20th Edition

HARRISON'S MANUAL OF MEDICINE

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20th Edition
HARRISON'S™
MANUAL OF
MEDICINE

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Harrison's Principles of Internal Medicine (HPIM), the premier medical textbook for students and clinicians, provides a comprehensive resource for understanding of the biological and clinical aspects of quality patient care. *Harrison's Manual of Medicine* aims to fulfill a different need: As a concise, fact-rich resource for point-of-care, the *Manual* presents clinical information drawn from the 20th edition of *HPIM,* covering the key features of the diagnosis, clinical manifestations, and treatment of the major diseases that are likely to be encountered on a medical inpatient service and in the clinic.

First published 30 years ago, the *Manual* is well established as a trusted resource for rapid access to clinically practical information. With each edition, it is updated by experts and has become ever more useful with the rapid expansion of medical knowledge and the increasing time constraints associated with heavy patient-care responsibilities in modern health care settings. The *Manual's* popularity and value reflect its abbreviated format, which has proven extremely useful for initial diagnosis and management in time-restricted clinical settings. In particular, the book's full-color format allows readers to locate and use information quickly. In addition, numerous tables and graphics facilitate decisions at the point of care.

Although not a substitute for in-depth analysis of clinical problems, the *Manual* serves as a ready source of informative summaries that will be useful "on the spot" and that will prepare the reader for more in-depth analysis through more extensive reading at a later time. Of note, McGraw-Hill's *Access Medicine* website (www.accessmedicine.com) provides online access to both the *Manual* and *Harrison's Principles of Internal Medicine*, making it very easy to seek additional information when needed. The *Manual* is also available in a variety of eBook and app formats.

Like previous editions, this latest edition of the *Manual* is intended to keep up with the continual evolution of internal medicine practices. To this end, every chapter from the prior edition has been closely reviewed and updated, with substantial revisions and new chapters provided where appropriate. The Editors learned much in the process of updating the *Manual* and we hope that you will find this edition uniquely valuable as a clinical and educational resource.

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GLOSSARY

A_2	aortic second sound
ABGs	arterial blood gases
ACE	angiotensin-converting enzyme
AF	atrial fibrillation
AIDS	acquired immunodeficiency syndrome
ALS	amyotrophic lateral sclerosis
ANA	antinuclear antibody
ARDS	acute respiratory distress syndrome
bid	two times daily
biw	twice a week
bp	blood pressure
BUN	blood urea nitrogen
CAPD	continuous ambulatory peritoneal dialysis
CBC	complete blood count
CF	complement fixation
CHF	congestive heart failure
CLL	chronic lymphocytic leukemia
CML	chronic myeloid leukemia
CMV	cytomegalovirus
CNS	central nervous system
CPK	creatine phosphokinase
CSF	cerebrospinal fluid
CT	computed tomography
CVP	central venous pressure
CXR	chest x-ray
DIC	disseminated intravascular coagulation
DVT	deep-venous thrombosis
EBV	Epstein-Barr virus
ECG	electrocardiogram
EEG	electroencephalogram
ELISA	enzyme-linked immunosorbent assay
EMG	electromyogram
ENT	ear, nose, and throat
EOM	extraocular movement
ESR	erythrocyte sedimentation rate
FDA	U.S. Food and Drug Administration
FEV_1	forced expiratory volume in first second
GFR	glomerular filtration rate
GI	gastrointestinal
G6PD	glucose-6-phosphate dehydrogenase
Hb	hemoglobin
Hct	hematocrit
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
hs	at bedtime
HSV	herpes simplex virus
ICU	intensive care unit
IFN	interferon
Ig	immunoglobulin
IL	interleukin
IM	intramuscular
IP	intraperitoneal
IV	intravenous
IVC	inferior vena cava
IVP	intravenous pyelogram

GLOSSARY

JVP	jugular venous pulse
LA	left atrium
LAD	left-axis deviation
LBBB	left bundle branch block
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LFT	liver function test
LLQ	left lower quadrant
LP	lumbar puncture
LUQ	left upper quadrant
LV	left ventricle
MI	myocardial infarction
MIC	minimal inhibitory concentration
MRI	magnetic resonance imaging
NPO	nothing by mouth
NSAIDs	nonsteroidal anti-inflammatory drugs
P_2	pulmonic second sound
PaO_2	partial pressure of O_2 in arterial blood
PAO_2	partial pressure of O_2 in alveolar blood
PCR	polymerase chain reaction
PFTs	pulmonary function tests
PMNs	polymorphonuclear cells or leukocytes
PO	by mouth
PPD	purified protein derivative, skin test for tuberculosis
prn	as needed
pt/pts	patient/patients
PT	prothrombin time
PTT	partial thromboplastin time
PVCs	premature ventricular contractions
QAM	every morning
qd	every day
qh	every hour
qhs	every bedtime
qid	four times daily
qod	every other day
RA	rheumatoid arthritis
RBBB	right bundle branch block
RBC	red blood (cell) count
RLQ	right lower quadrant
RR	respiratory rate
RUQ	right upper quadrant
RV	right ventricle
S1 . . . S4	heart sounds, 1st to 4th
SARS	severe acute respiratory syndrome
SC	subcutaneous
SL	sublingual
SLE	systemic lupus erythematosus
SVC	superior vena cava
TIA	transient ischemic attack
tid	three times daily
tiw	thrice a week
TLC	total lung capacity
TNF	tumor necrosis factor
UA	urinalysis
URI	upper respiratory infection
UTI	urinary tract infection
UV	ultraviolet
VDRL	test for syphilis
VZV	varicella-zoster virus
WBC	white blood (cell) count

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1 Electrolytes

SODIUM

Disturbances of sodium concentration [Na^+] result in most cases from abnormalities of H_2O homeostasis, which change the relative ratio of Na^+ to H_2O. Disorders of Na^+ balance per se are, in contrast, associated with changes in extracellular fluid volume, either hypo- or hypervolemia. Maintenance of "arterial circulatory integrity" is achieved in large part by changes in urinary sodium excretion and vascular tone, whereas H_2O balance is achieved by changes in both H_2O intake and urinary H_2O excretion (Table 1-1). Confusion can result from the coexistence of defects in both H_2O and Na^+ balance. For example, a hypovolemic pt may have an appropriately low urinary Na^+ due to increased renal tubular reabsorption of filtered NaCl; a concomitant increase in circulating arginine vasopressin (AVP)—part of the defense of effective circulating volume (Table 1-1)—will cause the renal retention of ingested H_2O and the development of hyponatremia.

HYPONATREMIA

This is defined as a serum [Na^+] <135 mmol/L and is among the most common electrolyte abnormalities encountered in hospitalized pts. Symptoms include nausea, vomiting, confusion, lethargy, and disorientation; if severe (<120 mmol/L) and/or abrupt, seizures, central herniation, coma, or death may result (see Acute Symptomatic Hyponatremia, below). Hyponatremia is almost always the result of an increase in circulating AVP and/or increased renal sensitivity to AVP; a notable exception is in the setting of low solute intake ("beer potomania"), wherein a markedly reduced urinary solute excretion is inadequate to support the excretion of sufficient free H_2O. The serum [Na^+] by itself does not yield diagnostic information regarding total-body Na^+ content; hyponatremia is primarily

TABLE 1-1 Osmoregulation versus Volume Regulation

	OSMOREGULATION	VOLUME REGULATION
What is sensed	Plasma osmolality	Arterial filling
Sensors	Hypothalamic osmoreceptors	Carotid sinus Afferent arteriole Atria
Effectors	AVP Thirst	Sympathetic nervous system Renin-angiotensin-aldosterone system ANP/BNP AVP
What is affected	Urine osmolality H_2O intake	Urinary sodium excretion Vascular tone

Note: See text for details.
Abbreviations: ANP, atrial natriuretic peptide; AVP, arginine vasopressin; BNP, brain natriuretic peptide.
Source: Adapted from Rose BD, Black RM (eds): *Manual of Clinical Problems in Nephrology*. Boston, Little Brown, 1988.

a disorder of H_2O homeostasis. Pts with hyponatremia are thus categorized diagnostically into three groups, depending on their clinical volume status: hypovolemic, euvolemic, and hypervolemic hyponatremia (Fig. 1-1). All three forms of hyponatremia share an exaggerated, "nonosmotic" increase in circulating AVP, in the setting of reduced serum osmolality. Notably, hyponatremia is often multifactorial; clinically important nonosmotic stimuli that can cause a release of AVP and increase the risk of hyponatremia include drugs, pain, nausea, and strenuous exercise.

Laboratory investigation of a pt with hyponatremia should include a measurement of serum osmolality to exclude "pseudohyponatremia" due to hyperlipidemia or hyperproteinemia. Serum glucose also should be measured; serum [Na^+] falls by approximately 1.4 m*M* for every 100-mg/dL increase in glucose, due to glucose-induced H_2O efflux from cells. Hyperkalemia may suggest adrenal insufficiency or hypoaldosteronism; increased blood urea nitrogen (BUN) and creatinine may suggest a renal cause. Urine electrolytes and osmolality are also critical tests in the initial evaluation of hyponatremia. In particular, a urine Na^+ <20 meq/L is consistent with hypovolemic hyponatremia in the clinical absence of a "hypervolemic," Na^+-avid syndrome such as congestive heart failure (CHF) (Fig. 1-1). Urine osmolality <100 mosmol/kg is suggestive of polydipsia or, in rare cases, of decreased solute intake; urine osmolality >400 mosmol/kg suggests that AVP excess is playing a more dominant role, whereas intermediate values are more consistent with multifactorial pathophysiology (e.g., AVP excess with a component of polydipsia). Finally, in the right clinical setting, thyroid, adrenal, and pituitary function should also be tested.

