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25(OH)D levels, which reflect vitamin D stores. Urinary calcium levels in 24-hour collections are low with both vitamin D deficiency and pri mary intestinal disease-causing severe calcium malabsorption. In the setting of nonnutritional rickets, with suspected vitamin D resistance, serum 1,25(OH)2D levels are informative.

TREATMENT Hypocalcemia The approach to treatment depends on the severity of the hypocal cemia, the rapidity with which it develops, and the accompanying complications (e.g., tetany, seizures, QTc prolongation). Acute, symptomatic hypocalcemia is initially managed with calcium glu conate, a 10-mL ampule of 10% wt/vol (90 mg or 2.2 mmol) diluted in 50 mL of 5% dextrose or 0.9% sodium chloride and given intravenously over 5–10 min with telemetry. After one or two additional ampules are given at 10-60 minute intervals as needed to initially resolve symptoms, while transitioning to oral medication symptomatic hypocalcemia often requires a period of continuous intravenous calcium infusion (often starting at 1 mg/min elemental calcium for adults) that is titrated to symptoms, ECG, and blood calcium levels targeting the lower limit of normal. Telemetry with serial exams and blood calcium levels every 4–6 hours should be closely monitored. Accompanying hypomagnesemia, if present, should be treated with appropriate magnesium supplementa tion, with initiation of chronic-phase treatment once tetany has resolved, the patient is stable and able to safely take oral medication, and the QTc has normalized. PART 2 Cardinal Manifestations and Presentation of Diseases Chronic hypocalcemia due to hypoparathyroidism is treated with oral calcium supplements (1000–3000 mg/d elemental cal cium in divided doses), with careful titration of oral calcitriol [1,25(OH)2D, 0.25–1 µg/d] to achieve albumin-corrected low-normal serum calcium levels. Because calcium resorption in the distal con voluted tubule (about 10% of the filtered load) is dependent upon PTH, normalization of calcium to above the low-normal range in the absence of PTH replacement increases hypercalciuria with risk of nephrolithiasis and nephrocalcinosis. Urine 24-hour calcium targets are under 250 mg (women) to 300 mg (men). Adequate vitamin D3 nutrition (1000–2000 IU daily for most adults) must still be maintained and monitored every 6–12 months, measuring serum 25(OH)D levels. PTH (1-84) (Natpara), approved by the Food and Drug Admin istration for treatment of hypoparathyroidism, has now been discontinued by the manufacturer. PTH (1-34), also known as teriparatide, is approved for osteoporosis, but has been success fully used off-label (20 µg subcutaneously twice daily) for treating refractory hypoparathyroidism. Dosing may need to be decreased in patients with chronic renal insufficiency to avoid hypercalcemia. Palopegteriparatide, a pegylated prodrug form of teriparatide with pharmacokinetics that enable daily subcutaneous dosing for PTH replacement, is

now under consideration for regulatory approval. Routine daily vitamin D (~1000 IU D3) and calcium (~1000 mg elemental calcium) nutrition suffices, and hypercalciuria should be absent, with PTH replacement strategies. Hypocalcemia from vitamin D deficiency is best treated using vitamin D supplementa tion, with the dose depending on the severity of the deficit and the underlying cause. Thus, nutritional vitamin D deficiency generally responds to moderate doses of oral vitamin D (e.g., ergocalciferol at 50,000 IU, 2–3 times per week for several months), whereas vita min D deficiency due to severe enteric malabsorption may require much higher doses (e.g., ergocalciferol carefully titrated up to 100,000 IU/d), as is often the case following Roux-en-Y bariatric surgery. In the setting of intestinal disease, calcium supplementation as calcium citrate is preferred because it is better absorbed, and this formulation increases urinary citrate to mitigate the risk of nephro lithiasis in this setting due to increased dietary oxalate absorption. Serum calcium, phosphate, and PTH should be monitored initially every 4 weeks when treating the hypocalcemia of severe vitamin

D insufficiency or gastrointestinal calcium malabsorption, with the goal of normalizing serum biochemistries and 24-hour urine calcium levels to low normal. ■ ■GLOBAL CONSIDERATIONS In countries with limited access to health care or screening laboratory testing of serum calcium levels, pHPT often presents in its advanced form with severe skeletal complications (osteitis fibrosa cystica), in contrast to the incidental finding of asymptomatic hypercalcemia com mon in developed countries. Climate change increases the negative impacts of hypercalcemia on risks for nephrolithiasis and heat-related ill ness with dehydration in those with previously asymptomatic disease. In addition, vitamin D deficiency is paradoxically common in some countries despite extensive sunlight (e.g., India) due to poor dietary vitamin D intake and avoidance of sun exposure. Acknowledgment The author gratefully acknowledges the contributions of Dr. Sundeep Khosla to this chapter in previous editions of Harrison’s. ■ ■FURTHER READING El-Hajj Fuleihan G: Treatment of hypercalcemia of malignancy in adults: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 108:507, 2023. Hannan FM et al: The calcium-sensing receptor in physiology and in calcitropic and noncalcitropic diseases. Nat Rev Endocrinol 15:33, 2018. Kahn AA et al: Evaluation and management of hypoparathyroidism. Summary statement and guidelines from the Second International Workshop. J Bone Miner Res 37:2568, 2022. Minisola S et al: Epidemiology, pathophysiology, and genetics of primary hyperparathyroidism. J Bone Miner Res 37:2315, 2022. Motlaghzadeh Y et al: Rare causes of hypercalcemia: 2021 update. J Clin Endocrinol Metab 106:3113, 2021. Walker MD, Shane E: Hypercalcemia. A review. JAMA 328:1624, 2022. Thomas D. DuBose, Jr.

Acidosis and Alkalosis NORMAL ACID-BASE HOMEOSTASIS Systemic arterial pH is maintained between 7.35 and 7.45 by extracel lular and intracellular chemical buffering together with respiratory and renal regulatory mechanisms. The control of arterial CO2 tension (Paco2) by the central nervous system (CNS) and respiratory system and the control of plasma bicarbonate by the kidney stabilize the arte rial pH by excretion or retention of acid or alkali. The metabolic and respiratory components that regulate systemic pH are described by the Henderson-Hasselbalch equation and solved for pH when the solubil ity of CO2 is considered (dissolved CO2 in mmol/L = 0.03 × Paco2 in mmHg), at a pK′ of 6.1: − K pH p log [HCO] PCO

= ′+ α CO

Under most circumstances, CO2 production and excretion are matched, and the usual steady-state Paco2 is maintained at ~40 mmHg. Underexcretion of CO2 produces hypercapnia, and overexcretion causes hypocapnia. Nevertheless, production and excretion are again

matched at a new steady-state Paco2. Therefore, the Paco2 is regulated primarily by neural respiratory factors and is not subject to regulation by the rate of CO2 production. Hypercapnia is usually the result of hypoventilation rather than of increased CO2 production. Increases or decreases in Paco2 represent derangements of neural respiratory control or are due to compensatory changes in response to a primary alteration in the plasma [HCO3 −]. DIAGNOSIS OF GENERAL TYPES OF DISTURBANCES The most common clinical disturbances are simple acid-base disor ders; i.e., metabolic acidosis or alkalosis or respiratory acidosis or alka losis occurring individually. Recognition of simple acid-base disorders requires appreciation of the limits of physiologic compensation for a primary disturbance. ■ ■SIMPLE ACID-BASE DISORDERS Primary respiratory disturbances (primary changes in Paco2) invoke compensatory metabolic responses (secondary changes in [HCO3 −]), and primary metabolic disturbances elicit predictable compensa tory respiratory responses (secondary changes in Paco2). Physiologic compensation can be predicted from the relationships displayed in Table 58-1. In general, with one exception, compensatory responses return the pH toward, but not to, the normal value. Chronic respira tory alkalosis when prolonged is an exception to this rule and may return the pH to a normal value. Metabolic acidosis due to an increase in endogenous acid production (e.g., ketoacidosis or lactic acid aci dosis) lowers extracellular fluid [HCO3 −] and decreases extracellular pH. This change stimulates the medullary chemoreceptors to increase ventilation and to return the ratio of [HCO3 −] to Paco2, and, thus, pH, toward, but not typically to, the normal value. The degree of respiratory compensation expected in a metabolic acidosis can be predicted from the relationship: Paco2 = (1.5 × [HCO3 −]) + 8 ± 2 (Winter’s equation). For example, applying this equation, a patient with metabolic acidosis and [HCO3 −] of 12 mmol/L would be expected to have a Paco2 of approximately 26 mmHg. Therefore, if values for Paco2 were <24 or TABLE 58-1 Prediction of Compensatory Responses to Simple

Acid-Base Disturbances and Pattern of Changes RANGE OF VALUES – Paco2 Metabolic acidosis DISORDER PREDICTION OF COMPENSATION PH HCO3 Paco2 = (1.5 × HCO3 –) + 8 ± 2 or Paco2 will ↓ 1.25 mmHg per mmol/L ↓ in [HCO3 Low Low Low –] or Paco2 = [HCO3 –] + 15 Metabolic alkalosis High High High Paco2 will ↑ 0.75 mmHg per mmol/L ↑ in [HCO3 –] or Paco2 will ↑ 6 mmHg per 10 mmol/L ↑ in [HCO3 –] or Paco2 = [HCO3 –] + 15 Respiratory alkalosis High Low Low Acute [HCO3 –] will ↓ 0.2 mmol/L per mmHg ↓ in Paco2 Chronic [HCO3 –] will ↓ 0.4 mmol/L per mmHg ↓ in Paco2 Respiratory acidosis Low High High Acute [HCO3 –] will ↑ 0.1 mmol/L per mmHg ↑ in Paco2 Chronic [HCO3 –] will ↑ 0.4 mmol/L per mmHg ↑ in Paco2

Arterial blood [H+] (nmol/L) 100 90 80 70 60

100 90 80

Metabolic alkalosis Chronic respiratory acidosis Arterial plasma [HCO3] (mmol/L) –

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Acute respiratory acidosis

Normal

Acute respiratory alkalosis

Chronic respiratory alkalosis

Metabolic acidosis

PCO2(mmHg)

7.0 7.1 7.2 7.3 7.4 7.5 7.6 7.7 7.8 Arterial blood, pH FIGURE 58-1 Acid-base nomogram. Shown are the 90% confidence limits (range of values) of the normal respiratory and metabolic compensations for primary acidbase disturbances. (Reproduced with permission from LL Hamm and TD DuBose Jr, in Alan S.L. Yu, et al (eds): Brenner and Rector's The Kidney, 11th ed. Philadelphia, Elsevier, 2020.)

