

19th Edition

# HARRISON'S<sup>TM</sup> MANUAL OF MEDICINE

KASPER

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LONGO

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# GLOSSARY

<b>A<sub>2</sub></b>	aortic second sound	<b>EBV</b>	Epstein-Barr virus
<b>ABGs</b>	arterial blood gases	<b>ECG</b>	electrocardiogram
<b>ACE</b>	angiotensin converting enzyme	<b>EEG</b>	electroencephalogram
<b>AF</b>	atrial fibrillation	<b>ELISA</b>	enzyme-linked immunosorbent assay
<b>AIDS</b>	acquired immunodeficiency syndrome	<b>EMG</b>	electromyogram
<b>ALS</b>	amyotrophic lateral sclerosis	<b>ENT</b>	ear, nose, and throat
<b>ANA</b>	antinuclear antibody	<b>EOM</b>	extraocular movement
<b>ARDS</b>	acute respiratory distress syndrome	<b>ESR</b>	erythrocyte sedimentation rate
<b>bid</b>	two times daily	<b>FDA</b>	US Food and Drug Administration
<b>biw</b>	twice a week	<b>FEV<sub>1</sub></b>	forced expiratory volume in first second
<b>bp</b>	blood pressure	<b>GFR</b>	glomerular filtration rate
<b>BUN</b>	blood urea nitrogen	<b>GI</b>	gastrointestinal
<b>CAPD</b>	continuous ambulatory peritoneal dialysis	<b>G6PD</b>	glucose-6-phosphate dehydrogenase
<b>CBC</b>	complete blood count	<b>Hb</b>	hemoglobin
<b>CF</b>	complement fixation	<b>Hct</b>	hematocrit
<b>CHF</b>	congestive heart failure	<b>HDL</b>	high-density lipoprotein
<b>CLL</b>	chronic lymphocytic leukemia	<b>HIV</b>	human immunodeficiency virus
<b>CML</b>	chronic myeloid leukemia	<b>hs</b>	at bedtime
<b>CMV</b>	cytomegalovirus	<b>HSV</b>	herpes simplex virus
<b>CNS</b>	central nervous system	<b>ICU</b>	intensive care unit
<b>CPK</b>	creatine phosphokinase	<b>IFN</b>	interferon
<b>CSF</b>	cerebrospinal fluid	<b>Ig</b>	immunoglobulin
<b>CT</b>	computed tomography	<b>IL</b>	interleukin
<b>CVP</b>	central venous pressure	<b>IM</b>	intramuscular
<b>CXR</b>	chest x-ray	<b>IP</b>	intraoperative
<b>DIC</b>	disseminated intravascular coagulation	<b>IV</b>	intravenous
<b>DVT</b>	deep venous thrombosis	<b>IVC</b>	inferior vena cava
		<b>IVP</b>	intravenous pyelogram

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# CONTENTS

Contributors .....	xv
Preface .....	xvii
Acknowledgments .....	xix

## SECTION 1 CARE OF THE HOSPITALIZED PATIENT

1 Electrolytes/Acid-Base Balance .....	1
2 Diagnostic Imaging in Internal Medicine .....	23
3 Procedures Commonly Performed by Internists .....	26
4 Principles of Critical Care Medicine .....	31
5 Pain and Its Management .....	35
6 Assessment of Nutritional Status .....	40
7 Enteral and Parenteral Nutrition .....	43
8 Transfusion and Pheresis Therapy .....	46
9 Palliative and End-of-Life Care .....	48

## SECTION 2 MEDICAL EMERGENCIES

10 Cardiovascular Collapse and Sudden Death .....	57
11 Shock .....	61
12 Sepsis and Septic Shock .....	65
13 Acute Pulmonary Edema .....	69
14 Acute Respiratory Distress Syndrome .....	71
15 Respiratory Failure .....	73
16 Confusion, Stupor, and Coma .....	76
17 Stroke .....	82
18 Subarachnoid Hemorrhage .....	91
19 Increased Intracranial Pressure and Head Trauma .....	93
20 Spinal Cord Compression .....	98
21 Hypoxic-Ischemic Encephalopathy .....	100
22 Status Epilepticus .....	101
23 Diabetic Ketoacidosis and Hyperosmolar Coma .....	104
24 Hypoglycemia .....	107
25 Oncologic Emergencies .....	109
26 Anaphylaxis .....	114
27 Bites, Venoms, Stings, and Marine Poisonings .....	115