Hypovolemic Hyponatremia

Hypovolemia from both renal and extrarenal causes is associated with hyponatremia. Renal causes of hypovolemia include primary adrenal insufficiency and hypoaldosteronism, salt-losing nephropathies (e.g., reflux nephropathy, nonoliguric acute tubular necrosis), diuretics, and osmotic diuresis. Random "spot" urine Na^+ is typically >20 meq/L in these cases but may be <20 meq/L in diuretic-associated hyponatremia if tested long after administration of the drug. Nonrenal causes of hypovolemic hyponatremia include GI loss (e.g., vomiting, diarrhea, tube drainage) and integumentary loss (sweating, burns); urine Na^+ is typically <20 meq/L in these cases.

Hypovolemia causes profound neurohumoral activation, inducing systems that preserve arterial circulatory integrity, such as the renin-angiotensin-aldosterone (RAA) axis, the sympathetic nervous system, and AVP (Table 1-1). The increase in circulating AVP serves to increase the retention of ingested-free H_2O, leading to hyponatremia. The optimal treatment of hypovolemic hyponatremia is volume administration, generally as isotonic crystalloid, i.e., 0.9% NaCl ("normal saline"). If the history suggests that hyponatremia has been "chronic," i.e., present for 48 h, care should be taken to avoid overcorrection (see below), which can easily occur as AVP levels plummet in response to volume-resuscitation; if necessary, the administration of desmopressin (DDAVP) and free water can reinduce or arrest the correction of hyponatremia (see below). An alternative strategy is to "clamp" AVP bioactivity by administering DDAVP while correcting the serum [Na^+] with hypertonic saline in a more controlled, linear fashion.

Hypervolemic Hyponatremia

The edematous disorders (CHF, hepatic cirrhosis, and nephrotic syndrome) are often associated with mild to moderate degrees of hyponatremia ([Na^+] = 125–135 mmol/L); occasionally, pts with severe CHF or cirrhosis may present with serum [Na^+] <120 mmol/L. The pathophysiology is similar to that in hypovolemic hyponatremia, except that arterial filling and circulatory integrity are

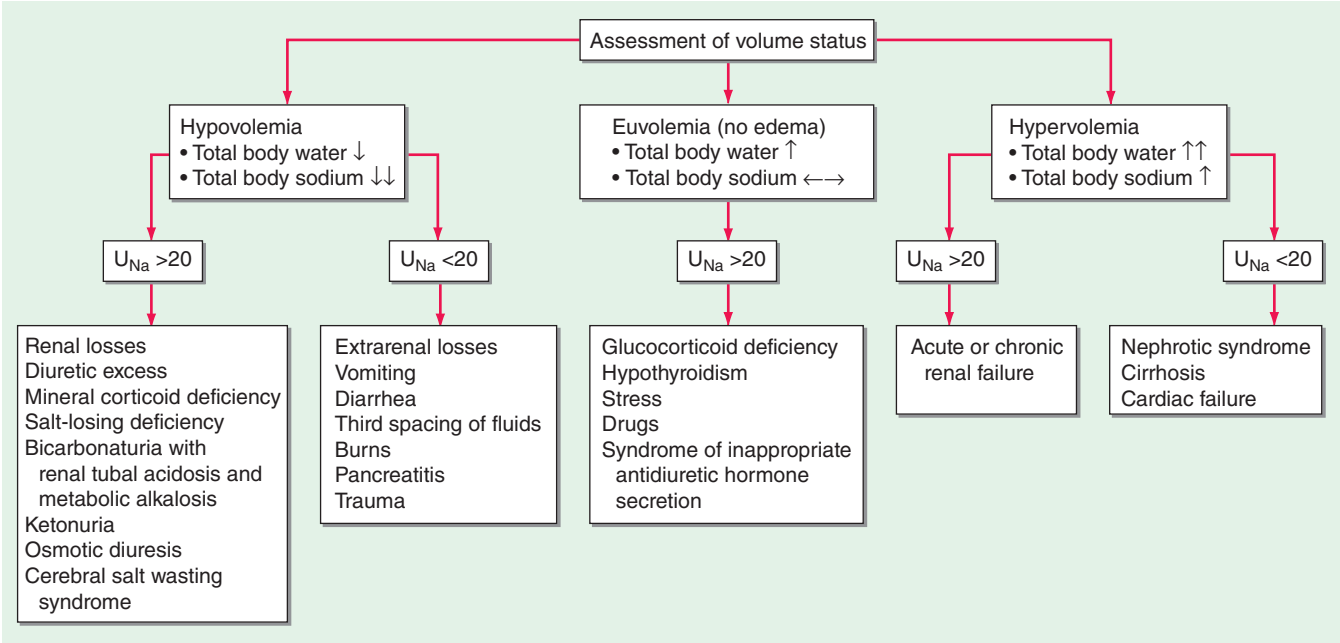


FIGURE 1-1 The diagnostic approach to hyponatremia. See text for details. *(Reprinted from Kumar S, Berl T: Diseases of water metabolism. In: Atlas of Diseases of the Kidney, Vol I, Schrier RW [ed]. Philadelphia, Current Medicine, Inc, 1999; with permission.)*

decreased due to the specific etiologic factors, i.e., cardiac dysfunction, peripheral vasodilation in cirrhosis, and hypoalbuminemia in nephrotic syndrome. The degree of hyponatremia is an indirect index of the associated neurohumoral activation (Table 1-1) and an important prognostic indicator in hypervolemic hyponatremia.

Management consists of treatment of the underlying disorder (e.g., afterload reduction in heart failure, intravenous administration of albumin in cirrhosis, immunomodulatory therapy in some forms of nephrotic syndrome), Na^+ restriction, diuretic therapy, and, in some pts, H_2O restriction. Vasopressin antagonists (e.g., tolvaptan and conivaptan) are also effective in normalizing hypervolemic hyponatremia associated with CHF; hepatic toxicity of tolvaptan limits its clinical utility in cirrhosis.

Euvolemic Hyponatremia

The syndrome of inappropriate ADH secretion (SIADH) characterizes most cases of euvolemic hyponatremia. Other causes of euvolemic hyponatremia include hypothyroidism and secondary adrenal insufficiency due to pituitary disease; notably, repletion of glucocorticoid levels in the latter may cause a rapid drop in circulating AVP levels and overcorrection of serum $[Na^+]$ (see below).

Common causes of SIADH include pulmonary disease (e.g., pneumonia, tuberculosis, pleural effusion) and central nervous system (CNS) diseases (e.g., tumor, subarachnoid hemorrhage, meningitis); SIADH also occurs with malignancies (primarily small cell carcinoma of the lung) and drugs (e.g., selective serotonin reuptake inhibitors, tricyclic antidepressants, nicotine, vincristine, carbamazepine, narcotic analgesics, antipsychotic drugs, cyclophosphamide, ifosfamide). Optimal treatment of euvolemic hyponatremia includes treatment of the underlying disorder. H_2O restriction to <1 L/d is a cornerstone of therapy, but may be ineffective or poorly tolerated. However, vasopressin antagonists are predictably effective in normalizing serum $[Na^+]$ in SIADH. Alternatives include the administration of loop diuretics to inhibit the countercurrent mechanism and reduce urinary concentration, combined with oral salt tablets to abrogate diuretic-induced salt loss and attendant hypovolemia. More recently, a palatable form of oral urea has become available; oral urea is equivalent to tolvaptan in the management of SIADH, increasing urinary solute (urea) and, thus, urinary H_2O excretion.

Acute Symptomatic Hyponatremia

Acute symptomatic hyponatremia is a medical emergency; a sudden drop in serum $[Na^+]$ can overwhelm the capacity of the brain to regulate cell volume, leading to cerebral edema, seizures, and death. Women, particularly premenopausal women, are particularly prone to such sequelae; neurologic consequences are comparatively rare in male pts. Many of these pts develop hyponatremia from iatrogenic causes, including hypotonic fluids in the postoperative period, prescription of a thiazide diuretic, colonoscopy preparation, or intraoperative use of glycine irrigants. Polydipsia with an associated cause of increased AVP may also cause acute hyponatremia, as can increased H_2O intake in the setting of strenuous exercise, e.g., a marathon. The recreational drug Ecstasy (methylenedioxymethamphetamine [MDMA]) can cause acute hyponatremia, rapidly inducing both AVP release and increased thirst.

Severe symptoms may occur at relatively modest levels of serum $[Na^+]$, e.g., in the mid-120s. Nausea and vomiting are common premonitory symptoms of more severe sequelae. An important concomitant is respiratory failure, which may be hypercapnic due to CNS depression or normocapnic due to neurogenic, noncardiogenic pulmonary edema; the attendant hypoxemia amplifies the impact of hyponatremic encephalopathy.

TREATMENT

Hyponatremia

Three considerations are critical in the therapy of hyponatremia. First, the presence, absence, and/or severity of symptoms determine the urgency of therapy (see above for acute symptomatic hyponatremia). Second, pts with hyponatremia that has been present for >48 h ("chronic hyponatremia") are at risk for osmotic demyelination syndrome, typically central pontine myelinolysis, if serum Na^+ is corrected by >10–12 m*M* within the first 24 h and/or by >18 m*M* within the first 48 h. Third, the response to interventions, such as hypertonic saline or vasopressin antagonists, can be highly unpredictable, such that frequent monitoring of serum Na^+ (initially every 2–4 h) is imperative.