> 28 mmHg, values that exceed the boundaries for compensation for a simple disorder, a mixed disturbance should be recognized (metabolic acidosis plus respiratory alkalosis or metabolic acidosis plus respiratory acidosis, respectively). Compensatory responses for primary meta bolic disorders move the Paco2 in the same direction as the change in [HCO3 −], while compensation for primary respiratory disorders moves the [HCO3 −] in the same direction as the primary change in Paco2 (Table 58-1). Therefore, changes in Paco2 and [HCO3 −] in opposite directions (i.e., Paco2 or [HCO3 −] is increased, but the accompanying value is decreased) indicate a mixed acid-base disturbance. Another way to judge the appropriateness of the response in [HCO3 −] or Paco2 is to use an acid-base nomogram (Fig. 58-1). While the shaded areas of the nomogram show the 95% confidence limits for physiologic com pensation in simple disturbances, finding acid-base values within the shaded area does not necessarily rule out a mixed disturbance. Impo sition of one disorder over another may result in values lying within the area of a third. Thus, the nomogram, while convenient, is not a substitute for the equations in Table 58-1.
> ■ ■MIXED ACID-BASE DISORDERS Acid-base disorders in this category are defined as independently coex isting disorders, not merely compensatory responses. These types of disturbances are often seen in critically ill patients and can lead to dan gerous extremes of pH (Table 58-2). The diagnosis of mixed acid-base disorders requires consideration of the anion gap (AG). To be accurate, the AG requires the presence of, or correction to, a normal serum albumin of 4.5 g/dL (see below, "Evaluate the Anion Gap"). If a patient with diabetic ketoacidosis (metabolic acidosis) and a high AG has an independent and concomitant respiratory disorder (e.g., pneumonia), the latter may lead to a superimposed respiratory acidosis or alkalosis and the Paco2 will deviate from the predicted value for the response to a pure high-AG metabolic acidosis (Table

> 58-2). Patients with underlying chronic obstructive pulmonary disease may not respond to metabolic acidosis with an appropriate ventilatory response owing to insufficient respiratory reserve (Table 58-2). The combined presence of respiratory acidosis and metabolic acidosis can lead to severe acidemia. In contrast, when metabolic acidosis and metabolic alkalosis coexist in the same patient, the pH may be in the normal range. In this

TABLE 58-2 Clinical Examples of Mixed Acid-Base Disorders Mixed Metabolic and Respiratory Metabolic acidosis—respiratory alkalosis Key: High-AG metabolic acidosis; prevailing Paco2 below predicted value (Table 58-1) Example: Na+, 140; K+, 4.0; Cl−, 106; HCO3 −, 14; AG, 20; Paco2, 24; pH, 7.39 (etiology: lactic acidosis, sepsis in ICU) Metabolic acidosis—respiratory acidosis Key: High-AG metabolic acidosis; prevailing Paco2 above predicted value (Table 58-1) Example: Na+, 140; K+, 4.0; Cl−, 102; HCO3 −, 18; AG, 20; Paco2, 42; pH, 7.25 (etiology: severe pneumonia or pulmonary edema) PART 2 Cardinal Manifestations and Presentation of Diseases Metabolic alkalosis—respiratory alkalosis Key: Paco2 does not increase as predicted; pH higher than expected Example: Na+, 140; K+, 4.0; Cl−, 91; HCO3 −, 33; AG, 16; Paco2, 38; pH, 7.56

(end-stage liver disease with ascites in patient receiving diuretics) Metabolic alkalosis—respiratory acidosis Key: Paco2 higher than predicted; pH normal although both Paco2 and HCO3 − abnormal Example: Na+, 140; K+, 3.5; Cl−, 88; HCO3 −, 42; AG, 10; Paco2, 67; pH, 7.42

(COPD in patient receiving diuretics) Mixed Metabolic Disorders Metabolic acidosis—metabolic alkalosis Key: Only detectable if in patient with high-AG acidosis; ΔAG (10) >> ΔHCO3 (0) Example: Na+, 140; K+, 3.0; Cl−, 95; HCO3 −, 25; AG, 20; Paco2, 40; pH, 7.42 (uremia with vomiting) Metabolic acidosis—metabolic acidosis Key: Mixed high-AG—normal-AG acidosis; ΔHCO3 – accounted for by combined change in ΔAG and ΔCl− Example: Na+, 135; K+, 3.0; Cl−, 110; HCO3 −, 10; AG, 15; Paco2, 25; pH, 7.20 (diarrhea and lactic acidosis, toluene toxicity, treatment of diabetic ketoacidosis) Abbreviations: AG, anion gap; COPD, chronic obstructive pulmonary disease;

ICU, intensive care unit. circumstance, it is the recognition of an elevated AG (see below) that denotes the existence of an accompanying metabolic acidosis. Assum ing a normal value for the AG of 10 mmol/L, incongruity in the ΔAG (existing AG minus normal AG) and the ΔHCO3 − (normal value of

25 mmol/L minus abnormal HCO3 − in the patient) indicates the pres ence of a mixed high-gap acidosis—metabolic alkalosis (see example below). A diabetic patient with ketoacidosis may have acute or chronic kidney failure resulting in a combination of metabolic acidoses from accumulation of both ketoacids and uremic acids. Patients who have ingested an overdose of drug combinations such as sedatives and salicylates may have mixed disturbances as a result of the acid-base response to the individual drugs (metabolic acidosis mixed with respi ratory acidosis or respiratory alkalosis, respectively). Triple acid-base disturbances are more complex. For example, patients with metabolic acidosis due to alcoholic ketoacidosis may develop metabolic alkalosis due to vomiting and superimposed respiratory alkalosis due to the hyperventilation of hepatic dysfunction or alcohol withdrawal. APPROACH TO THE PATIENT Acid-Base Disorders The accurate diagnosis of acid-base disorders requires adherence to a stepwise approach (Table 58-3). Blood for plasma

electrolytes and arterial blood gases should be drawn simultaneously, prior to therapy. An increase in [HCO3 −] occurs with either metabolic alkalosis or respiratory acidosis. Conversely, a decrease in [HCO3 −] occurs with either metabolic acidosis or respiratory alkalosis. In the determination of arterial blood gases by the clinical laboratory, both pH and Paco2 are measured, and the [HCO3 −] is calculated from

TABLE 58-3 Steps in Accurate Diagnosis of Acid-Base Disorders

1. Obtain arterial blood gas (ABG) and venous electrolytes simultaneously.
2. Calculated [HCO3 −] on ABG and measured value on electrolyte panel should be approximately same; if not, suspect lab error or sampling error.
3. Assess anion gap (AG); correct to albumin concentration of 4.5 g/dL if hypoalbuminemia; high AG present if AG >10 mEq/L.
4. Known causes of high-AG acidosis (Table 58-4; ketoacidosis, lactic acid acidosis, advanced kidney disease, or toxic alcohol ingestion).
5. Known causes of nongap acidosis (Table 58-5; bicarbonate loss from gastrointestinal tract, renal tubular acidosis).
6. Estimate predicted compensatory response (Table 58-1).
7. Compare delta values (ΔAG and ΔHCO3 −).
8. Compare change in [Cl−] with change in [Na+]s on the electrolyte panel. the Henderson-Hasselbalch equation. This calculated value should be compared with the measured [HCO3 −] (or total CO2) on the electrolyte panel. These two values should agree within ±2 mmol/L. If the values do not agree, the blood samples may not have been drawn simultaneously, or a laboratory error may be present. After verifying the blood acid-base values, the precise acid-base disorder can then be classified. EVALUATE THE ANION GAP Evaluations of acid-base disorders should begin with appreciation of the patient’s AG. The AG is calculated, either by the clinical labo ratory or the clinician, as follows: AG = Na+ – (Cl− + HCO3 −). The value for plasma [K+] is typically omitted from the calculation of the AG in the United States. The “normal” value for the AG reported by clinical laboratories has declined with improved methodology for measuring plasma electrolytes and ranges from 6−12 mmol/L, with an average of approximately 10 mmol/L. The unmeasured anions normally present in plasma include anionic proteins (e.g., albumin), phosphate, sulfate, and organic anions. When acid anions, such as acetoacetate and lactate, accumulate in extracellular fluid, the AG increases, causing a high-AG acidosis. An increase in the AG is most often due to an increase in unmeasured anions but, less com monly, may be due to a decrease in unmeasured cations (calcium, magnesium, potassium). In addition, the AG may increase with an increase in anionic albumin (e.g., severe dehydration). A decrease in the AG can be due to (1) an increase in unmeasured cations; (2) the addition to the blood of abnormal cations, such as lithium (lithium intoxication) or cationic immunoglobulins (plasma cell dyscrasias); (3) a reduction in the plasma anion albumin concen tration (nephrotic syndrome, liver disease, or malabsorption); or (4) hyperviscosity and severe hyperlipidemia, which can lead to an underestimation of sodium and chloride concentrations. Since a normal AG of the normal AG of approximately 10 mmol/L assumes that the serum albumin is normal if hypoalbuminemia is present, the value for the calculated AG must be corrected. For each g/dL of serum albumin below the normal value (4.5 g/dL), 2.5 mmol/L should be added to the reported (uncorrected) AG. Therefore, in a