## SECTION 3 COMMON PATIENT PRESENTATIONS

28	Fever, Hyperthermia, and Rash.....	127
29	Generalized Fatigue .....	131
30	Weight Loss.....	135
31	Chest Pain .....	137
32	Palpitations.....	141
33	Dyspnea.....	142
34	Cyanosis .....	145
35	Cough and Hemoptysis.....	146
36	Edema.....	150
37	Abdominal Pain .....	154
38	Nausea, Vomiting, and Indigestion .....	158
39	Dysphagia .....	162
40	Diarrhea, Malabsorption, and Constipation .....	167
41	Gastrointestinal Bleeding.....	174
42	Jaundice and Evaluation of Liver Function.....	178
43	Ascites .....	187
44	Lymphadenopathy and Splenomegaly .....	189
45	Anemia and Polycythemia.....	194
46	Azotemia and Urinary Abnormalities.....	197
47	Pain and Swelling of Joints.....	203
48	Back and Neck Pain .....	207
49	Headache.....	215
50	Syncope .....	222
51	Dizziness and Vertigo .....	226
52	Acute Visual Loss and Double Vision.....	229
53	Weakness and Paralysis.....	233
54	Tremor and Movement Disorders.....	236
55	Aphasia.....	239
56	Sleep Disorders.....	241
57	Dysuria and Bladder Pain .....	245

## SECTION 4 OTOLARYNGOLOGY

58	Sore Throat, Earache, and Upper Respiratory Symptoms .....	247
----	---	-----



**SECTION 5** DERMATOLOGY

- 59** General Examination of the Skin .....255
- 60** Common Skin Conditions .....258

**SECTION 6** HEMATOLOGY AND ONCOLOGY

- 61** Examination of Blood Smears and Bone Marrow .....265
- 62** Red Blood Cell Disorders .....267
- 63** Leukocytosis and Leukopenia .....274
- 64** Bleeding and Thrombotic Disorders.....277
- 65** Myeloid Leukemias, Myelodysplasia, and Myeloproliferative Syndromes .....283
- 66** Lymphoid Malignancies.....293
- 67** Skin Cancer .....305
- 68** Head and Neck Cancer .....308
- 69** Lung Cancer .....310
- 70** Breast Cancer .....316
- 71** Tumors of the Gastrointestinal Tract.....321
- 72** Genitourinary Tract Cancer .....333
- 73** Gynecologic Cancer.....338
- 74** Prostate Hyperplasia and Carcinoma .....342
- 75** Cancer of Unknown Primary Site .....345
- 76** Paraneoplastic Endocrine Syndromes.....348
- 77** Neurologic Paraneoplastic Syndromes .....352

**SECTION 7** INFECTIOUS DISEASES

- 78** Infections Acquired in Health Care Facilities .....357
- 79** Infections in the Immunocompromised Host .....362
- 80** Infective Endocarditis .....372
- 81** Intraabdominal Infections.....382
- 82** Infectious Diarrheas .....386
- 83** Sexually Transmitted and Reproductive Tract Infections ....399
- 84** Infections of the Skin, Soft Tissues, Joints, and Bones .....415
- 85** Pneumococcal Infections.....422
- 86** Staphylococcal Infections.....425

<b>87</b>	<b>Streptococcal/Enterococcal Infections, Diphtheria, and Infections Caused by Other Corynebacteria and Related Species .....</b>	<b>434</b>
<b>88</b>	<b>Meningococcal and Listerial Infections .....</b>	<b>443</b>
<b>89</b>	<b>Infections Caused by <i>Haemophilus</i>, <i>Bordetella</i>, <i>Moraxella</i>, and HACEK Group Organisms.....</b>	<b>448</b>
<b>90</b>	<b>Diseases Caused by Gram-Negative Enteric Bacteria and <i>Pseudomonas</i> .....</b>	<b>453</b>
<b>91</b>	<b>Infections Caused by Miscellaneous Gram-Negative Bacilli .....</b>	<b>462</b>
<b>92</b>	<b>Anaerobic Infections .....</b>	<b>469</b>
<b>93</b>	<b>Nocardiosis, Actinomycosis, and Whipple's Disease .....</b>	<b>477</b>
<b>94</b>	<b>Tuberculosis and Other Mycobacterial Infections.....</b>	<b>482</b>
<b>95</b>	<b>Lyme Disease and Other Nonsyphilitic Spirochetal Infections .....</b>	<b>494</b>
<b>96</b>	<b>Rickettsial Diseases .....</b>	<b>500</b>
<b>97</b>	<b><i>Mycoplasma pneumoniae</i>, <i>Legionella</i> Species, and <i>Chlamydia pneumoniae</i> .....</b>	<b>510</b>
<b>98</b>	<b><i>Chlamydia trachomatis</i> and <i>C. psittaci</i> .....</b>	<b>514</b>
<b>99</b>	<b>Herpesvirus Infections .....</b>	<b>516</b>
<b>100</b>	<b>Cytomegalovirus and Epstein-Barr Virus Infections .....</b>	<b>525</b>
<b>101</b>	<b>Influenza and Other Viral Respiratory Diseases .....</b>	<b>530</b>
<b>102</b>	<b>Rubeola, Rubella, Mumps, and Parvovirus Infections .....</b>	<b>538</b>
<b>103</b>	<b>Enteroviral Infections.....</b>	<b>543</b>
<b>104</b>	<b>Insect- and Animal-Borne Viral Infections .....</b>	<b>546</b>
<b>105</b>	<b>HIV Infection and AIDS .....</b>	<b>554</b>
<b>106</b>	<b>Fungal Infections.....</b>	<b>568</b>
<b>107</b>	<b><i>Pneumocystis</i> Infections.....</b>	<b>583</b>
<b>108</b>	<b>Protozoal Infections .....</b>	<b>586</b>
<b>109</b>	<b>Helminthic Infections and Ectoparasite Infestations .....</b>	<b>599</b>