Treatment of acute symptomatic hyponatremia should include hypertonic saline to acutely increase serum Na^+ by 1–2 m*M*/h to a total increase of 4–6 m*M*; this increase is typically sufficient to alleviate acute symptoms from cerebral edema, after which corrective guidelines for "chronic" hyponatremia are appropriate (see below). A number of equations and algorithms have been developed to estimate the required rate of hypertonic solution; one popular approach is to calculate a "Na^+ deficit," where the Na^+ deficit = 0.6 × body weight × (target $[Na^+]$ – starting $[Na^+]$). Regardless of the method used to determine the rate of administered hypertonic saline, the increase in serum $[Na^+]$ can be highly unpredictable, due to rapid changes in the underlying physiology; serum $[Na^+]$ should be monitored every 2–4 h during and after treatment with hypertonic saline. The administration of supplemental O_2 and ventilatory support can also be critical in acute hyponatremia, if pts develop acute pulmonary edema or hypercapnic respiratory failure. IV loop diuretics will help treat associated acute pulmonary edema and will also increase free H_2O excretion by interfering with the renal countercurrent multiplier system. It is noteworthy that vasopressin antagonists do not have a role in the management of acute hyponatremia.

The rate of correction should be comparatively slow in *chronic* hyponatremia (<10–12 m*M* in the first 24 h and <18 m*M* in the first 48 h), so as to avoid osmotic demyelination syndrome. Vasopressin antagonists are highly effective in SIADH and in hypervolemic hyponatremia due to heart failure. Abnormalities in liver function tests have been reported during the use of tolvaptan, prohibiting use in cirrhosis; in pts without preexisting liver disease, therapy with this agent should be restricted to 1–2 months with close monitoring of liver function. Should pts overcorrect serum $[Na^+]$ in response to vasopressin antagonists, hypertonic saline, or isotonic saline (in chronic hypovolemic hyponatremia), hyponatremia can be safely reinduced or stabilized by the administration of the vasopressin *agonist* DDAVP and the administration of free H_2O, typically IV D_5W; again, close monitoring of the response of serum $[Na^+]$ is essential to adjust therapy. Alternatively, the treatment of pts with marked hyponatremia can be initiated with the twice-daily administration of DDAVP to maintain constant AVP bioactivity, combined with the administration of hypertonic saline to slowly correct the serum $[Na^+]$ in a more controlled fashion, thus reducing upfront the risk of overcorrection.

HYPERNATREMIA

This is rarely associated with hypervolemia, where the association is typically iatrogenic, e.g., administration of hypertonic sodium bicarbonate. More commonly, hypernatremia is the result of a combined H_2O and volume deficit, with losses of H_2O in excess of Na^+. Elderly individuals with reduced thirst and/or diminished access to fluids are at the highest risk of hypernatremia due to decreased free

TABLE 1-2 Correction of Hypernatremia

H_2O Deficit

1. Estimate TBW: 50–60% body weight (kg) depending on body composition
2. Calculate free-water deficit: $[(Na^+ - 140)/140] \times TBW$
3. Administer deficit over 48–72 h

Ongoing H_2O Losses

4. Calculate free-water clearance, C_eH_2O:

$$C_eH_2O = V\left(1 - \frac{U_{Na} + U_K}{S_{Na}}\right)$$

where V is urinary volume, U_{Na} is urinary $[Na^+]$, U_K is urinary $[K^+]$, and S_{Na} is serum $[Na^+]$.

Insensible Losses

5. ~10 mL/kg per day: less if ventilated, more if febrile

Total

6. Add components to determine H_2O deficit and ongoing H_2O loss; correct the H_2O deficit over 48–72 h and replace daily H_2O loss.

Abbreviation: TBW, total-body water.

H_2O intake. Common causes of renal H_2O loss are osmotic diuresis secondary to hyperglycemia, postobstructive diuresis, or drugs (radiocontrast, mannitol, etc.); H_2O diuresis occurs in central or nephrogenic diabetes insipidus (DI) (Chap. 172). In pts with hypernatremia due to renal loss of H_2O, it is critical to quantify *ongoing* daily losses in addition to calculation of the baseline H_2O deficit (Table 1-2).

TREATMENT

Hypernatremia

The approach to correction of hypernatremia is outlined in Table 1-2. As with hyponatremia, it is advisable to correct the H_2O deficit slowly to avoid neurologic compromise, decreasing the serum $[Na^+]$ over 48–72 h. Depending on the blood pressure or clinical volume status, it may be appropriate to initially treat with hypotonic saline solutions (1/4 or 1/2 normal saline); blood glucose should be monitored in pts treated with large volumes of D_5W, should hyperglycemia ensue. Calculation of urinary electrolyte-free H_2O clearance is helpful to estimate daily, ongoing loss of free H_2O in pts with nephrogenic or central DI (Table 1-2). Other forms of therapy may be helpful in selected cases of hypernatremia, once water deficits have been repleted. Pts with central DI may respond to the administration of intranasal DDAVP. Stable pts with nephrogenic DI may reduce their polyuria with hydrochlorothiazide (12.5–50 mg/d). This diuretic is thought to increase proximal H_2O reabsorption and decrease distal solute delivery, thus reducing polyuria. Pts with lithium-associated nephrogenic DI may respond to amiloride (2.5–10 mg/d), which decreases the entry of lithium into principal cells in the distal nephron by inhibiting the amiloride-sensitive epithelial sodium channel (ENaC). Notably, however, most pts with lithium-induced nephrogenic DI can adequately accommodate by increasing their H_2O intake. Occasionally, nonsteroidal anti-inflammatory drugs (NSAIDs) or COX-2 inhibitors have also been used to treat polyuria associated with nephrogenic DI, reducing the negative effect of local prostaglandins on urinary concentration; however, the nephrotoxic potential of these drugs typically makes them a less attractive therapeutic option.

POTASSIUM

Because potassium (K^+) is the major intracellular cation, discussion of disorders of K^+ balance must take into consideration changes in the exchange of intra- and extracellular K^+ stores. (Extracellular K^+ constitutes <2% of total-body K^+ content.) Insulin, β_2-adrenergic agonists, and alkalosis tend to promote K^+ uptake by cells; acidosis, insulinopenia, or acute hyperosmolality (e.g., after treatment with mannitol or $D_{50}W$) promotes the efflux or reduced uptake of K^+. A corollary is that tissue necrosis and the attendant release of K^+ can cause severe hyperkalemia, particularly in the setting of acute kidney injury. Hyperkalemia due to rhabdomyolysis is thus particularly common, due to the enormous store of K^+ in muscle; hyperkalemia may also be prominent in tumor lysis syndrome.

The kidney plays a dominant role in K^+ excretion. Although K^+ is transported along the entire nephron, it is the principal cells of the connecting segment and cortical collecting duct that play a dominant role in K^+ excretion. Apical Na^+ entry into principal cells via the amiloride-sensitive ENaC generates a lumen-negative potential difference, which drives passive K^+ exit through apical K^+ channels. *This relationship is key to the bedside understanding of potassium disorders.* For example, decreased distal delivery of Na^+ tends to blunt the ability to excrete K^+, leading to hyperkalemia. Abnormalities in the renin-angiotensin-aldosterone system (RAAS) can cause both hypo- and hyperkalemia; aldosterone has a major influence on potassium excretion, increasing the activity of ENaC channels and the basolateral Na+/K+-ATPase, thus amplifying the driving force for K^+ secretion across the luminal membrane of principal cells.

HYPOKALEMIA

Major causes of hypokalemia are outlined in **Table 1-3**. Atrial and ventricular arrhythmias are the most serious health consequences of hypokalemia. Pts with concurrent Mg deficit and/or digoxin therapy are at a particularly increased risk of arrhythmias. Hypokalemia can directly prolong the QT interval and is a significant cofactor in arrhythmias due to other causes of a prolonged QT interval. Other clinical manifestations include muscle weakness, which may be profound at serum $[K^+]$ <2.5 mmol/L, and, if hypokalemia is sustained, hypertension, ileus, polyuria, renal cysts, and even renal failure.

The cause of hypokalemia is usually obvious from history, physical examination, and/or basic laboratory tests. However, persistent hypokalemia may require a more thorough, systematic evaluation (**Fig. 1-2**). Initial laboratory evaluation should include electrolytes, BUN, creatinine, serum osmolality, Mg^{2+}, and Ca^{2+}, a complete blood count, and urinary pH, osmolality, creatinine, and electrolytes. Serum and urine osmolality are required for calculation of the transtubular K^+ gradient (TTKG), which should be <3 in the presence of hypokalemia (see also Hyperkalemia). Alternatively, a urinary K^+-to-creatinine ratio of >13-mmol/g creatinine (>1.5-mmol/mmol creatinine) is compatible with excessive K^+ excretion. Further tests such as urinary Mg^{2+} and Ca^{2+} and/or plasma renin and aldosterone levels may be necessary in specific cases.

