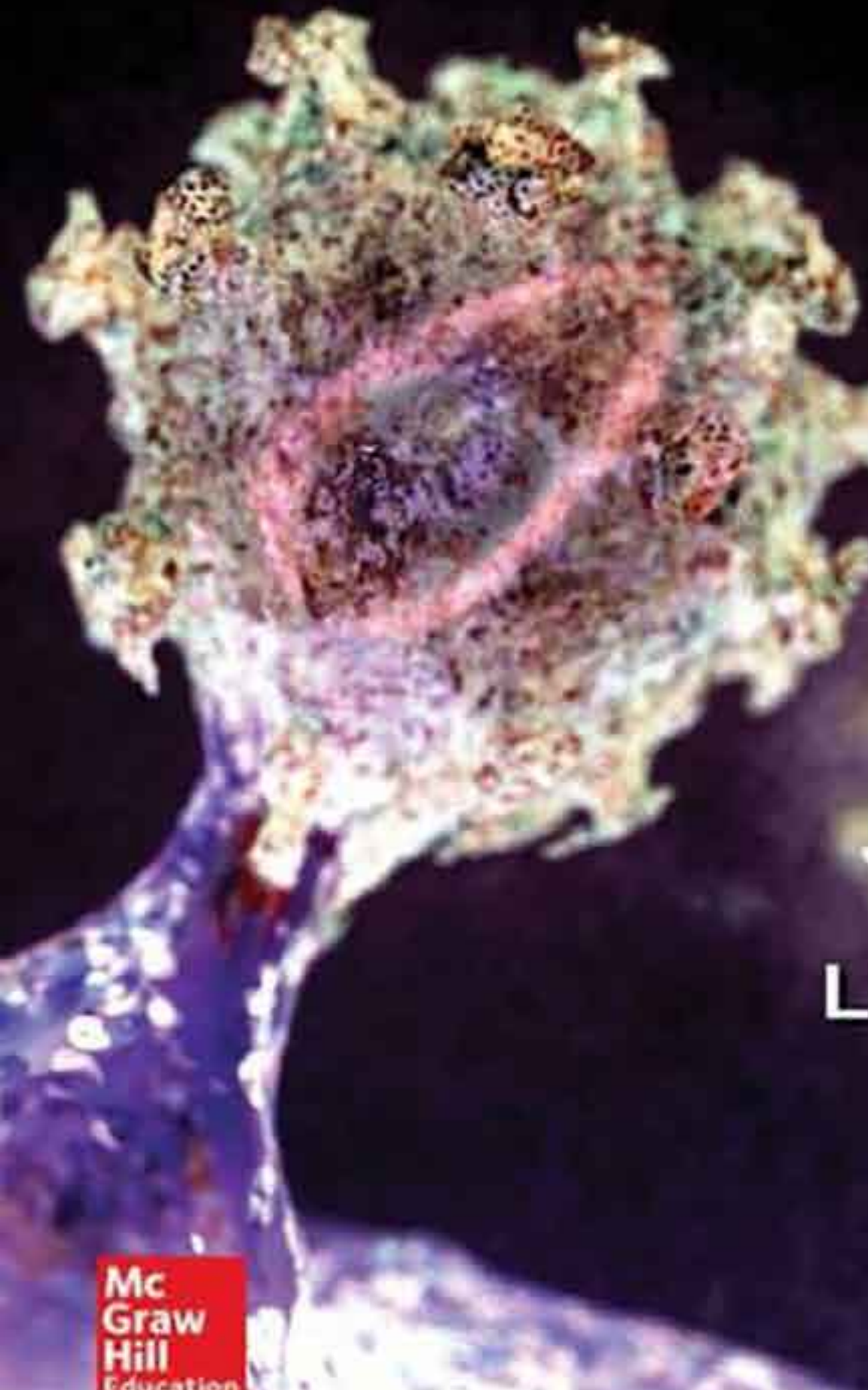
19th Edition

HARRISON'S™ MANUAL OF MEDICINE



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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	US 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

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CONTENTS

SECTION 3 COMMON PATIENT PRESENTATIONS

SECTION 4 OTOLARYNGOLOGY

SECTION 5 DERMATOLOGY

SECTION 6 HEMATOLOGY AND ONCOLOGY

SECTION 7 INFECTIOUS DISEASES

NOTICE

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3, 5, 16-22, 48-56, 77, 180-200, 204

J. LARRY JAMESON, MD, PhD
2, 6, 7, 23, 24, 29, 30, 118, 168-179, 198, 201, 205

S. ANDREW JOSEPHSON, MD
5, 16-22, 48-56, 77, 180-197, 199, 200, 204

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12, 27, 28, 57, 58, 78-104, 106-109, 132, 144

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153

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10, 11, 13, 31, 32, 34, 110-117, 119-127

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8, 9, 25, 37-41, 44, 45, 61-76, 147-149, 203

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PREFACE

Harrison's Principles of Internal Medicine (HPIM), the premier medical textbook for students and clinicians, provides a detailed body of information important to an 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 bedside care, the *Manual* presents clinical information drawn from the 19th 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 service.