patient with a serum albumin of 2.5 g/dL (2 g/dL below the normal value) and an uncorrected AG of 15, the corrected AG is calculated by adding 5 mmol/L (2.5 × 2 = 5); thus, adding this value to the calculated AG (5 + 15), a corrected AG of 20 mmol/L is appreciated. Since clinical laboratories do not correct the AG for coexisting hypoalbuminemia and typically report the uncorrected value, the attention of the clinician to the prevailing serum albumin concentration is necessary. The clinical disorders that may cause a high-AG acidosis are displayed in Table 58-4. A high AG is usually due to accumulation of non–chloride-con taining acids that contain inorganic (phosphate, sulfate), organic (ketoacids, lactate, uremic organic anions), exogenous (salicylate or ingested toxins with organic acid production), or unidentified anions. The high AG is meaningful even if the [HCO3 −] or pH is normal. Simultaneous metabolic acidosis of the high-AG variety

plus either chronic respiratory acidosis or metabolic alkalosis rep resents a situation in which [HCO3 −] may be normal or even high (Table 58-3). In cases of high-AG metabolic acidosis, it is valu able to compare the decline in [HCO3 −] from the normal value (ΔHCO3 −: 25 – patient's [HCO3 −]) with the increase in the AG (ΔAG: patient's AG – 10). Similarly, normal values for [HCO3 −], Paco2, and pH do not ensure the absence of an acid-base disturbance. For example, an alcoholic who has been vomiting prior to admission may develop a metabolic alkalosis with a pH of 7.55, Paco2 of 47 mmHg, [HCO3 −] of 40 mmol/L, [Na+] of 135, [Cl−] of 80, and [K+] of 2.8. If such a patient were then to develop a superimposed alcoholic ketoacidosis with a β-hydroxybutyrate concentration of 15 mmol/L, the arterial pH would fall to 7.40, the [HCO3 −] to 25 mmol/L, and the Paco2 to 40 mmHg. Although these values are normal, the AG is signifi cantly elevated at 30 mmol/L, documenting that a mixed metabolic alkalosis and metabolic acidosis coexist. A mixture of high-gap acidosis and metabolic alkalosis is recognized easily by comparing the differences (Δ values) in the normal to prevailing patient values. In this example, the ΔHCO3 − is 0 (25 − 25 mmol/L), but the ΔAG is 20 (30 – 10 mmol/L). Therefore, 20 mmol/L is unaccounted for in the Δ/Δ value (ΔAG to ΔHCO3 −). METABOLIC ACIDOSIS Metabolic acidosis can occur because of an increase in endogenous acid production (such as lactate and ketoacids), loss of bicarbonate (as in diarrhea), or accumulation of endogenous acids because of inappro priately low excretion of net acid by the kidney (as in chronic kidney disease). Metabolic acidosis has profound effects on the respiratory, cardiac, and nervous systems. The fall in blood pH is accompanied by a characteristic increase in ventilation. Intrinsic cardiac contractility may be depressed, but inotropic function can be normal because of catecholamine release. Both peripheral arterial vasodilation and central venoconstriction may be present; accordingly, the decrease in central and pulmonary vascular compliance predisposes to pulmonary edema with even minimal volume overload. CNS function is depressed, with headache, lethargy, stupor, and, in some cases, coma. Glucose intoler ance may also occur. There are two major categories of clinical metabolic acidosis: highAG and non-AG acidosis (Tables 58-3 and 58-4). The presence of metabolic acidosis, a normal AG, and hyperchloremia denotes the presence of a non-AG metabolic acidosis. TREATMENT Metabolic Acidosis Treatment of metabolic acidosis with alkali should be reserved for severe acidemia except when the patient has no "potential HCO3 −" in plasma. The potential [HCO3 −] can be estimated from the increment (Δ) in the AG (ΔAG = patient's AG – 10), only if the acid anion that has accumulated in plasma is metaboliz able (i.e., β-hydroxybutyrate, acetoacetate, and lactate). Conversely, nonmetabolizable anions that may accumulate in advanced-stage chronic kidney disease or after toxin ingestion are not metaboliz able and do not represent "potential" HCO3 −. In

patients with acute

kidney failure or acute-on-chronic kidney failure, improvement in TABLE 58-4 Causes of High-Anion Gap Metabolic Acidosis Lactic acidosis Toxins Ketoacidosis Ethylene glycol Diabetic Methanol Alcoholic Salicylates Starvation Propylene glycol Pyroglutamic acid (5-oxoproline) Kidney failure (acute and chronic)

kidney function after volume resuscitation may improve the serum [HCO3

−], but this is a slow and unpredictable process. Conse quently, patients with a non-AG acidosis (hyperchloremic acidosis) or an AG acidosis attributable to a nonmetabolizable anion due to advanced kidney failure (“uremic” acidosis) should receive alkali therapy, either PO (NaHCO3 tablets or Shohl’s solution) or IV (NaHCO3), in an amount necessary to slowly increase the plasma [HCO3 −] to a target value of 22 mmol/L. Importantly, overcorrec tion should be avoided. Bicarbonate therapy in diabetic ketoacidosis (DKA) is reserved for adult patients with severe acidemia (pH <7.00) and/or evidence of shock. In such circumstances, bicarbonate may be administered IV, as a slow infusion of 50 meq of NaHCO3 diluted in 300 mL of a saline solution, over 30–45 min, during the initial 1–2 h of therapy. Bolus administration should be avoided. Administration of NaHCO3 requires careful monitoring of plasma electrolytes dur ing the course of therapy because of the risk for hypokalemia as urine output is reestablished. A reasonable initial goal in DKA is to increase the [HCO3 Acidosis and Alkalosis CHAPTER 58 −] to a target of 10–12 mmol/L and the pH to approximately 7.20, but definitely not to increase these values to normal. ■ ■HIGH-ANION GAP ACIDOSES APPROACH TO THE PATIENT High-Anion Gap Acidoses There are four principal causes of a high-AG acidosis: (1) lactic acidosis, (2) ketoacidosis, (3) ingested toxins, and (4) acute and chronic kidney failure (Table 58-4). Initial screening to differenti ate the high-AG acidoses should include (1) a careful history of whether drug or toxin ingestion is present and measurement of arterial blood gas to detect coexistent respiratory alkalosis (e.g., salicylate intoxication); (2) a history of diabetes mellitus (DKA); (3) evidence of alcohol abuse or increased levels of β-hydroxybutyrate (alcoholic ketoacidosis); (4) a history of progressive chronic kidney disease (CKD) and an increase in the patient’s baseline blood urea nitrogen (BUN) and creatinine values (uremic acidosis); (5) inspec tion of the urine for oxalate crystals (ethylene glycol ingestion); and (6) recognition of the numerous clinical settings in which lactate levels may be increased (hypotension, shock, cardiac failure, leuke mia, cancer, and drug or toxin ingestion). Lactic Acidosis An increase in plasma l-lactate may be secondary to poor tissue perfusion (“type A” lactic acidosis)—circulatory insuf ficiency (shock, cardiac failure), severe anemia, mitochondrial enzyme defects, and inhibitors (carbon monoxide, cyanide)—or to aerobic dis orders (“type B” lactic acidosis)—malignancies, nucleoside analogue reverse transcriptase inhibitors in HIV, diabetes mellitus, kidney or hepatic failure, thiamine deficiency, severe infections (cholera, malaria), seizures, or drugs/toxins (biguanides, ethanol, and the toxic alcohols: ethylene glycol, methanol, or propylene glycol). Unrecog nized bowel ischemia or infarction in a patient with severe atheroscle rosis or cardiac decompensation receiving vasopressors is a relatively common cause of lactic acidosis in elderly patients. Pyroglutamic acidemia may occur in critically ill patients receiving acetaminophen, because of depletion of glutathione and accumulation of 5-oxyprolene. d-Lactic acid acidosis, which may be associated with jejunoileal bypass, short bowel syndrome, or intestinal obstruction, is due to formation of d-lactate by gut bacteria. APPROACH TO THE PATIENT l-Lactic Acid Acidosis The overarching goal of treatment in lactic acidosis is to correct the underlying

condition that disrupts lactate metabolism; e.g., tissue perfusion should be restored when inadequate, but vasoconstrictors

