (500 mmol). See page 18.

Question 8: The correct answer is C.
Pseudohyperkalemia can be a result of a traumatic blood draw, use of a tourniquet during a blood draw, or repeated fist clenching by the patient during a blood draw. It may also be seen in patients with chronic leukemias or thrombocytosis. Insulin is responsible for an intracellular shift of potassium, lowering blood levels; it would not be expected to cause hyperkalemia. Elevated platelet levels may be associated with hyperkalemia. Hypomagnesemia is often associated with hypokalemia, making it more difficult to correct. See Section Two, Table 3 and page 20.

Question 9: The correct answer is C.
A low pH on blood gas measurement represents acidosis. In metabolic disorders, changes in bicarbonate level (elevated in alkalosis, decreased in acidosis) cause the primary disorder, with compensatory change in carbon dioxide in the same direction (elevated in alkalosis, decreased in acidosis). In respiratory disorders, changes in carbon dioxide level (elevated in acidosis, decreased in alkalosis) cause the primary disturbance, with com-

pensatory change in bicarbonate level in the same direction (elevated in acidosis, decreased in alkalosis). See Section Three, Table 1.

Question 10: The correct answer is B.
This patient has metabolic alkalosis because the pH and bicarbonate levels are elevated. Elevated carbon dioxide indicates some respiratory compensation. Causes of metabolic alkalosis with urine chloride 20 mEq/L (20 mmol/L) or greater and increased blood pressure include Cushing syndrome and hyperaldosteronism. Vomiting, diarrhea, and diuretic use can cause metabolic alkalosis but are usually associated with a urine chloride less than 20 mEq/L. Guillain-Barré syndrome may be associated with a respiratory acidosis due to hypoventilation. See Section Three, Table 1 and Table 3.

Question 11: The correct answer is A.
Common causes of high anion gap metabolic acidosis can be recalled using the mnemonic KULOST (ketoacidosis [due to diabetes or alcohol use with starvation], uremia [attributable to kidney failure], lactic acidosis [caused by inadequate tissue oxidation or defects in cellular metabolism], osmolar gap etiologies [methanol, ethylene glycol, or propylene glycol ingestion], salicylates or acetaminophen, and toxins). Stroke, sedative use, and obesity hypoventilation syndrome are all more commonly associated with respiratory acidosis due to hypoventilation. See Section Three, Table 3 and page 24.

Question 12: The correct answer is B.
Respiratory alkalosis is characterized by excessive loss of carbon dioxide due to hyperventilation, which results in elevation of the serum pH. Due to normal physiologic changes, pregnancy is associated with a chronic respiratory alkalosis, which is usually asymptomatic. Chronic obstructive pulmonary disease, obstructive sleep apnea, and amyotrophic lateral sclerosis are associated with hypoventilation, accumulation of carbon dioxide, and respiratory acidosis. See Section Three, Table 3.

Question 13: The correct answer is C.
In a patient with hypercalcemia and a normal or increased parathyroid hormone (PTH) level, primary hyperparathyroidism is the most likely cause of elevated calcium levels. Bone metastases, primary hyperthyroidism, and sarcoidosis are alternative causes that are non–PTH-mediated, but they are less common, especially in a patient with no other pertinent medical history. See Section Four, Figure 2 and Table 2.

Question 14: The correct answer is C.
Hyperthyroidism is the most likely explanation for this patient's hypercalcemia. A low parathyroid hormone (PTH) level suggests that she does not have primary hyperparathyroidism. A low PTH-related peptide makes humoral hypercalcemia of malignancy less likely. A 24-hour urine calcium level greater than 100 mg/day suggests that familial hypocalciuric hypercalcemia is an unlikely cause. If PTH, PTH-related peptide, and vitamin D metabolites are not increased, other causes of hypercalcemia to consider include bone metastases, immobilization, milk-alkali syndrome, multiple myeloma, pheochromocytoma, and vitamin A toxicity. See Section 4, Figure 2.

Question 15: The correct answer is A.
This patient presents with symptoms consistent with acute hypocalcemia, which may be caused by kidney failure or hypoparathyroidism, among other causes. Signs consistent with hypocalcemia include Chvostek sign, which is characterized by contraction of the ipsilateral facial muscles when the facial nerve anterior to the ear is tapped, and Trousseau sign, which is carpal spasm after inflation of a sphygmomanometer cuff above systolic blood pressure for 3 minutes. See page 31.

Question 16: The correct answer is C.
In the presence of hypocalcemia, parathyroid hormone (PTH) should be increased. If PTH is low, then hypoparathyroidism is likely present. Normal levels of PTH are also considered inappropriately normal and often indicate hypoparathyroidism. More than 75% of hypoparathyroidism is postsurgical, and it occurs in 20% to 25% of patients who have undergone neck surgeries such as thyroidectomy or parathyroidectomy. Most postsurgical cases of hypocalcemia are transient and resolve within 2 months, but up to 5% of patients may develop chronic hypoparathyroidism. See Section Four, Table 1 and page 32.

Notes

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