TREATMENT

Hypokalemia

The goals of therapy in hypokalemia are to prevent life-threatening and/or serious chronic consequences, to replace the associated K^+ deficit, and to correct the underlying cause and/or mitigate future hypokalemia. The urgency of therapy depends on the severity of hypokalemia, associated clinical factors (cardiac disease, digoxin therapy, etc.), and the rate of decline in serum K^+. Pts with a prolonged QT interval and/or other risk factors for arrhythmia should

TABLE 1-3 Causes of Hypokalemia

I. Decreased intake
   A. Starvation
   B. Clay ingestion

II. Redistribution into cells
   A. Acid-base
      1. Metabolic alkalosis
   B. Hormonal
      1. Insulin
      2. Increased β_2-adrenergic sympathetic activity: post–myocardial infarction, head injury, theophylline
      3. β_2-Adrenergic agonists: bronchodilators, tocolytics
      4. α-Adrenergic antagonists
      5. Thyrotoxic periodic paralysis
      6. Downstream stimulation of Na^+/K^+-ATPase: theophylline, caffeine
   C. Anabolic state
      1. Vitamin B_{12} or folic acid administration (red blood cell production)
      2. Granulocyte-macrophage colony-stimulating factor (white blood cell production)
      3. Total parenteral nutrition
   D. Other
      1. Pseudohypokalemia
      2. Hypothermia
      3. Familial hypokalemic periodic paralysis
      4. Barium toxicity: systemic inhibition of "leak" K^+ channels

III. Increased loss
   A. Nonrenal
      1. Gastrointestinal loss (diarrhea)
      2. Integumentary loss (sweat)
   B. Renal
      1. Increased distal flow and distal Na^+ delivery: diuretics, osmotic diuresis, salt-wasting nephropathies
      2. Increased secretion of potassium
         a. Mineralocorticoid excess: primary hyperaldosteronism (APAs), PAH or UAH, IHA due to bilateral adrenal hyperplasia and adrenal carcinoma, familial hyperaldosteronism (FH-I, FH-II, congenital adrenal hyperplasias), secondary hyperaldosteronism (malignant hypertension, renin-secreting tumors, renal artery stenosis, hypovolemia), Cushing's syndrome, Bartter's syndrome, Gitelman's syndrome
         b. Apparent mineralocorticoid excess: genetic deficiency of 11β-dehydrogenase-2 (syndrome of apparent mineralocorticoid excess), inhibition of 11β-dehydrogenase-2 (glycyrrhetinic/glycyrrhizinic acid and/or carbenoxolone; licorice, food products, drugs), Liddle's syndrome (genetic activation of ENaC)

(*Continued*)

TABLE 1-3 Causes of Hypokalemia (*Continued*)

c. Distal delivery of nonreabsorbed anions: vomiting, nasogastric suction, proximal renal tubular acidosis, diabetic ketoacidosis, glue sniffing (toluene abuse), penicillin derivatives (penicillin, nafcillin, dicloxacillin, ticarcillin, oxacillin, and carbenicillin)

3. Magnesium deficiency, amphotericin B, Liddle's syndrome

Abbreviations: APA, aldosterone-producing adenoma; ENaC, epithelial Na^+ channels; IHA, idiopathic hyperaldosteronism; PAH, primary adrenal hyperplasia; UAH, unilateral adrenal hyperplasia.

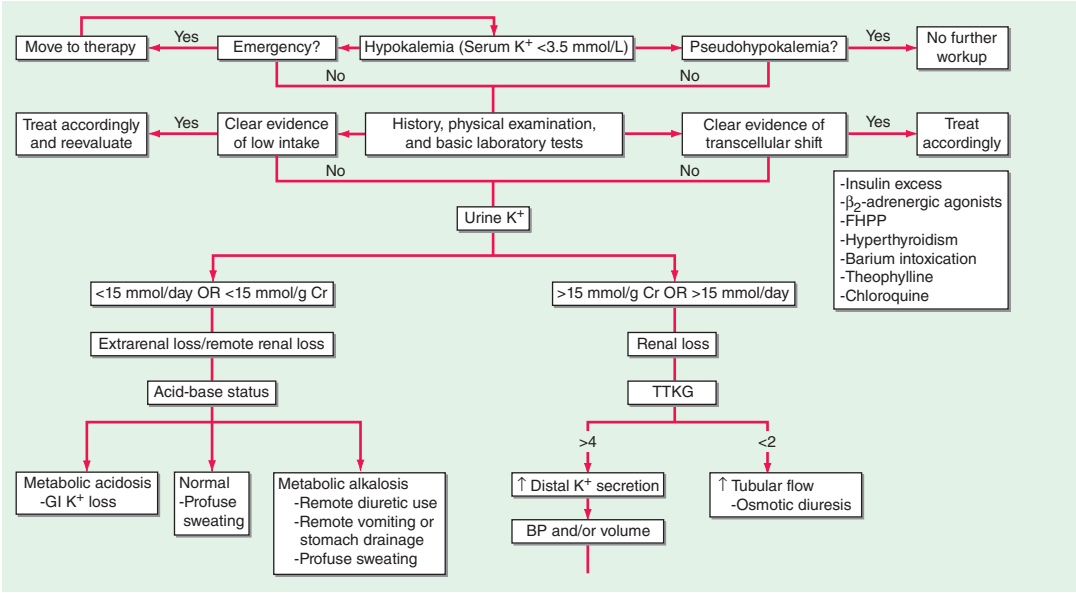
be monitored by continuous cardiac telemetry during repletion. Urgent but cautious K^+ replacement should be considered in pts with severe redistributive hypokalemia (plasma K^+ concentration <2.5 m*M*) and/or when serious complications ensue; however, this approach has a risk of rebound hyperkalemia following acute resolution of the underlying cause. When excessive activity of the sympathetic nervous system is thought to play a dominant role in redistributive hypokalemia, as in thyrotoxic periodic paralysis, theophylline overdose, and acute head injury, high-dose propranolol (3 mg/kg) should be considered; this nonspecific β-adrenergic blocker will correct hypokalemia without the risk of rebound hyperkalemia. It should be noted that hypokalemia is refractory to correction in the presence of Mg^{++} deficiency, which also should be corrected when present; renal wasting of both cations may be particularly prominent after renal tubular injury, e.g., from cisplatin nephrotoxicity.

Oral replacement with K^+-Cl^- is the mainstay of therapy in hypokalemia. Potassium phosphate, oral or IV, may be appropriate in pts with combined hypokalemia and hypophosphatemia. Potassium bicarbonate or potassium citrate should be considered in pts with concomitant metabolic acidosis. The deficit of K^+ and the rate of correction should be estimated as accurately as possible; renal function, medications, and comorbid conditions such as diabetes should also be considered so as to gauge the risk of overcorrection. In the absence of abnormal K^+ redistribution, the total deficit correlates with serum K^+ such that serum K^+ drops by approximately 0.27 m*M* for every 100-mmol reduction in total-body stores. Notably, given the delay in redistributing potassium into intracellular compartments, this deficit must be replaced gradually over 24–48 h, with frequent monitoring of plasma K^+ concentration to avoid transient over-repletion and transient hyperkalemia if otherwise appropriate. If hypokalemia is severe (<2.5 mmol/L) and/or if oral supplementation is not feasible or tolerated, IV KCl can be administered through a central vein with cardiac monitoring in an intensive care setting, at rates that should not exceed 20 mmol/h. KCl should always be administered in saline solutions, rather than dextrose; the dextrose-induced increase in insulin can acutely exacerbate hypokalemia.

Strategies to minimize K^+ losses should also be considered. These measures may include minimizing the dose of non-K^+-sparing diuretics, restricting Na^+ intake, and using clinically appropriate combinations of non-K^+-sparing and K^+-sparing medications (e.g., loop diuretics with angiotensin-converting enzyme inhibitors).

HYPERKALEMIA

Causes are outlined in Table 1-4; in most cases, hyperkalemia is due to decreased renal K^+ excretion. However, increases in dietary K^+ intake can have a major effect in susceptible pts, e.g., diabetics with hyporeninemic hypoaldosteronism and chronic kidney disease (CKD). Drugs that impact on the RAA axis are also a major cause of hyperkalemia.


Hypokalemia (Serum K+ <3.5 mmol/L)
Emergency?
Yes
Move to therapy
Pseudohypokalemia?
Yes
No further workup
No
No
History, physical examination, and basic laboratory tests
Clear evidence of low intake
Yes
Treat accordingly and reevaluate
Clear evidence of transcellular shift
Yes
Treat accordingly
No
No
-Insulin excess
-β2-adrenergic agonists
-FHPP
-Hyperthyroidism
-Barium intoxication
-Theophylline
-Chloroquine
Urine K+
<15 mmol/day OR <15 mmol/g Cr
>15 mmol/g Cr OR >15 mmol/day
Extrarenal loss/remote renal loss
Renal loss
Acid-base status
TTKG
>4
<2
Metabolic acidosis
-GI K+ loss
Normal
-Profuse sweating
Metabolic alkalosis
-Remote diuretic use
-Remote vomiting or stomach drainage
-Profuse sweating
↑ Distal K+ secretion
↑ Tubular flow
-Osmotic diuresis
BP and/or volume

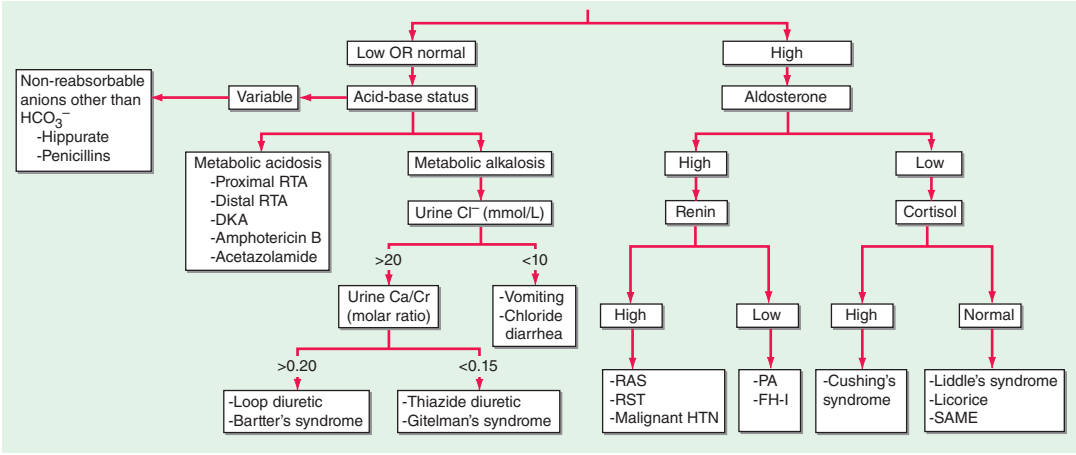


FIGURE 1-2 The diagnostic approach to hypokalemia. See text for details. bp, blood pressure; DKA, diabetic ketoacidosis; FH-I, familial hyperaldosteronism type I; FHPP, familial hypokalemic periodic paralysis; HTN, hypertension; PA, primary aldosteronism; RAS, renal artery stenosis; RST, renin-secreting tumor; RTA, renal tubular acidosis; SAME, syndrome of apparent mineralocorticoid excess; TTKG, transtubular potassium gradient. *(Reprinted with permission from Mount DB, Zandi-Nejad K: Disorders of potassium balance. In: Brenner and Rector's The Kidney, 8th ed, Brenner BM [ed]. Philadelphia, Saunders, 2008.)*