should be avoided, if possible, or used cautiously, because they may worsen tissue perfusion. Alkali therapy is generally advocated for acute, severe acidemia (pH <7.00) to improve cardiovascular function. However, NaHCO3 therapy may paradoxically depress cardiac performance and exacerbate acidosis by enhancing lactate production (HCO_3^- stimulates phosphofructokinase). While the use of alkali in moderate lactic acidosis is controversial, it is gener ally agreed that attempts to return the pH or [HCO_3^-] to normal by administration of exogenous NaHCO3 are deleterious. A reasonable approach with severe acidemia is to infuse sufficient NaHCO3 to raise arterial pH to no more than 7.2 or the [HCO_3^-] to no more than 12 mmol/L. PART 2 Cardinal Manifestations and Presentation of Diseases NaHCO3 therapy can cause fluid overload, hypercapnia, and hypertension because the amount required can be massive when accumulation of lactic acid is relentless. Fluid administration is poorly tolerated, especially in the oliguric patient, when central venoconstriction coexists. If the underlying cause of the lactic acidosis can be remedied, blood lactate will be converted to HCO_3^- and may result in an overshoot alkalosis if exogenous NaHCO3 has been administered excessively. Ketoacidosis • DIABETIC KETOACIDOSIS (DKA) This condition is caused by increased fatty acid metabolism and the accumulation of ketoacids (acetoacetate and β-hydroxybutyrate). DKA usually occurs in insulin-dependent diabetes mellitus in association with cessation of insulin administration or an intercurrent illness such as an infection, gastroenteritis, pancreatitis, or myocardial infarction, which increases insulin requirements temporarily and acutely. DKA is characterized by hyperglycemia, ketonemia, and a high-AG acidosis. Nevertheless, the plasma glucose may be normal or only slightly elevated in the set ting of starvation ketoacidosis or in diabetics receiving an agent that inhibits the proximal tubule sodium-glucose co-transporter 2 (SGLT2 inhibitors) (euglycemic DKA [eDKA]). These agents cause glycosuria, an osmotic diuresis, volume depletion, and decreased plasma glucose. Although the accumulation of ketoacids in plasma accounts for the increment in the AG in both classical DKA and eDKA, the plasma glucose is elevated in classical DKA but is typically in the normal range in eDKA. Measurement of urine ketones (by the dipstick nitroprus side reaction) does not detect β-hydroxybutyrate accurately and may underestimate the degree of ketosis (see below). Excretion of ketoacids obligates the excretion of cations, such as Na^+ and K^+, contributing to volume depletion and Cl^- retention. In some circumstances, a mixed non-AG–high-AG acidosis may occur simultaneously and is recog nized when the ΔHCO_3^- exceeds the ΔAG. It should be noted that bicarbonate therapy is rarely necessary in DKA in adults, except with extreme acidemia (pH <7.00) or if the patient is in shock. If adminis tered, NaHCO3 should be given in only limited amounts because of the risk for cerebral edema. Patients with DKA are typically volume depleted and require fluid resuscitation with isotonic saline. Volume overexpansion with isotonic saline should be avoided, however, because aggressive saline administration may cause overt volume over load and/or hyperchloremic acidosis during or following treatment of DKA. Regular insulin should be administered IV as an initial bolus of 0.1 U/kg followed by an infusion of 0.1 U/kg/h until the AG returns to normal; see Chap. 417 for more detail. ALCOHOLIC KETOACIDOSIS (AKA) AKA is usually associated with chronic alcoholism, binge drinking, vomiting, abdominal pain, poor nutrition, and volume depletion. The glucose concentration is variable, and acidosis may be severe because of elevated ketones, predominantly β-hydroxybutyrate. The presence of a high-AG acidosis, in the absence of hyperglycemia, in a patient with chronic alcoholism suggests the diagnosis of AKA. Mixed acid-base disorders are common in AKA. Hypoperfusion may enhance lactic acid production

(mixed high-AG acidosis), chronic respiratory alkalosis may accompany liver disease (mixed high-AG acidosis and respiratory alkalosis), and metabolic alkalosis can result from vomiting (mixed high-AG acidosis and metabolic alkalosis: ΔAG exceeds ΔHCO3 −). As the circulation is restored by administration of IV fluids, the preferential accumulation

of β-hydroxybutyrate is then shifted to acetoacetate. This explains the common clinical observation of an increasingly positive nitroprusside reaction (ketones) as the circulation is restored. The nitroprusside reaction can detect acetoacetic acid but not β-hydroxybutyrate, so that the degree of ketosis and ketonuria can not only change with therapy but can also be underestimated initially. Therefore, the plasma β-hydroxybutyrate level should be measured specifically. Patients with AKA usually present with relatively normal kidney function, as opposed to DKA, where kidney function is often compromised because of volume depletion (osmotic diuresis) or diabetic nephropathy. The AKA patient with normal kidney function may excrete relatively large quantities of ketoacids and retain Cl– and, therefore, may have a mixed high-AG–non-AG metabolic acidosis (ΔHCO3 − exceeds ΔAG). TREATMENT Alcoholic Ketoacidosis Extracellular fluid deficits almost always accompany AKA and should be repaired by IV administration, initially, of saline and glucose (5% dextrose in 0.9% NaCl). Hypophosphatemia, hypoka lemia, and hypomagnesemia may coexist and should be monitored carefully and corrected when indicated. Hypophosphatemia typically emerges 12–24 h after admission and may be severe. Hypophosphate mia is exacerbated by glucose infusion, and, if severe, may induce marked muscle weakness, hemolysis, rhabdomyolysis, or respira tory arrest. Upper gastrointestinal hemorrhage, pancreatitis, and pneumonia may accompany this disorder. Drug- and Toxin-Induced Acidosis • SALICYLATES (See also Chap. 469) Salicylate intoxication in adults usually causes respiratory alkalosis or a mixture of high-AG metabolic acidosis and respiratory alkalosis. Only a portion of the AG is due to salicylates. Lactic acid production is also often increased. TREATMENT Salicylate-Induced Acidosis Vigorous gastric lavage with isotonic saline (not NaHCO3) should be initiated immediately. All patients should receive at least one round of activated charcoal per nasogastric tube (1 g/kg up to 50 g). To facilitate excretion of salicylate in the acidotic patient, IV NaHCO3 is administered in amounts adequate to alkalinize the urine (urine pH >7.5) and to maintain urine output. Raising urine pH from 6.5 to 7.5 increases salicylate clearance fivefold. Patients with coex isting respiratory alkalosis may also receive NaHCO3, but if given, it should be administered cautiously to avoid excessive alkalemia. Acetazolamide may be administered with coexisting alkalemia, when an alkaline diuresis cannot be achieved, or to ameliorate volume overload associated with NaHCO3 administration. Caution is needed because acetazolamide may cause systemic metabolic acidosis if the excreted HCO3 − is not replaced, a circumstance that can markedly reduce salicylate clearance. Hypokalemia should be anticipated with vigorous bicarbonate therapy and should be treated promptly and aggressively. Glucose-containing fluids should be administered because of the danger of hypoglycemia. Exces sive insensible fluid losses may cause severe volume depletion and hypernatremia. If acute kidney injury prevents rapid clearance of salicylate, hemodialysis should be performed against a standard bicarbonate dialysate ([HCO3 –] = 30–35 meq/L). ALCOHOLS Under most physiologic conditions, sodium, urea, and glucose generate the osmotic pressure of blood. Plasma osmolality is calculated according to the following expression: Posm = 2Na+ + Glu + BUN (all in mmol/L), or using conventional laboratory values in which glucose and BUN are expressed in mg/dL: Posm = 2Na+ + Glu/18 + BUN/2.8. The calculated and determined osmolality should agree within 10–15 mmol/kg H2O. When the measured osmolality exceeds the calculated osmolality by >10–15 mmol/kg H2O, one of two

circumstances prevails. Either the serum sodium is spuriously low, as with hyperlipidemia or hyperproteinemia (pseudohyponatremia), or osmolytes other than sodium salts, glucose, or urea have accumulated in plasma. Examples of such osmolytes include mannitol, radiocontrast media, ethanol, isopropyl alcohol, ethylene glycol, propylene glycol, methanol, and acetone. In this situation, the difference between the calculated osmolality and the measured osmolality (osmolar gap) is proportional to the concentration of the unmeasured solute. With an appropriate clinical history and index of suspicion, identification of a serum osmolar gap is helpful in identifying the presence of toxic alcohol-associated AG acidosis. Three alcohols may cause fatal intoxi cations: ethylene glycol, methanol, and isopropyl alcohol. All cause an elevated osmolar gap, but only the first two cause a high-AG acidosis. Isopropyl alcohol ingestion does not typically elevate the AG unless extreme overdose causes hypotension and lactic acid acidosis. ETHYLENE GLYCOL (See also Chap. 469) Ethylene glycol (EG) (com monly used in antifreeze, but also in brake fluid and windshield washer fluid deicers) is metabolized by alcohol dehydrogenase. Ingestion of EG leads to metabolic acidosis and severe damage to the CNS, heart, lungs, and kidneys. The combination of both a high AG and osmolar gap is highly suspicious for EG or methanol intoxication. The osmolar gap is determined by comparing the calculated and measured serum osmolality (Measured Sosm – Calculated Sosm). The serum osmolality is calculated as follows: Osmolality = 2 [Na+] + [BUN]/2.8 + [Glucose]/18 The serum osmolality is measured in the clinical laboratory most accurately by freezing point depression. The combination of a high AG and high osmolar gap in a patient suspected of EG ingestion should be taken as evidence of EG toxicity prior to measurement of EG levels, especially when the history is suspicious or highly suggestive of EG ingestion. Most importantly, in the face of an elevated osmolar gap and anion gap, treatment should not be delayed while awaiting return of ethylene glycol or methanol levels from the laboratory. The osmolar gap is typically elevated earlier than the AG, and as the osmolar gap declines, the AG usually increases. The increased AG and osmolar gap in EG intoxication are attributable to accumulation of EG and its metabolites, glycolate, oxalate, and other organic acids. Lactic acid pro duction (l-lactate) increases secondary to inhibition of the tricarbox ylic acid cycle and an altered intracellular redox state, thus contributing to the high AG. Acute tubule injury is caused initially by glycolate and later is amplified by tubule obstruction from oxalate crystals. TREATMENT Ethylene Glycol Intoxication Therapy requires prompt institution of IV isotonic fluids, thiamine and pyridoxine supplements, fomepizole, and usually, hemodialy sis. Ethanol is of historic interest and is no longer recommended as initial therapy unless fomepizole is not available. Both fomepizole and ethanol compete with EG for metabolism by alcohol dehydro genase. Fomepizole (4-methylpyrazole; 15 mg/kg IV over 30 min as a loading dose, then 10 mg/kg for four doses every 12 h) is the agent of choice and offers the advantage of a predictable decline in EG levels without excessive obtundation, as commonly seen during ethyl alcohol infusion. Fomepizole should be continued until blood pH is normal or the osmolar gap is <10 mOsm/kg H_2O. Hemodi alysis is indicated when the arterial pH is <7.3, a high-AG acidosis is present, the osmolar gap exceeds 20 mOsm/kg H_2O, or there is evidence of end organ damage such as CNS manifestations and kidney failure. METHANOL (See also Chap. 469) The ingestion of methanol (wood alcohol) causes metabolic acidosis, and its metabolites formaldehyde and formic acid cause severe optic nerve and CNS damage. Lactic acid, ketoacids, and other unidentified organic acids contribute to the aci dosis. Due to its low molecular mass (32 Da), an osmolar gap is present and may precede the elevation of the AG.