First published in 1988, the *Manual* 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.

The *Manual* has been written for easy and seamless reference to the full text of the 19th edition of *HPIM*, and the Editors recommend that the full textbook be consulted as soon as time allows. 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. 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 19th edition of the *Manual* is available in print and in portable format for the smartphone and tablet.

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1 Electrolytes/Acid-Base Balance

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

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	Sympathetic nervous system
	Thirst	Renin-angiotensin-aldosterone system
		ANP/BNP
		AVP
What is affected	Urine osmolality	Urinary sodium excretion
	H_2O intake	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; with permission.

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 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 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).

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 decreased due to the specific

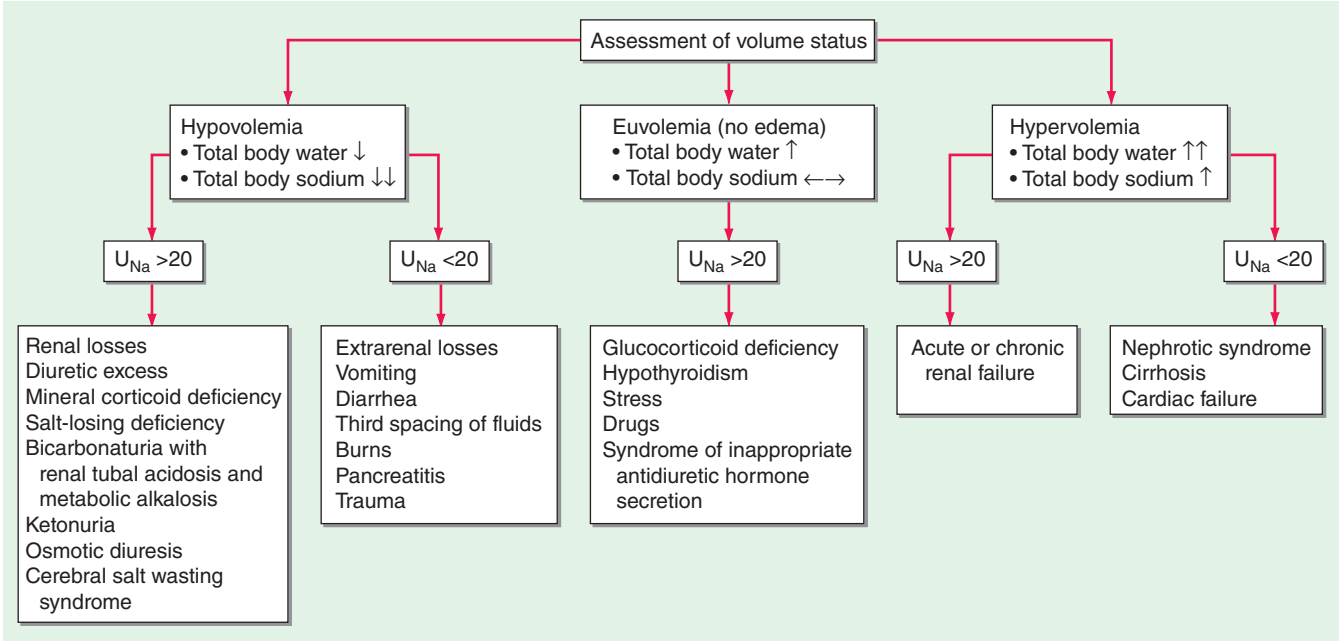

FIGURE 1-1 The diagnostic approach to hyponatremia. See text for details. *(From S Kumar, T Berl: Diseases of water metabolism, in Atlas of Diseases of the Kidney, RW Schrier [ed]. Philadelphia, Current Medicine, Inc, 1999; with permission.)*

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, large-volume paracentesis 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 hyponatremia associated with both cirrhosis and CHF.

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 (e.g., small cell carcinoma of the lung) and drugs (e.g., selective serotonin reuptake inhibitors, tricyclic antidepressants, nicotine, vincristine, chlorpropamide, 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.

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, 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 or cirrhosis. Abnormalities in liver function tests have been reported during the use of tolvaptan; hence, 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 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. 168). 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

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 SNa 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.

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. 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 NSAIDs 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 epithelial Na^+ channel (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^+]

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

(*Continued*)

TABLE 1-3 CAUSES OF HYPOKALEMIA (*CONTINUED*)

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)
     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.

<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 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.

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;