TABLE 1-4 Causes of Hyperkalemia

I. "Pseudo" hyperkalemia
   A. Cellular efflux: thrombocytosis, erythrocytosis, leukocytosis, in vitro hemolysis
   B. Hereditary defects in red cell membrane transport

II. Intra- to extracellular shift
   A. Acidosis
   B. Hyperosmolality; radiocontrast, hypertonic dextrose, mannitol
   C. β-Adrenergic antagonists (noncardioselective agents)
   D. Digoxin and related glycosides (yellow oleander, foxglove, bufadienolide)
   E. Hyperkalemic periodic paralysis
   F. Lysine, arginine, and ε-aminocaproic acid (structurally similar, positively charged)
   G. Succinylcholine; thermal trauma, neuromuscular injury, disuse atrophy, mucositis, or prolonged immobilization
   H. Rapid tumor lysis

III. Inadequate excretion
   A. Inhibition of the renin-angiotensin-aldosterone axis; ↑ risk of hyperkalemia when used in combination or at higher than recommended dosages
      1. ACE inhibitors
      2. Renin inhibitors: aliskiren (in combination with ACE inhibitors or ARBs)
      3. ARBs
      4. Blockade of the mineralocorticoid receptor: spironolactone, eplerenone, drospirenone
      5. Blockade of ENaC: amiloride, triamterene, trimethoprim, pentamidine, nafamostat
   B. Decreased distal delivery
      1. Congestive heart failure
      2. Volume depletion
   C. Hyporeninemic hypoaldosteronism
      1. Tubulointerstitial diseases: SLE, sickle cell anemia, obstructive uropathy
      2. Diabetes, diabetic nephropathy
      3. Drugs: nonsteroidal anti-inflammatory drugs, COX-2 inhibitors, β blockers, cyclosporine, tacrolimus
      4. Chronic kidney disease, advanced age
      5. Pseudohypoaldosteronism type II: defects in WNK1 or WNK4 kinases, Kelch-like 3 (KLHL3), or Cullin 3 (CUL3)
   D. Renal resistance to mineralocorticoid
      1. Tubulointerstitial diseases: SLE, amyloidosis, sickle cell anemia, obstructive uropathy, post–acute tubular necrosis
      2. Hereditary: pseudohypoaldosteronism type I: defects in the mineralocorticoid receptor or ENaCE. Advanced renal insufficiency with low GFR
   E. Advanced renal insufficiency with low GFR
      1. Chronic kidney disease
      2. End-stage renal disease
      3. Acute oliguric kidney injury
   F. Primary adrenal insufficiency
      1. Autoimmune: Addison's disease, polyglandular endocrinopathy
      2. Infectious: HIV, cytomegalovirus, tuberculosis, disseminated fungal infection
      3. Infiltrative: amyloidosis, malignancy, metastatic cancer
      4. Drug-associated: heparin, low-molecular-weight heparin
      5. Hereditary: adrenal hypoplasia congenita, congenital lipoid adrenal hyperplasia, aldosterone synthase deficiency
      6. Adrenal hemorrhage or infarction, including in antiphospholipid syndrome

Abbreviations: ARB, angiotensin receptor blocker; COX-2, cyclooxygenase 2; ENaC, epithelial Na^+ channels.

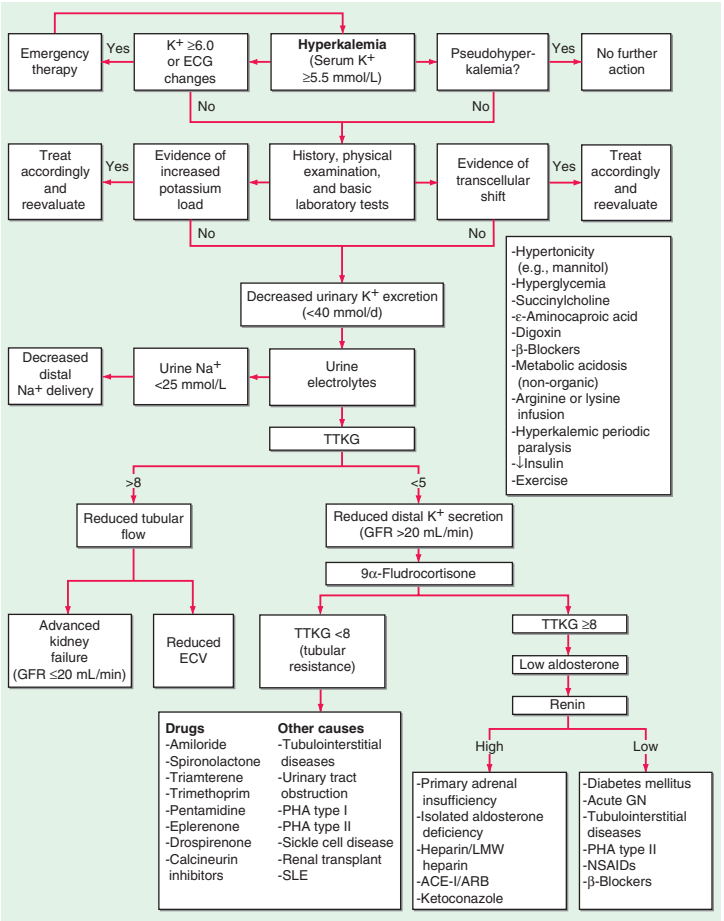


FIGURE 1-3 The diagnostic approach to hyperkalemia. See text for details. ACEI, angiotensin-converting enzyme inhibitor; acute GN, acute glomerulonephritis; ARB, angiotensin II receptor blocker; ECV, effective circulatory volume; LMW heparin, low-molecular-weight heparin; PHA, pseudohypoaldosteronism; TTKG, transtubular potassium gradient. *(Reprinted with permission from Mount DB, Zandi-Nejad K: Disorders of potassium balance. In: Brenner and Rector's The Kidney, 8th ed, Brenner BM [ed]. Philadelphia, Saunders, 2008.)*

The first priority in the management of hyperkalemia is to assess the need for emergency treatment (ECG changes and/or K^+ ≥6.0 m*M*). This should be followed by a comprehensive workup to determine the cause (Fig. 1-3). History and physical examination should focus on medications (e.g., ACE inhibitors, NSAIDs, trimethoprim/sulfamethoxazole), diet and dietary supplements (e.g., salt substitute), risk factors for acute kidney failure, reduction in urine output, blood pressure, and volume status. Initial laboratory tests should include electrolytes, BUN, creatinine, serum osmolality, Mg^{2+}, and Ca^{2+}, a complete blood count, and urinary pH, osmolality, creatinine, and electrolytes. A urine $[Na^+]$ <20 meq/L suggests that distal Na^+ delivery is a limiting factor in K^+ excretion;

volume repletion with 0.9% saline or treatment with furosemide may then be effective in reducing serum [K^+] by increasing distal Na^+ delivery. Serum and urine osmolality are required for calculation of the TTKG. The expected values of the TTKG are largely based on historic data: <3 in the presence of hypokalemia and >7–8 in the presence of hyperkalemia.

$$\text{TTKG} = \frac{[K^+]_{\text{urine}} \times \text{OSM}_{\text{serum}}}{[K^+]_{\text{serum}} \times \text{OSM}_{\text{urine}}}$$

TREATMENT

Hyperkalemia

The most important consequence of hyperkalemia is altered cardiac conduction, with the risk of bradycardic cardiac arrest. **Figure 1-4** shows serial ECG patterns of hyperkalemia; ECG manifestations of hyperkalemia should be considered a true medical emergency and treated urgently. However, ECG changes of hyperkalemia are notoriously insensitive, particularly in pts with CKD; given these limitations, pts with significant hyperkalemia (K^+ ≥6–6.5 mmol/L) in the absence of ECG changes should also be aggressively managed.

Urgent management of hyperkalemia constitutes a 12-lead ECG, admission to the hospital, continuous cardiac monitoring, and immediate treatment. Treatment of hyperkalemia is divided into three categories: (1) antagonism of the cardiac effects of hyperkalemia, (2) rapid reduction in [K^+] by redistribution into cells, and (3) removal of K^+ from the body. Treatment of hyperkalemia is summarized in **Table 1-5**. Kayexalate, a mainstay of hyperkalemia treatment, has

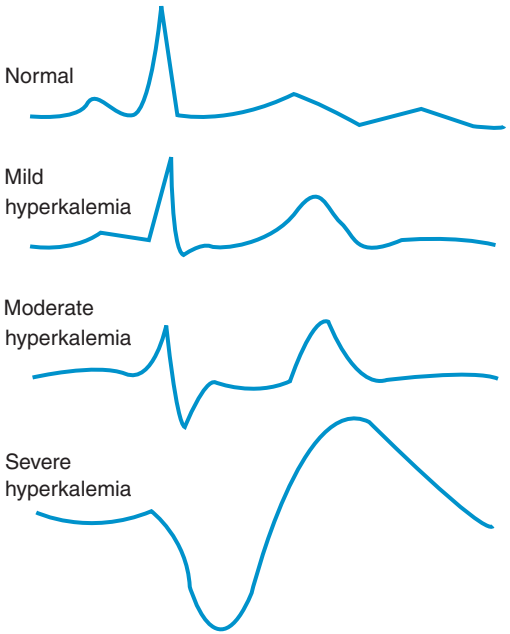


FIGURE 1-4 Diagrammatic ECGs at normal and high serum K. Peaked T waves (precordial leads) are followed by diminished R wave, wide QRS, prolonged P-R, loss of P wave, and ultimately a sine wave.