TREATMENT Methanol Intoxication Treatment of methanol intoxication is similar to that for EG intoxi cation, including general supportive measures, fomepizole, and hemodialysis. PROPYLENE

GLYCOL Propylene glycol is the vehicle used in the IV preparation of diazepam, lorazepam, phenobarbital, nitroglycerine, etomidate, enoximone, and phenytoin. Propylene glycol is generally safe for limited use in these IV preparations, but toxicity has been reported in the setting of the intensive care unit in patients receiving frequent or continuous administration, because propylene glycol may accumulate in plasma. This form of high-gap acidosis should be con sidered in patients with unexplained high-gap acidosis, hyperosmolal ity, and clinical deterioration, especially in the setting of treatment for alcohol withdrawal. Propylene glycol, like EG and methanol, is metabolized by alcohol dehydrogenase. With intoxication by propylene glycol, the first response is to stop the offending infusion. Additionally, fomepizole may be administered in severely acidotic patients. Acidosis and Alkalosis CHAPTER 58 ISOPROPYL ALCOHOL Ingested isopropanol is absorbed rapidly and may be fatal when as little as 150 mL of rubbing alcohol, solvent, or deicer is consumed. A plasma level >400 mg/dL is life-threatening. Isopropyl alcohol is metabolized by alcohol dehydrogenase to acetone. The characteristic features differ significantly from EG and methanol intoxication in that the parent compound (isopropyl alcohol), not its metabolites, causes toxicity, and a high-AG acidosis is not present because acetone is rapidly excreted. Both isopropyl alcohol and acetone increase the osmolar gap, and hypoglycemia is common. Alternative diagnoses should be considered if the patient does not improve sig nificantly within a few hours. Patients with hemodynamic instability and/or plasma levels above 400 mg/dL should be considered for acute hemodialysis. TREATMENT Isopropyl Alcohol Toxicity Isopropanol alcohol toxicity is treated by supportive therapy, IV flu ids, pressors, ventilatory support if needed, and acute hemodialysis for prolonged coma, hemodynamic instability, or levels >400 mg/dL. PYROGLUTAMIC ACID Acetaminophen-induced high-AG metabolic acidosis is being recognized more frequently and is observed in patients with acetaminophen overdose and in malnourished or critically ill patients receiving acetaminophen in standard dosage. 5-Oxoproline accumulation after acetaminophen should be suspected in the set ting of an unexplained high-AG acidosis in the absence of an elevated osmolar gap in patients receiving acetaminophen. The first step in treatment is to immediately discontinue acetaminophen. Additionally, sodium bicarbonate should be given IV. Although N-acetylcysteine has been suggested, it has not been demonstrated unequivocally that it hastens the metabolism of 5-oxoproline by increasing intracellular glutathione concentrations in this setting, as assumed. Chronic Kidney Disease (See also Chap. 322) The hyperchlo remic acidosis of moderate CKD (stage 3B) is eventually converted to the high-AG acidosis of advanced renal failure (stages 4 and 5 CKD). Poor filtration and reabsorption of organic anions contribute to the pathogenesis. As renal disease progresses, the number of functioning nephrons eventually becomes insufficient to keep pace with net acid production. Uremic acidosis in advanced CKD is characterized by a reduced rate of NH_4

- production and excretion. Alkaline salts from bone buffer the acid retained in CKD. Despite significant retention of acid (up to 20 mmol/d), the serum [HCO_3^-] does not typically decrease further, indicating participation of buffers outside the extra cellular compartment. Therefore, a recognized trade-off in untreated chronic metabolic acidosis of CKD stages 3 and 4 is significant loss of bone mass due to reduction in bone calcium carbonate. Chronic

acidosis also contributes significantly to muscle wasting and disability in advancing CKD. Evidence has been advanced recently that the high anion gap acidosis of chronic kidney disease contributes significantly per se to the progressive loss of kidney function.

TREATMENT Metabolic Acidosis of Chronic Kidney Disease Because chronic metabolic acidosis in advanced CKD is clearly associated with muscle catabolism, bone disease, and more rapid progression of CKD, both the “uremic acidosis” of end-stage renal disease and the non-AG metabolic acidosis of stages 3 and 4 CKD require oral alkali replacement to increase and maintain the [HCO3 PART 2 Cardinal Manifestations and Presentation of Diseases −] to a value >22–24 mmol/L. This can be accomplished with relatively modest amounts of alkali (1.0–1.5 mmol/kg body weight per day) and has been shown to slow the progression of CKD. Either NaHCO3 tablets (650-mg tablets contain 7.8 meq) or oral sodium citrate (Shohl’s solution) is effective. The addition of fruits and vegetables (citrate) to the diet increases the plasma [HCO3 –] and slows progression of CKD safely and is well tolerated. Hyperka lemia is not a common complication of increasing the dietary intake of fruits and vegetables. ■ ■NON–ANION GAP METABOLIC ACIDOSES Alkali can be lost from the gastrointestinal tract as a result of diarrhea or from the kidneys due to renal tubular abnormalities (e.g., renal tubular acidosis [RTA]). In these disorders (Table 58-5), reciprocal changes in [Cl−] and [HCO3 −] maintain a normal AG. In non-AG acidosis the increase in [Cl−] above the normal value approximates the decrease in [HCO3 −]. The absence of such a relationship (disparity in the D values) suggests a mixed disturbance. Stool contains a higher concentration of HCO3 − and decomposed HCO3 − than plasma so that metabolic acidosis develops in diarrhea. Instead of an acid urine pH (as anticipated with systemic acidosis), urine pH is usually >6 because metabolic acidosis and hypokalemia increase renal synthesis and excretion of NH4 +, thus providing a uri nary buffer that increases urine pH. Metabolic acidosis due to gastro intestinal losses with a high urine pH can be differentiated from RTA because urinary NH4

- excretion is typically low in RTA and high with diarrhea. Urinary NH4
- levels are not routinely measured by clinical laboratories, but can be estimated by calculating the urine anion gap (UAG): UAG = [Na+ + K+]u – [Cl−]u. When [Cl−]u > [Na+ + K+]u, the UAG is negative by definition. This suggests that the urine ammonium level is appropriately increased, supporting an extrarenal cause of the acidosis. Conversely, when the UAG is positive, the urine ammonium level is predictably low, suggesting a renal tubular origin of the acidosis. Recent studies have shown a poor correlation between the UAG and the measured urine ammonium, thus calling the estimation of urine ammonium by calculation of the UAG into question. Therefore, clini cal laboratories should be encouraged to measure urine ammonium by adaptation of automated plasma ammonium assays, using the enzy matic method. This is easily accomplished if the urine sample is diluted 1:200 in normal saline. Proximal RTA (type 2 RTA) (Chap. 327) is often due to generalized proximal tubular dysfunction manifested by glycosuria, generalized aminoaciduria, and phosphaturia (Fanconi syndrome). When the plasma [HCO3 −] is low, the urine pH is acid (pH <5.5) but exceeds 5.5 with exogenous alkali therapy. The fractional excretion of [HCO3 −] may exceed 10–15% when the serum HCO3 − is >20 mmol/L. Because of the defect in HCO3 − reabsorption by the proximal tubule, therapy with NaHCO3 will enhance delivery of HCO3 – to the distal nephron and enhance renal potassium secretion, thereby causing hypokalemia. For this reason, potassium supplementation is often added to alkali therapy and may be accomplished by administration of potassium citrate–citric acid solution (Polycitra K or Cytra-K), as discussed below. Distal RTA (type 1 RTA) may be seen as an acquired or inher ited disorder. The features of classical distal RTA (type 1 RTA) include hypokalemia, a non-AG metabolic acidosis, low urinary NH4

TABLE 58-5 Causes of Non–Anion Gap Acidosis I. Gastrointestinal bicarbonate loss A. Diarrhea B. External pancreatic or small-bowel drainage/fistula C. Diversion of ureter: ureterosigmoidostomy, jejunal loop, ileal loop D. Drugs

1. Calcium chloride (acidifying agent)
2. Magnesium sulfate (diarrhea)
3. Cholestyramine (bile acid diarrhea) II. Renal acidosis A. Hypokalemia
4. Proximal RTA (type 2 RTA) Drug-induced: acetazolamide, topiramate Inherited: (a) autosomal recessive missense mutation of SLCA4 (encodes for basolateral NBCe1) (accompanied by ocular abnormalities); (b) autosomal dominant mutation of NHE3 (apical Na+/H+ exchanger) (rare; associated with short stature)
5. Distal (classic) RTA (type 1 RTA) Drug-induced: amphotericin B, ifosfamide Inherited: defect of ATP6V1B1 (encodes for basolateral HCO3 –/Cl– exchanger of distal tubule and collecting duct) B. Hyperkalemia
6. Generalized distal nephron dysfunction (type 4 RTA) a. Selective aldosterone deficiency b. Mineralocorticoid resistance (PHA I, autosomal dominant) c. Voltage defect (PHA I, autosomal recessive, and PHA II) d. Hyporeninemic hypoaldosteronism e. Tubulointerstitial disease C. Normokalemia
7. Chronic progressive kidney disease III. Drug-induced hyperkalemia (with CKD) A. Potassium-sparing diuretics (amiloride, triamterene, spironolactone, eplerenone) B. Trimethoprim C. Pentamidine D. ACE-Is and ARBs E. Nonsteroidal anti-inflammatory drugs F. Calcineurin inhibitors G. Heparin in critically ill patients IV. Other A. Acid loads (ammonium chloride, IV hyperalimentation [uncommon]) B. Loss of potential bicarbonate: ketosis with ketone excretion C. Expansion acidosis (rapid saline administration) D. Hippurate E. Cation exchange resins Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; PHA, pseudohypoaldosteronism; RTA, renal tubular acidosis. excretion (positive UAG, low urine [NH4 +]), and an inappropriately high urine pH (pH >5.5) for the prevailing metabolic acidosis. Most patients have hypocitraturia and hypercalciuria. Therefore, nephroli thiasis, nephrocalcinosis, and bone disease are common. In contrast, in generalized distal RTA (type 4 RTA), hyperkalemia is disproportion ate to the accompanying reduction in glomerular filtration rate (GFR) because of coexisting impairment of potassium and acid secretion. Urinary ammonium excretion is invariably depressed, and kidney function may be compromised secondary to diabetic nephropathy, obstructive uropathy, or chronic tubulointerstitial disease. Hyporeninemic hypoaldosteronism typically presents as a non-AG metabolic acidosis in older adults with diabetes mellitus or tubuloin terstitial disease and stage 3 or 4 CKD. These patients typically have hyperkalemia ([K+] 5.2–6.0 mmol/L), hypertension, and congestive heart failure. Both the metabolic acidosis and the hyperkalemia are out of proportion to the reduction in GFR. Nonsteroidal anti-inflammatory

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drugs, trimethoprim, pentamidine, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) may also increase the risk for hyperkalemia and a non-AG metabolic acidosis in patients with CKD, especially from diabetic nephropathy (Table 58-5). TREATMENT Non–Anion Gap Metabolic Acidoses For non-AG acidosis due to gastrointestinal losses

of bicarbon ate, NaHCO3 may be administered intravenously or orally, as indicated by the severity of both the acidosis and the accompany ing volume depletion. Proximal RTA is the most challenging of the RTAs to treat if the goal is to restore the serum [HCO3 –] to normal (as recommended to support normal growth in children with isolated bicarbonate wasting), because administration of oral alkali increases urinary excretion of bicarbonate and potassium. In patients with proximal RTA (type 2), potassium administration is typically necessary. An oral solution of sodium and potassium citrate (citric acid 334 mg, sodium citrate 500 mg, and potas sium citrate 550 mg per 5 mL) may be prescribed for this purpose (Virtrate or Cytra-3). In classical distal RTA (type 1), hypokalemia should be corrected initially. When accomplished, alkali therapy with either sodium citrate (Shohl's solution) or NaHCO3 tablets (650-mg tablets contain 7.8 meq) should be initiated to correct and maintain the serum [HCO3 –] in the range of 24–26 meq/L. Type 1 RTA patients typically respond to chronic alkali therapy readily. The long-term benefits of adequate alkali therapy in distal (type 1) RTA include a decrease in the frequency of nephrolithia sis, improvement in bone density, resumption of normal growth patterns in children, and preservation of kidney function in both adults and children. For type 4 RTA, it is necessary to correct the metabolic acidosis, using the same approach as for classical distal RTA (type 1 RTA), and also to correct the plasma [K+]. Hyper kalemia directly reduces ammoniagenesis and net acid excretion. Therefore, restoration of normokalemia increases urinary net acid excretion and consequently can greatly improve the metabolic aci dosis. Historically, hyperkalemia was treated by chronic administra tion of oral sodium polystyrene sulfonate (15 g of power prepared as an oral solution, without sorbitol, once daily 2–3 times per week). However, this preparation is often unpalatable and patient compli ance is low. The nonabsorbed, calcium-potassium cation exchange polymer, patiromer, may be considered for type 4 RTA patients with hyperkalemia because it is more palatable and more effective but has very few side effects. Patiromer is administered as 8.4-g packets of powder for suspension PO twice daily with dose adjustment at weekly intervals, based on the plasma [K+], not to exceed 25.2 g/d. Additionally, the diet should be low in potassium-containing foods or supplements (e.g., salt substitute). Potassium-retaining medica tions should be discontinued. Finally, patients with documented isolated hypoaldosteronism should receive fludrocortisone, but the dose varies with the cause of the hormone deficiency. This agent should be administered very cautiously and in combination with furosemide in patients with edema and hypertension because of potential aggravation of these conditions. METABOLIC ALKALOSIS Metabolic alkalosis is established by an elevated arterial pH, an increase in the serum [HCO3 −], and an increase in Paco2 as a result of compensatory alveolar hypoventilation (Table 58-1). It is often accom panied by hypochloremia and hypokalemia. The elevation in arterial pH establishes the diagnosis because pH is decreased in respiratory acidosis, even though both have an elevated Paco2. Metabolic alkalosis may present as a mixed acid-base disorder in association with either respiratory acidosis, respiratory alkalosis, or metabolic acidosis. ■ ■ETIOLOGY AND PATHOGENESIS Metabolic alkalosis occurs as a result of net gain of [HCO3 −] or loss of nonvolatile acid (usually HCl by vomiting) from the extracellular fluid.

When vomiting causes loss of HCl from the stomach, HCO3 − secretion cannot be initiated in the small bowel, so that HCO3

− is retained in the extracellular fluid. Thus, vomiting or nasogastric suction is an example of the generation stage of metabolic alkalosis, in which the loss of acid typically causes alkalosis. Upon cessation of vomiting, the maintenance stage ensues because secondary factors prevent the

kidneys from excreting HCO3 − appropriately. Maintenance of metabolic alkalosis, therefore, represents a failure of the kidneys to eliminate excess HCO3 − from the extracellular compart ment. The kidneys will retain, rather than excrete, the excess alkali and maintain the alkalosis if (1) volume deficiency, chloride deficiency, and K+ deficiency exist in combination with a reduced GFR (associated with a low urine [Cl–]) or (2) hypokalemia exists because of autono mous hyperaldosteronism (normal urine [Cl–]). In the first example, saline-responsive metabolic alkalosis is corrected by extracellular fluid volume (ECFV) restoration (IV administration of NaCl and KCl), whereas, in the latter, it may be necessary to repair the alkalosis by pharmacologic or surgical intervention, not with saline administration (saline-unresponsive metabolic alkalosis). Acidosis and Alkalosis CHAPTER 58 ■ ■DIFFERENTIAL DIAGNOSIS To establish the cause of metabolic alkalosis (Table 58-6), it is nec essary to assess the status of the patient's ECFV. It is important to measure the recumbent and upright blood pressure and pulse (to determine if orthostasis is present) and to obtain a serum [K+] and a urine [Cl–]. When hyperreninemia or isolated hyperaldosteronism is suspected, renin and aldosterone should be measured. For example, the presence of chronic hypertension and chronic hypokalemia in an alkalotic patient suggests either mineralocorticoid excess or that the hypertensive patient is receiving diuretics. Low plasma renin activity and values for urine [Cl−] >20 meq/L in a patient not receiving diuretics suggest primary mineralocorticoid excess. The combination of hypo kalemia and alkalosis in a normotensive, nonedematous patient may be due to Bartter's or Gitelman's syndrome, magnesium deficiency, vomit ing, exogenous alkali, or diuretic ingestion. Measurement of urine elec trolytes (especially the urine [Cl−]) is recommended, and occasionally, screening of the urine for diuretics may be necessary if surreptitious diuretic abuse is suspected. If the urine is alkaline, with an elevated [Na+]u and [K+]u but low [Cl−]u, the diagnosis of either vomiting (overt or surreptitious) or alkali ingestion should be considered. If the urine is relatively acid with low concentrations of Na+, K+, and Cl−, the most likely possibilities are prior vomiting, the posthypercapnic state, or prior diuretic ingestion. If the urine sodium, potassium, and chloride concentrations are not depressed, magnesium deficiency, Bartter's or Gitelman's syndrome, or current diuretic ingestion should be consid ered. Bartter's syndrome is distinguished from Gitelman's syndrome by the presence of hypocalciuria in the latter disorder. Alkali Administration Chronic administration of alkali to indi viduals with normal renal function rarely causes alkalosis. However, in patients with coexistent hemodynamic disturbances associated with effective ECFV depletion (e.g., congestive heart failure), alkalosis can develop because of diminished capacity to excrete HCO3 − or enhanced reabsorption of HCO3 −. Such patients include those who receive NaHCO3 (PO or IV), citrate loads IV (transfusions of whole blood or therapeutic apheresis), or antacids plus cation-exchange resins (alu minum hydroxide and sodium polystyrene sulfonate [uncommon]). Nursing home patients receiving enteral tube feedings have a higher incidence of metabolic alkalosis than nursing home patients receiving regular diets. ■ ■METABOLIC ALKALOSIS ASSOCIATED WITH ECFV CONTRACTION, K+ DEPLETION, AND SECONDARY HYPERRENINEMIC HYPERALDOSTERONISM Gastrointestinal Origin Gastrointestinal loss of H+ from vomit ing or gastric aspiration causes simultaneous addition of HCO3 − into the extracellular fluid. During active vomiting, the filtered load of bicarbonate reaching the kidneys is acutely increased and will exceed the reabsorptive capacity of the proximal tubule for HCO3 − absorption.