TABLE 1-5 Treatment of Hyperkalemia

MECHANISM	THERAPY	DOSE	ONSET	DURATION	COMMENTS
Stabilize membrane potential	Calcium	10% Ca gluconate, 10 mL over 10 min	1–3 min	30–60 min	Repeat in 5 min if persistent electrocardiographic changes; avoid in digoxin toxicity.
Cellular K^+ uptake	Insulin	10 U R with 50 mL of D_{50}, if blood sugar <250	30 min	4–6 h	Can repeat in 15 min; initiate $D_{10}W$ IV at 50–75 mL/h to avoid rebound hypoglycemia.
	β_2-Agonist	Nebulized albuterol, 10–20 mg in 4-mL saline	30 min	2–4 h	Can be synergistic/additive to insulin; should not be used as sole therapy; use with caution in cardiac disease; may cause tachycardia/hyperglycemia.
K^+ removal	Kayexalate	30–60 g PO in 20% sorbitol	6 h	?	May cause fatal colonic necrosis; **if available, sodium zirconium cyclosilicate (ZS-9) or patiromer is preferred to kayexalate.**
	Furosemide	20–250 mg IV	15 min	4–6 h	Depends on adequate renal response/function.
	Hemodialysis		Immediate		Efficacy depends on pretreatment of hyperkalemia (with attendant decrease in serum K^+), the dialyzer used, blood flow and dialysate flow rates, duration, and serum to dialysate K^+ gradient.

been linked to fatal colonic necrosis; if available, sodium zirconium cyclosilicate (ZS-9) or patiromer, newer potassium binders that do not cause colonic necrosis, should be used in preference to kayexalate.

2 Acid-Base Disorders

Regulation of normal pH (7.35–7.45) depends on both the lungs and kidneys. By the Henderson-Hasselbalch equation, pH is a function of the ratio of HCO_3^- (regulated by the kidney) to PCO_2 (regulated by the lungs). The HCO_3/PCO_2 relationship is useful in classifying disorders of acid-base balance. Acidosis is due to gain of acid or loss of alkali; causes may be metabolic (fall in serum HCO_3^-) or respiratory (rise in PCO_2). Alkalosis is due to loss of acid or addition of base and is either metabolic (↑ serum $[HCO_3^-]$) or respiratory (↓ PCO_2) (**Fig. 2-1**).

To limit the change in pH, metabolic disorders evoke an immediate compensatory response in ventilation; full renal compensation for respiratory disorders is a slower process, such that "acute" compensations are of lesser magnitude than "chronic" compensations. Simple acid-base disorders consist of one primary disturbance and its compensatory response. In mixed disorders, a combination of primary disturbances is present.

The cause of simple acid-base disorders is usually obvious from history, physical examination, and/or basic laboratory tests. Initial laboratory evaluation depends on the dominant acid-base disorder, but for metabolic acidosis and alkalosis this should include electrolytes, BUN, creatinine, albumin, urinary pH, and urinary electrolytes. An arterial blood gas (ABG) is not always required for pts with a simple acid-base disorder, e.g., mild metabolic acidosis in the context of chronic renal failure. However, concomitant ABG and serum electrolytes are necessary to fully evaluate more complex acid-base disorders. The compensatory response should be estimated from the ABG; Winter's formula $[PaCO_2 = (1.5 \times [HCO_3^-]) + 8 \pm 2]$ is particularly useful for assessing the respiratory response to metabolic acidosis. The anion gap should also be calculated; the anion gap = $[Na^+] - ([HCO_3^-] + [Cl^-])$ = unmeasured anions – unmeasured cations. The anion gap should be adjusted for changes in the concentration of albumin, a dominant unmeasured anion; the "adjusted anion gap" = anion gap + ~2.5 × (4 – albumin mg/dL). Other supportive tests will elucidate the specific form of anion-gap acidosis (see below).

METABOLIC ACIDOSIS

The low HCO_3^- in metabolic acidosis results from the addition of acids (organic or inorganic) or from a loss of HCO_3^-; causes of metabolic acidosis are classically categorized by presence or absence of an increase in the anion gap (**Table 2-1**). Increased anion-gap acidosis (>12 mmol/L) is due to addition of acid (other than HCl) and unmeasured anions to the body. Common causes include ketoacidosis (diabetes mellitus [DKA], starvation, alcohol), lactic acidosis, poisoning (salicylates, ethylene glycol, and methanol), and renal failure.

Rare and newly appreciated causes of anion-gap acidosis include D-lactic acidosis, propylene glycol toxicity, and 5-oxoprolinuria (also known as pyroglutamic aciduria). D-Lactic acidosis (an increase in the D-enantiomer of lactate) can occur in pts with removal, disease, or bypass of the short bowel, leading

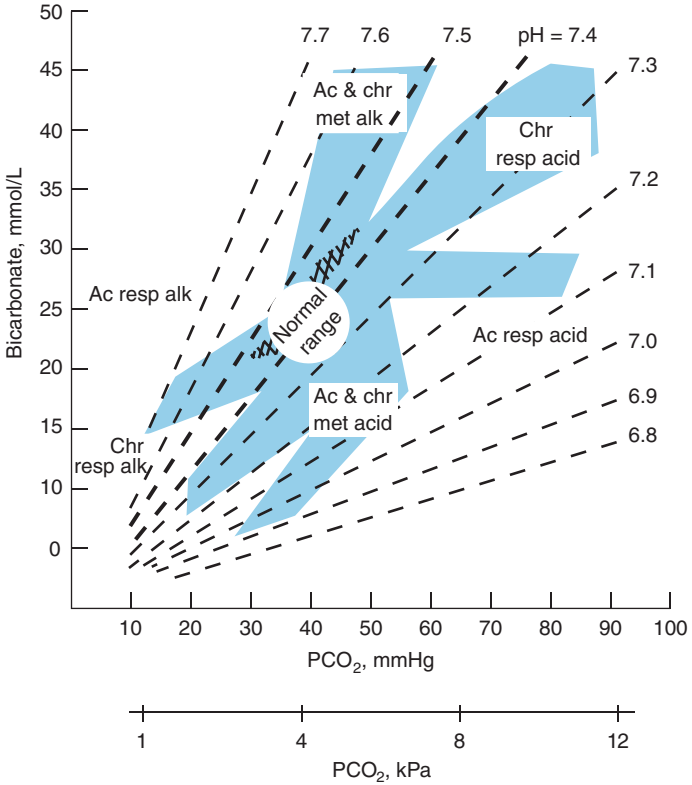


FIGURE 2-1 Nomogram showing bands for uncomplicated respiratory or metabolic acid-base disturbances in intact subjects. Each confidence band represents the mean ±2 SD for the compensatory response of normal subjects or pts to a given primary disorder. Ac, acute; acid, acidosis; alk, alkalosis; chr, chronic; met, metabolic; resp, respiratory. *(Reprinted with permission from Arbus GS. An in vivo acid-base nomogram for clinical use. Can Med Assoc J 109:291, 1973.)*

to increased delivery of carbohydrates to colon. Intestinal overgrowth of organisms that metabolize carbohydrate to D-lactate results in D-lactic acidosis; a wide variety of neurologic symptoms can ensue, with resolution following treatment with appropriate antibiotics to change the intestinal flora. Propylene glycol is a common solvent for IV preparations of a number of drugs, most prominently lorazepam. Pts receiving high rates of these drugs may develop a hyperosmolar anion-gap metabolic acidosis, due mostly to increased lactate, often accompanied by acute kidney failure. Pyroglutamic aciduria (5-oxoprolinuria) is a high anion-gap acidosis caused by dysfunction of the γ-glutamyl cycle that replenishes intracellular glutathione; 5-oxoproline is an intermediate product of the cycle. Hereditary defects in the γ-glutamyl cycle are associated with 5-oxoprolinuria; acquired defects occur in the context of acetaminophen therapy, due to derepression of the cycle by reduced glutathione and overproduction of 5-oxoproline. Resolution occurs after withdrawal of acetaminophen; treatment with *N*-acetyl cysteine to replenish glutathione stores may hasten recovery.