TABLE 58-6 Causes of Metabolic Alkalosis I. Exogenous HCO3 – loads A. Acute alkali administration B. Milk-alkali syndrome II. Effective ECFV depletion, normal or low BP (with orthostasis), K+ deficiency, and secondary hyperreninemic hyperaldosteronism A. Gastrointestinal origin

1. Vomiting
2. Gastric aspiration
3. Congenital chloridorrhea
4. Gastrocystoplasty
5. Villous adenoma B. Renal origin PART 2 Cardinal Manifestations and Presentation of Diseases
6. Diuretic use (thiazides and loop diuretics)
7. Posthypercapnic state
8. Hypercalcemia/hypoparathyroidism
9. Recovery from lactic acidosis or ketoacidosis
10. Nonreabsorbable anion administration (e.g., IV penicillin, carbenicillin)
11. Mg2+ deficiency
12. K+ depletion
13. Bartter's syndrome (loss-of-function mutations of transporters and ion channels in TALH)
14. Gitelman's syndrome (loss-of-function mutation of Na+-Cl– cotransporter in DCT and collecting duct) III. ECFV expansion, hypertension, K+ deficiency, and mineralocorticoid excess A. High renin
15. Renal artery stenosis
16. Accelerated hypertension
17. Renin-secreting tumor
18. Estrogen therapy B. Low renin
19. Primary aldosteronism a. Adenoma b. Hyperplasia c. Carcinoma
20. Adrenal enzyme defects a. 11β-Hydroxylase deficiency b. 17α-Hydroxylase deficiency
21. Cushing's syndrome or disease
22. Other a. Licorice b. Carbenoxolone c. Chewer's tobacco IV. Gain-of-function mutation of sodium channel in DCT (ENaC) with ECFV expansion, hypertension, K+ deficiency, and hyporeninemic-hypoaldosteronism A. Liddle's syndrome Abbreviations: DCT, distal convoluted tubule; ECFV, extracellular fluid volume; TALH, thick ascending limb of Henle's loop. Subsequently, enhanced delivery of HCO3 – to the distal nephron, where the capacity for HCO3 – reabsorption is lower, will result in excretion of alkaline urine that stimulates potassium secretion. When vomiting ceases, the persistence of volume, potassium, and chloride depletion triggers maintenance of the alkalosis because these conditions promote HCO3 − reabsorption. Correction of the contracted ECFV with NaCl and repair of K+ deficits with KCl correct the acid-base disorder by restoring the ability of the kidney to excrete the excess bicarbonate. Renal Origin • diuretics (See also Chap. 265) Diuretics such as thiazides and loop diuretics (furosemide, bumetanide, torsemide) increase excretion of salt and acutely diminish the ECFV without alter ing the total body bicarbonate content. The serum [HCO3 −] increases because the reduced ECFV "contracts" around the [HCO3 −] in plasma (contraction alkalosis). The chronic administration of diuretics tends

to generate an alkalosis by increasing distal salt delivery so that both K+ and H+ secretion are stimulated. The alkalosis is maintained by persis tence of the contraction of the ECFV, secondary hyperaldosteronism, K+ deficiency, and the direct effect of the diuretic (as long as diuretic administration continues). Discontinuing the diuretic and providing isotonic saline to correct the ECFV deficit will repair the alkalosis. SOLUTE LOSING DISORDERS: BARTTER'S AND GITELMAN'S

SYNDROMES

See Chap. 327. NON-REABSORBABLE ANIONS AND MAGNESIUM DEFICIENCY Admin istration of large quantities of the penicillin derivatives carbenicillin or ticarcillin causes their non-reabsorbable anions to appear in the distal tubule, causing an increase in the transepithelial potential difference in the collecting tubule. The more negative potential difference increases both H+ and K+ secretion across the apical membrane. Mg2+ deficiency may occur with chronic administration of thiazide diuretics, alcohol ism, and malnutrition. In Gitelman's syndrome, the development of hypokalemic alkalosis occurs through stimulation of renin and aldo sterone secretion to enhance distal acidification. POTASSIUM DEPLETION Chronic K+ depletion, as a result of extreme dietary potassium restriction, diuretics, or alcohol abuse, may initiate metabolic alkalosis by increasing urinary net acid excretion. Potas sium depletion often occurs concurrent with magnesium deficiency in alcoholics with malnutrition. The renal generation of NH4

- (ammonia genesis) is upregulated directly by hypokalemia. Chronic K+ deficiency also upregulates the H+, K+-ATPases in the distal tubule and collecting duct to increase K+ absorption while simultaneously increasing H+ secretion. Alkalosis associated with severe K+ depletion is resistant to salt administration, but repair of the K+ deficiency corrects the alkalosis. AFTER TREATMENT OF LACTIC ACIDOSIS OR KETOACIDOSIS When an underlying stimulus for the generation of lactic acid or ketoacid is corrected, such as correction of shock or severe volume depletion by volume restoration, or with insulin therapy for DKA, the lactate or ketones are metabolized to yield an equivalent amount of HCO3 −. If there have been exogenous sources of HCO3 −, this additional HCO3 − will be additive to that amount generated by organic anion metabolism that together may create a surfeit of HCO3 − ("rebound alkalosis"). POSTHYPERCAPNIA Prolonged CO2 retention with chronic respira tory acidosis enhances renal HCO3 − absorption and the generation of new HCO3 − (increased net acid excretion). Metabolic alkalosis occurs when the elevated Paco2 is abruptly returned toward normal because of residual stimulation of HCO3 − absorption by the prior chronic increase in Paco2. ■ ■METABOLIC ALKALOSIS ASSOCIATED WITH ECFV EXPANSION, HYPERTENSION, AND MINERALOCORTICOID EXCESS An increase in aldosterone may be the result of autonomous primary adrenal overproduction or of secondary aldosterone secretion in response to overproduction of renin by the kidney. Mineralocorti coid excess increases net acid excretion and may result in metabolic alkalosis, which is typically exacerbated by associated K+ deficiency. The characteristic salt retention and hypertension are due to upregula tion of the epithelial Na+ channel (ENaC) in the collecting tubule in response to aldosterone. The kaliuresis persists because of mineralo corticoid excess and stimulation of ENaC, causing an increase in tran sepithelial voltage that enhances K+ secretion by the collecting duct. Persistent K+ depletion may cause polydipsia and polyuria. Liddle's syndrome (Chap. 327) results from an inherited gain-offunction mutation of genes that regulate the collecting duct Na+ chan nel, ENaC. This rare monogenic form of hypertension is the result of volume expansion that secondarily suppresses aldosterone elaboration. Patients typically present with hypertension, hypokalemia, and meta bolic alkalosis. Symptoms With metabolic alkalosis, changes in CNS and periph eral nervous system function are similar to those of hypocalcemia

(Chap. 421); symptoms include mental confusion; obtundation; and a predisposition to seizures, paresthesias, muscular cramping, tetany, aggravation of arrhythmias, and hypoxemia in chronic obstructive pul monary disease. Related electrolyte abnormalities include hypokalemia and hypophosphatemia. TREATMENT Metabolic Alkalosis The first goal of therapy is to correct the underlying stimulus for HCO_3^- generation. If primary aldosteronism or Cushing's syn drome is present, correction of the underlying cause will reverse the hypokalemia and alkalosis. [H+] loss by the stomach or kidneys can be mitigated by the use of proton pump inhibitors or the discon tinuation of diuretics, respectively. The second aspect of treatment is to eliminate factors that sustain the inappropriate increase in HCO_3^- reabsorption, such as ECFV contraction or K+ deficiency. K+ deficits should always be repaired. Isotonic saline is recommended to reverse the alkalosis when ECFV contraction is present. If associ ated conditions, such as congestive heart failure, preclude infusion of isotonic saline, renal HCO_3^- loss can be accelerated by adminis tration of acetazolamide (125–250 mg IV), a carbonic anhydrase inhibitor, which is usually effective in patients with adequate kidney function. Close monitoring is required since acetazolamide triggers urinary K+ losses and may cause hypokalemia that should be cor rected promptly. Dilute hydrochloric acid IV (0.1 N HCl) has been advocated in extreme cases of metabolic alkalosis but causes hemo lysis and must be delivered slowly in a central vein. This preparation is not available generally and requires preparation by the pharmacy. Because serious errors or harm may occur with dilute HCl infusion, its use is not advised. Therapy in Liddle's syndrome should include a potassium-sparing diuretic (amiloride or triamterene) to inhibit ENaC and correct both the hypertension and the hypokalemia. RESPIRATORY ACIDOSIS Respiratory acidosis occurs as a result of severe pulmonary disease, respiratory muscle fatigue, or abnormalities in ventilatory control. It is characterized by an elevated Paco2 and reduced pH (Table 58-7). In acute respiratory acidosis, there is a compensatory elevation in HCO_3^- (due to cellular buffering mechanisms) that increases the serum [HCO_3^-] 1 mmol/L for every 10-mmHg increase in Paco2. In chronic respiratory acidosis (>24 h), renal adaptation increases the [HCO_3^-] by 4 mmol/L for every 10-mmHg increase in Paco2. The serum HCO_3^- usually does not increase above 38 mmol/L in respiratory acidosis. The clinical features of respiratory acidosis vary according to the severity and duration of the disorder, the underlying disease, and whether there is accompanying hypoxemia. A rapid increase in Paco2 (acute hypercapnia) may cause anxiety, dyspnea, confusion, psychosis, and hallucinations and may progress to coma. Chronic hypercapnia may cause sleep disorders; loss of memory; daytime somnolence; per sonality changes; impairment of coordination; and motor disturbances such as tremor, myoclonic jerks, and asterixis. Headaches and other signs that mimic raised intracranial pressure, such as papilledema, abnormal reflexes, and focal muscle weakness, may also occur. Depression of the respiratory center by a variety of drugs, injury, or disease can produce respiratory acidosis. This may occur acutely with general anesthetics, sedatives, and head trauma or chronically with sedatives, alcohol, intracranial tumors, and the syndromes of sleep-

disordered breathing including the primary alveolar and obesityhypoventilation syndromes (Chaps. 296 and 308). Abnormalities or disease in the motor neurons, neuromuscular junction, and skel etal muscle can cause hypoventilation via respiratory muscle fatigue. Mechanical ventilation, when not properly adjusted, may result in respiratory acidosis, particularly if CO_2 production suddenly rises (because of fever, agitation, sepsis, or overfeeding) or alveolar ventila tion decreases because of worsening pulmonary function. High levels of positive end-expiratory pressure in the presence of reduced cardiac output may cause hypercapnia as a result of large increases in alveolar