TABLE 2-1 Metabolic Acidosis

NON-ANION-GAP ACIDOSIS		ANION-GAP ACIDOSIS	
CAUSE	**CLUE**	**CAUSE**	**CLUE**
Diarrhea enterostomy	Hx; ↑ K^+ drainage	DKA	Hyperglycemia, ketones
RF	Early chronic kidney disease	RF	Late chronic kidney disease
RTA		Lactic acidosis	Clinical setting + ↑ serum lactate
Proximal	↓ K^+, presence of other proximal tubular defects (Fanconi syndrome)	(L-lactate)	
		Alcoholic ketoacidosis	Hx; weak + ketones; + osm gap
Distal—hypokalemic	↓ K^+; hypercalciuria; UpH >5.5	Starvation	Hx; mild acidosis; + ketones
Distal—hyperkalemic	↑ K^+; nl PRA/aldo; UpH >5.5	Salicylates	Hx; tinnitus; high serum level; + ketones; + lactate
Distal—hyporeninemic hypoaldosteronism	↑ K^+; ↓ PRA/aldo; UpH <5.5	Methanol	Large AG; concomitant respiratory alkalosis; retinitis; + toxic screen; + osm gap
Dilutional	Massive volume expansion with saline		
Ureterosigmoidostomy	Obstructed ileal loop	Ethylene glycol	RF; CNS symptoms; + toxic screen; crystalluria; + osm gap
Hyperalimentation	Amino acid infusion	D-lactic acidosis	Small-bowel disease; prominent neuro symptoms
Acetazolamide, NH_4Cl, lysine HCl, arginine HCl, sevelamer-HCl	Hx of administration of these agents	Propylene glycol	IV infusions, e.g., lorazepam; + osm gap; RF
		Pyroglutamic aciduria, 5-oxoprolinuria	Large AG; chronic acetaminophen

Abbreviations: AG, anion gap; DKA, diabetic ketoacidosis; osm gap, osmolar gap; PRA, plasma renin activity; RF, renal failure; RTA, renal tubular acidosis; UpH, urinary pH.

The differentiation of the various anion-gap acidoses depends on the clinical scenario and routine laboratory tests (Table 2-1) in conjunction with measurement of serum lactate, ketones, toxicology screens (if ethylene glycol or methanol ingestion are suspected), and serum osmolality. D-Lactic acidosis can be diagnosed by a specific assay for the D-enantiomer; 5-oxoprolinuria can be diagnosed by the clinical scenario and confirmed by gas chromatographic/mass spectroscopic (GC/MS) analysis of urine, a widely available pediatric screening test for inborn errors of metabolism (typically "urine for organic acids").

Pts with ethylene glycol, methanol, or propylene glycol toxicity may have an "osmolar gap," defined as a >10-mosmol/kg difference between calculated and measured serum osmolality. Calculated osmolality = $2 \times Na^+ + \text{glucose}/18 + \text{BUN}/2.8$. Of note, pts with alcoholic ketoacidosis and lactic acidosis may also exhibit a modest elevation in the osmolar gap; pts may alternatively metabolize ethylene glycol or methanol to completion by presentation, with an increased anion gap and no increase in the osmolar gap. However, the rapid availability of a measured serum osmolality may aid in the urgent assessment and management of pts with these medical emergencies.

Normal anion-gap acidosis can result from HCO_3^- loss from the GI tract. Diarrhea is by far the most common cause, but other GI conditions associated with external losses of bicarbonate-rich fluids may lead to large alkali losses—e.g., in ileus secondary to intestinal obstruction, in which liters of alkaline fluid may accumulate within the intestinal lumen. Various forms of kidney disease are associated with non-anion-gap acidosis due to reduced tubular reabsorption of filtered bicarbonate and/or reduced excretion of ammonium (NH_4^+). The early stages of progressive renal disease are frequently associated with a non-anion-gap acidosis, with development of an anion-gap component in more advanced renal failure. Non-anion-gap acidosis is also seen in renal tubular acidosis or in the context of tubulointerstitial injury, e.g., after acute tubular necrosis, allergic interstitial nephritis, or urinary tract obstruction. Finally, non-anion-gap acidosis due to exogenous acid loads may occur after rapid volume expansion with saline-containing solutions, the administration of NH_4Cl (a component of cough syrup), lysine HCl, or treatment with the phosphate binder sevelamer hydrochloride.

Calculation of the urinary anion gap may be helpful in the evaluation of hyperchloremic metabolic acidosis, along with a measurement of urine pH. The urinary anion gap is defined as urinary $([Na^+] + [K^+]) - [Cl^-]$ = [unmeasured anions] – [unmeasured cations]); the NH_4^+ ion is the major unmeasured urinary cation in metabolic acidosis, wherein the urinary anion gap should be strongly negative. A negative anion gap thus suggests GI losses of bicarbonate, with appropriate renal response and increased NH_4^+ excretion; a positive anion gap suggests altered urinary acidification, as seen in renal failure or distal renal tubular acidoses. An important caveat is that the rapid renal excretion of unmeasured anions in anion-gap acidosis, classically seen in DKA, may reduce the serum anion gap and generate a positive value for the urinary anion gap, despite the adequate excretion of urinary NH_4^+; this may lead to misdiagnosis as a renal tubular acidosis.

TREATMENT

Metabolic Acidosis

Treatment of metabolic acidosis depends on the cause and severity. DKA responds to insulin therapy and aggressive hydration; close attention to serum $[K^+]$ and administration of KCl is essential, given that the correction of insulinopenia can cause profound hypokalemia. The administration of alkali in anion-gap acidoses

is controversial and is rarely appropriate in DKA. It is reasonable to treat severe lactic acidosis with IV HCO_3^- at a rate sufficient to maintain a pH >7.20; treatment of moderate lactic acidosis with HCO_3^- is controversial. IV HCO_3 is however appropriate to reduce acidosis in D-lactic acidosis, ethylene glycol and methanol toxicity, and 5-oxoprolinuria.

Chronic metabolic acidosis should be treated when HCO_3^- is <18–20 mmol/L. In pts with CKD, there is some evidence that acidosis promotes protein catabolism and may worsen bone disease. There is also evidence that correction of metabolic acidosis in CKD leads to a reduced rate of progression to end-stage renal disease (ESRD). Sodium citrate may be more palatable than oral $NaHCO_3$. Oral therapy with $NaHCO_3$ usually begins with 650 mg tid and is titrated upward to maintain serum [HCO_3^-].

METABOLIC ALKALOSIS

Metabolic alkalosis is due to a primary increase in serum [HCO_3^-], distinguished from chronic respiratory acidosis—with a compensatory increase in renal HCO_3^- reabsorption—by the associated increase in arterial pH (normal or decreased in chronic respiratory acidosis). Administered, exogenous alkali (HCO_3^-, acetate, citrate, or lactate) may cause alkalosis if the normal capacity to excrete HCO_3^- is reduced or if renal HCO_3^- reabsorption is enhanced. A recently resurgent problem is "milk alkali syndrome," a triad of hypercalcemia, metabolic alkalosis, and acute renal failure due to ingested calcium carbonate, typically taken for the treatment or prevention of osteoporosis or for symptomatic relief of peptic ulcer disease.

Metabolic alkalosis is primarily caused by renal retention of HCO_3^- and is due to a variety of underlying mechanisms. Pts are typically separated into two major subtypes: Cl^--responsive and Cl^--resistant. Measurement of urine Cl^- affords this separation in the clinical setting (**Fig. 2-2**). The quintessential causes of Cl^--responsive alkalosis are GI induced from vomiting or gastric aspiration through a nasogastric tube, and renal induced from diuretic therapy. Hypovolemia, chloride deficiency, activation of the RAA axis, and hypokalemia play interrelated roles in the maintenance of this hypochloremic or "contraction" alkalosis. The various syndromes of true or apparent mineralocorticoid excess cause Cl^--resistant metabolic alkalosis (Fig. 2-2); most of these pts are hypokalemic, volume expanded, and/or hypertensive.

Common forms of metabolic alkalosis are generally diagnosed from the history, physical examination, and/or basic laboratory tests. ABGs will help determine whether an elevated [HCO_3^-] is reflective of metabolic alkalosis or chronic respiratory acidosis; ABGs are required for the diagnosis of mixed acid-base disorders. Measurement of urinary electrolytes will aid in separating Cl^--responsive and Cl^--resistant forms. Urinary [Na^+] may thus be >20 meq/L in Cl^--responsive alkalosis despite the presence of hypovolemia; however, urinary [Cl^-] will typically be very low, except in pts with severe hypokalemia. Notably, urinary [Cl^-] may be variable in pts with diuretic-associated alkalosis, depending on the temporal relationship to diuretic administration. Other diagnostic tests—e.g., plasma renin, aldosterone, cortisol—may be appropriate in Cl^--resistant forms with high urinary [Cl^-] (Fig. 2-2).

TREATMENT

Metabolic Alkalosis

The acid-base disorder in Cl^--responsive alkalosis will typically respond to saline infusion; however, the associated hypokalemia should also be corrected. Pts with true or apparent mineralocorticoid excess require specific treatment of

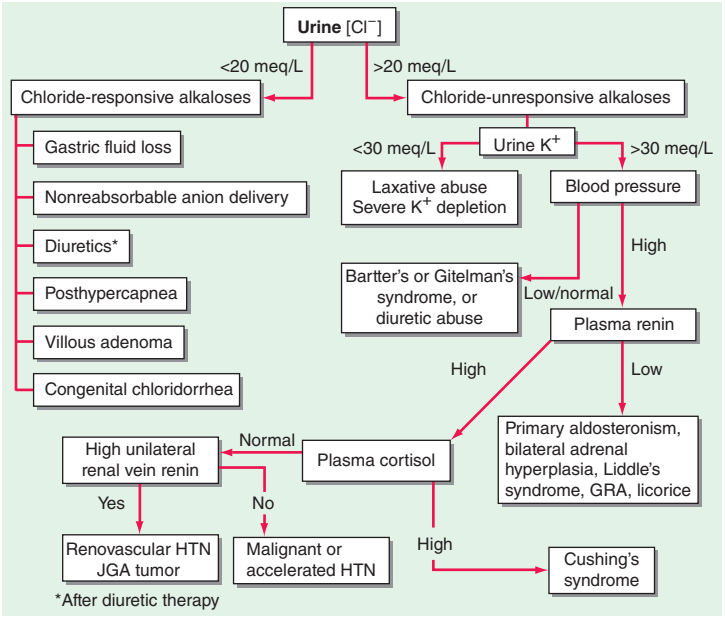


FIGURE 2-2 The diagnostic approach to metabolic alkalosis. See text for details. GRA, glucocorticoid-remediable aldosteronism; HTN, hypertension; JGA, juxtaglomerular apparatus. *(Modified from Dubose TD. Disorders of acid-base balance. In: Brenner and Rector's The Kidney, 8th ed, Brenner BM [ed]. Philadelphia, Saunders, 2008 with permission.)*

the underlying disorder. For example, hyperactive amiloride-sensitive ENaC channels cause Liddle's syndrome, which can respond to therapy with amiloride and related drugs; pts with hyperaldosteronism may in turn respond to blockade of the mineralocorticoid receptor with spironolactone or eplerenone. Finally, severe alkalosis in the critical care setting may require treatment with acidifying agents such as acetazolamide.