TABLE 58-7 Respiratory Acid-Base Disorders I. Alkalosis A. Central nervous system stimulation

1. Pain
2. Anxiety
3. Fever
4. Cerebrovascular accident
5. Meningitis, encephalitis
6. Tumor
7. Trauma B. Hypoxemia or tissue hypoxia Acidosis and Alkalosis CHAPTER 58
8. High-altitude acclimatization
9. Pneumonia, pulmonary edema
10. Aspiration
11. Severe anemia C. Drugs or hormones
12. Pregnancy, progesterone
13. Salicylates
14. Cardiac failure D. Stimulation of chest receptors
15. Hemothorax
16. Flail chest
17. Cardiac failure
18. Pulmonary embolism E. Miscellaneous
19. Septicemia
20. Hepatic failure
21. Mechanical hyperventilation
22. Heat exposure
23. Recovery from metabolic acidosis II. Acidosis A. Central
24. Drugs (anesthetics, morphine, sedatives)
25. Stroke
26. Infection B. Airway
27. Obstruction
28. Asthma C. Parenchyma
29. Emphysema
30. Pneumoconiosis
31. Bronchitis
32. Adult respiratory distress syndrome
33. Barotrauma D. Neuromuscular
34. Poliomyelitis
35. Kyphoscoliosis
36. Myasthenia
37. Muscular dystrophies E. Miscellaneous
38. Obesity
39. Hypoventilation
40. Permissive hypercapnia dead space (Chap. 296). Permissive hypercapnia may be used to mini mize intrinsic positive end-expiratory pressure in respiratory distress syndrome, but the consequential respiratory acidosis may require administration of $NaHCO_3$ to increase the arterial pH to approximately 7.20. The pH should not be increased to the normal value by $NaHCO_3$ infusion, however. Acute hypercapnia follows sudden occlusion of the upper

air way or generalized bronchospasm as in severe asthma, anaphylaxis,

inhalational burn, or toxin injury. Chronic hypercapnia and respiratory acidosis occur in end-stage obstructive lung disease. Restrictive disor ders involving both the chest wall and the lungs can cause respiratory acidosis because the high metabolic cost of respiration initiates ventila tory muscle fatigue. Advanced stages of intrapulmonary and extrapul monary restrictive defects present as chronic respiratory acidosis.

The diagnosis of respiratory acidosis requires the measurement of Paco2 and arterial pH. A detailed history and physical examination will typically identify the cause. Pulmonary function studies (Chap. 297), including spirometry, diffusion capacity for carbon monoxide, lung volumes, and arterial Paco2 and O2 saturation, usually make it pos sible to determine if respiratory acidosis is secondary to lung disease. The workup for nonpulmonary causes should include a detailed drug history, measurement of hematocrit, and assessment of upper airway, chest wall, pleura, and neuromuscular function. PART 2 Cardinal Manifestations and Presentation of Diseases TREATMENT Respiratory Acidosis The management of respiratory acidosis depends on the severity and rate of onset. Acute respiratory acidosis can be life-threatening, and measures to reverse the underlying cause should be undertaken simultaneously with restoration of adequate alveolar ventilation. This may necessitate tracheal intubation and assisted mechanical ventilation. Oxygen administration should be titrated carefully in patients with severe obstructive pulmonary disease and chronic CO2 retention who are breathing spontaneously (Chap. 307). When oxygen is used injudiciously, these patients may experience progres sion of the respiratory acidosis, causing severe acidemia. Aggressive and rapid correction of hypercapnia should be avoided, because the falling Paco2 may provoke the same complications noted with acute respiratory alkalosis (i.e., cardiac arrhythmias, reduced cerebral perfusion, and seizures). The Paco2 should be lowered gradually in chronic respiratory acidosis, aiming to restore the Paco2 to baseline levels and to provide sufficient Cl− and K+ to enhance the renal excretion of HCO_3^-. Chronic respiratory acidosis is frequently difficult to correct, but the primary goal is to institute measures that may improve lung function (Chap. 303). RESPIRATORY ALKALOSIS Alveolar hyperventilation decreases Paco2 and increases the HCO_3^-/ Paco2 ratio, thus increasing pH (Table 58-7). Nonbicarbonate cellular buffers respond by consuming HCO_3^-. Hypocapnia develops when a sufficiently strong ventilatory stimulus causes CO2 output in the lungs to exceed its metabolic production by tissues. Plasma pH and [HCO_3^-] appear to vary proportionately with Paco2 over a range from 40–15 mmHg. The relationship between arterial [H+] concentration and Paco2 is ~0.7 mmol/L per mmHg (or 0.01 pH unit/mmHg), and that for plasma [HCO_3^-] is 0.2 mmol/L per mmHg. Hypocapnia sustained for >2–6 h is further compensated by a decrease in renal ammonium and titratable acid excretion and a reduction in filtered HCO_3^- reab sorption. Full renal adaptation to respiratory alkalosis may take sev eral days and requires normal volume status and renal function. The kidneys appear to respond directly to the lowered Paco2 rather than to alkalosis per se. In chronic respiratory alkalosis, a 1-mmHg decrease in Paco2 causes a 0.4- to 0.5-mmol/L decrease in [HCO_3^-] and a 0.3-mmol/L decrease in [H+] (or 0.003 unit increase in pH). The effects of respiratory alkalosis vary according to duration and severity but are primarily those of the underlying disease. Reduced cerebral blood flow as a consequence of a rapid decline in Paco2 may cause dizziness, mental confusion, and seizures, even in the absence of hypoxemia. The cardiovascular effects of acute hypocapnia in the conscious human are generally minimal, but in the anesthetized or mechanically ventilated patient, cardiac output and blood pressure may fall because of the depressant effects of anesthesia and

positivepressure ventilation on heart rate, systemic resistance, and venous return. Cardiac arrhythmias may occur in patients with heart disease as a

result of changes in oxygen unloading by blood from a left shift in the hemoglobin-oxygen dissociation curve (Bohr effect). Acute respiratory alkalosis causes intracellular shifts of Na+, K+, and PO4 2− and reduces free [Ca2+] by increasing the protein-bound fraction. Hypocapnia-induced hypokalemia is usually minor. Chronic respiratory alkalosis is the most common acid-base distur bance in critically ill patients and, when severe, portends a poor prog nosis. Many cardiopulmonary disorders manifest respiratory alkalosis in their early to intermediate stages. Normocapnia and hypoxemia in a patient with hyperventilation may herald the onset of rapid respira tory failure. Therefore, prompt assessment is necessary to determine if the patient is becoming fatigued. Respiratory alkalosis is also common during mechanical ventilation. The hyperventilation syndrome may be disabling. Paresthesia; cir cumoral numbness; chest wall tightness or pain; dizziness; inability to take an adequate breath; and, rarely, tetany may be sufficiently stressful to perpetuate the disorder. Arterial blood-gas analysis demonstrates an acute or chronic respiratory alkalosis, often with hypocapnia in the range of 15–30 mmHg, but without hypoxemia. CNS diseases or injury can produce several patterns of hyperventilation and sustained Paco2 levels of 20–30 mmHg. Hyperthyroidism, high caloric loads, and exercise raise the basal metabolic rate, but ventilation usually increases in proportion so that arterial blood gases are unchanged and respira tory alkalosis does not develop. Salicylates are the most common cause of drug-induced respiratory alkalosis because of direct stimulation of the medullary chemoreceptor by salicylates (Chap. 469). In addi tion, the methylxanthines, theophylline and aminophylline stimulate ventilation and increase the ventilatory response to CO2. Progesterone increases ventilation and lowers arterial Paco2 by as much as 5–10 mmHg. Therefore, chronic respiratory alkalosis is a common feature of pregnancy. Respiratory alkalosis is also prominent in hepatic failure, and the severity correlates with the degree of hepatic insufficiency. Respiratory alkalosis may be an early finding in gram-negative septice mia, often occurring before fever, hypoxemia, or hypotension develops. The diagnosis of respiratory alkalosis depends on measurement of arterial pH and Paco2. The plasma [K+] is often reduced and the [Cl−] increased. In the acute phase, respiratory alkalosis is not associ ated with increased renal HCO3 − excretion, but within hours, net acid excretion is reduced. In general, the HCO3 − concentration falls by

2.0 mmol/L for each 10-mmHg decrease in Paco2. Chronic respiratory alkalosis occurs when hypocapnia persists for greater than 3–5 days. The decline in Paco2 reduces the serum [HCO3 −] by 4.0–5 mmol/L for each 10-mmHg decrease in Paco2. It is unusual to observe a plasma HCO3 − <12 mmol/L as a result of a pure respiratory alkalosis. The compensatory reduction in plasma [HCO3 –] is so effective in chronic respiratory alkalosis that the pH may not decline significantly from the normal value. Therefore, chronic respiratory alkalosis is the only acid-base disorder for which compensation can return the pH to the normal value. When the diagnosis of respiratory alkalosis is made, its cause should be investigated. The diagnosis of hyperventilation syndrome is made by exclusion. In difficult cases, it may be important to rule out other conditions such as pulmonary embolism, coronary artery disease, and hyperthyroidism. TREATMENT Respiratory Alkalosis The management of respiratory alkalosis is directed toward allevia tion of the underlying disorder. If respiratory alkalosis complicates ventilator management, changes in dead space and tidal volume can minimize the hypocapnia. Patients with the hyperventilation syn drome may benefit from reassurance, rebreathing from a paper bag during symptomatic attacks, and attention to underlying psycho logical stress. Antidepressants and sedatives are not recommended. β-

Adrenergic blockers may ameliorate peripheral manifestations of the hyperadrenergic state.

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