RESPIRATORY ACIDOSIS

Respiratory acidosis is characterized by CO_2 retention due to ventilatory failure. Causes include sedatives, stroke, chronic pulmonary disease, airway obstruction, severe pulmonary edema, neuromuscular disorders, and cardiopulmonary arrest. Symptoms include confusion, asterixis, and obtundation.

TREATMENT

Respiratory Acidosis

The goal is to improve ventilation through pulmonary toilet and reversal of bronchospasm. Intubation or noninvasive positive pressure ventilation (NPPV) may be required in severe acute cases. Acidosis due to hypercapnia is usually mild; however, combined respiratory and metabolic acidosis may cause a profound reduction in pH. Respiratory acidosis may accompany low tidal volume ventilation in ICU pts and may require metabolic "overcorrection" to maintain a neutral pH.

RESPIRATORY ALKALOSIS

Excessive ventilation causes a primary reduction in CO_2 and ↑ pH in pneumonia, pulmonary edema, interstitial lung disease, and asthma. Pain and psychogenic causes are common; other etiologies include fever, hypoxemia, sepsis, delirium tremens, salicylates, hepatic failure, mechanical overventilation, and CNS lesions. Pregnancy is associated with a mild respiratory alkalosis. Severe respiratory alkalosis may acutely cause seizures, tetany, cardiac arrhythmias, or loss of consciousness.

TREATMENT

Respiratory Alkalosis

Treatment should be directed at the underlying disorders. In psychogenic cases, sedation or a rebreathing bag may be required.

"MIXED" DISORDERS

In many circumstances, more than a single acid-base disturbance exists. Examples include combined metabolic and respiratory acidosis with cardiogenic shock; metabolic alkalosis and anion-gap acidosis in pts with vomiting and diabetic ketoacidosis; and anion-gap metabolic acidosis with respiratory alkalosis in pts with salicylate toxicity. The diagnosis may be clinically evident and/or suggested by relationships between the PCO_2 and $[HCO_3^-]$ that diverge from those found in simple disorders. For example, the PCO_2 in a pt with metabolic acidosis and respiratory alkalosis will be considerably less than that predicted from the $[HCO_3^-]$ and Winter's formula $[PaCO_2 = (1.5 \times [HCO_3^-]) + 8 + 2]$.

In "simple" anion-gap acidosis, the anion gap increases in proportion to the fall in $[HCO_3^-]$. A lesser drop in serum $[HCO_3^-]$ than in the anion gap suggests a coexisting metabolic alkalosis. Conversely, a proportionately *larger* drop in $[HCO_3^-]$ than in the anion gap suggests the presence of a mixed anion-gap and non-anion-gap metabolic acidosis. Notably, however, these interpretations assume 1:1 relationships between unmeasured anions and the fall in $[HCO_3^-]$, which are not uniformly present in individual pts or as acidoses evolve. For example, volume resuscitation of pts with DKA will typically increase glomerular filtration and the urinary excretion of ketones, resulting in a decrease in the anion gap in the absence of a supervening non-anion-gap acidosis.

3 Diagnostic Imaging in Internal Medicine

Clinicians have a wide array of imaging modalities at their disposal to aid them in noninvasive diagnosis. Despite the introduction of highly specialized imaging modalities, radiologic procedures such as chest radiographs and ultrasound continue to serve a vital role in the diagnostic approach to pt care. Increasingly, ultrasound is used as a point-of-care procedure to assist with intravenous line placement, and to extend the physical examination of the thyroid thorax, heart, and abdomen. At most institutions, CT is available on an emergent basis and is invaluable for initial evaluation of pts with trauma, suspected CNS hemorrhage, or ischemic stroke. MRI and related techniques (MR angiography, functional

MRI, MR spectroscopy) provide high resolution of many tissues including the brain, vascular system, joints, and most large organs. Radionuclide scans including positron emission tomography (PET) can provide functional assessment of organs or specific regions within organs. Combination of PET with MRI or CT scanning provides highly informative images of the location and configuration of metabolically active lesions, such as cancers.

This chapter will review the indications and utility of the most commonly utilized radiologic studies used by internists.

CHEST RADIOGRAPHY (FIG. 3-1)

- Accessible and should be part of the standard evaluation for pts with cardiopulmonary complaints.
- Able to identify life-threatening conditions such as pneumothorax, intraperitoneal air, pulmonary edema, pneumonia, and aortic dissection.
- Often normal in a pt with an acute pulmonary embolus.
- Repeat in 4–6 weeks in a pt with an acute pneumonic process to document resolution of the radiographic infiltrate.
- Used in conjunction with the physical examination to support the diagnosis of congestive heart failure. The diagnosis of heart failure is supported by findings of cardiomegaly, cephalization, Kerley B lines, and pleural effusions.
- Repeat frequently in intubated pts to examine endotracheal tube position and the possibility of barotrauma.
- Features of alveolar or airspace disease include inhomogeneous, patchy opacities and air-bronchograms.
- Helps to document the free-flowing nature of pleural effusions. Decubitus views should be obtained to exclude loculated pleural fluid prior to attempts to extract such fluid.

ABDOMINAL RADIOGRAPHY

- Initial imaging modality in a pt with suspected bowel obstruction. Signs of small-bowel obstruction on plain radiographs include multiple air-fluid levels, absence of colonic distention, and a "stepladder" appearance of small-bowel loops.
- Should not be performed with barium enhancement when perforated bowel, portal venous gas, or toxic megacolon is suspected.
- Used to evaluate the size of bowel:
  1. Normal small bowel is <3 cm in diameter.
  2. Normal caliber of the cecum is up to 9 cm, with the rest of the large bowel up to 6 cm in diameter.

ULTRASOUND

- More sensitive and specific than CT scanning in evaluating for the presence of gallstone disease.
- Used to assist with central line placement and with peripheral access when challenging.
- Used to assess the size of the kidneys in a pt with renal insufficiency and to exclude the presence of hydronephrosis.
- Evaluates for the presence of peritoneal fluid in a pt with blunt abdominal trauma.
- Evaluates cardiac valves and wall motion.
- Used to localize loculated pleural and peritoneal fluid prior to draining such fluid.

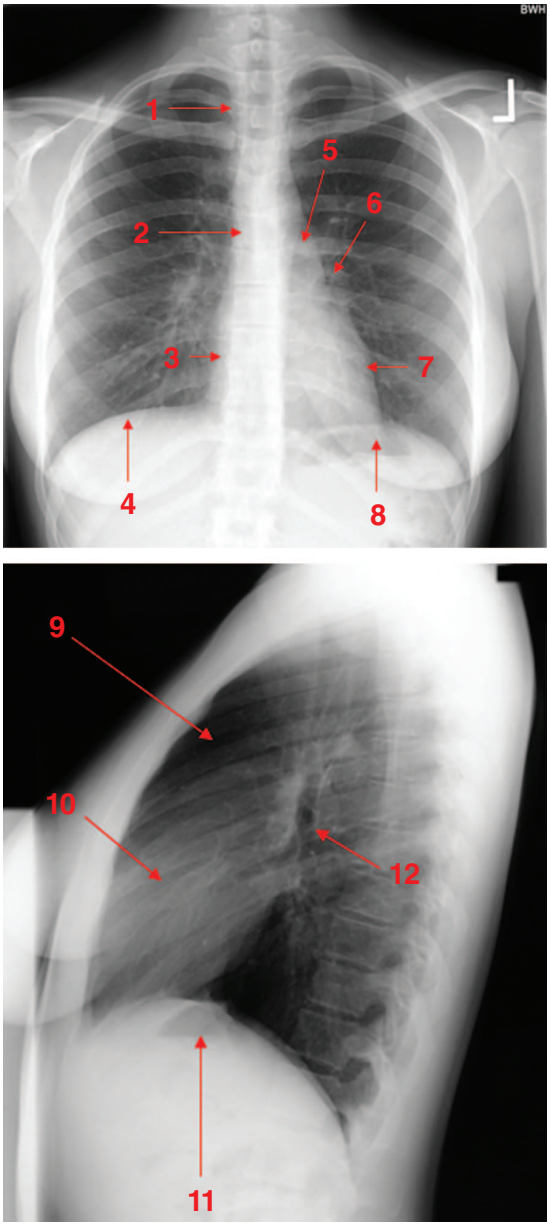


FIGURE 3-1 Normal chest radiograph-review of anatomy. **1.** Trachea. **2.** Carina. **3.** Right atrium. **4.** Right hemidiaphragm. **5.** Aortic knob. **6.** Left hilum. **7.** Left ventricle. **8.** Left hemidiaphragm (with stomach bubble). **9.** Retrosternal clear space. **10.** Right ventricle. **11.** Left hemidiaphragm (with stomach bubble). **12.** Left upper lobe bronchus.