## SECTION 8

## CARDIOLOGY

<b>110</b>	<b>Physical Examination of the Heart.....</b>	<b>613</b>
<b>111</b>	<b>Electrocardiography .....</b>	<b>618</b>
<b>112</b>	<b>Noninvasive Examination of the Heart .....</b>	<b>622</b>
<b>113</b>	<b>Congenital Heart Disease in the Adult .....</b>	<b>627</b>

114	Valvular Heart Disease.....	632
115	Cardiomyopathies and Myocarditis .....	639
116	Pericardial Disease .....	644
117	Hypertension .....	649
118	Metabolic Syndrome.....	656
119	ST-Segment Elevation Myocardial Infarction.....	658
120	Unstable Angina and Non-ST-Elevation Myocardial Infarction.....	668
121	Chronic Stable Angina .....	672
122	Bradycardias.....	677
123	Tachycardias .....	679
124	Heart Failure and Cor Pulmonale.....	687
125	Diseases of the Aorta .....	693
126	Peripheral Vascular Disease .....	696
127	Pulmonary Hypertension.....	699

## SECTION 9 PULMONOLOGY

128	Respiratory Function and Pulmonary Diagnostic Procedures.....	705
129	Asthma .....	711
130	Environmental Lung Diseases .....	715
131	Chronic Obstructive Pulmonary Disease.....	718
132	Pneumonia, Bronchiectasis, and Lung Abscess.....	722
133	Pulmonary Thromboembolism and Deep-Vein Thrombosis .....	730
134	Interstitial Lung Disease .....	734
135	Diseases of the Pleura and Mediastinum .....	740
136	Disorders of Ventilation.....	744
137	Sleep Apnea .....	745

## SECTION 10 NEPHROLOGY

138	Acute Renal Failure .....	747
139	Chronic Kidney Disease and Uremia.....	752
140	Dialysis .....	754
141	Renal Transplantation.....	756

<b>142</b>	<b>Glomerular Diseases .....</b>	<b>759</b>
<b>143</b>	<b>Renal Tubular Disease.....</b>	<b>769</b>
<b>144</b>	<b>Urinary Tract Infections and Interstitial Cystitis.....</b>	<b>775</b>
<b>145</b>	<b>Nephrolithiasis .....</b>	<b>779</b>
<b>146</b>	<b>Urinary Tract Obstruction.....</b>	<b>782</b>

## SECTION 11 GASTROENTEROLOGY

<b>147</b>	<b>Peptic Ulcer and Related Disorders .....</b>	<b>785</b>
<b>148</b>	<b>Inflammatory Bowel Diseases .....</b>	<b>790</b>
<b>149</b>	<b>Colonic and Anorectal Diseases .....</b>	<b>794</b>
<b>150</b>	<b>Cholelithiasis, Cholecystitis, and Cholangitis .....</b>	<b>799</b>
<b>151</b>	<b>Pancreatitis .....</b>	<b>804</b>
<b>152</b>	<b>Acute Hepatitis .....</b>	<b>809</b>
<b>153</b>	<b>Chronic Hepatitis.....</b>	<b>816</b>
<b>154</b>	<b>Cirrhosis and Alcoholic Liver Disease .....</b>	<b>826</b>
<b>155</b>	<b>Portal Hypertension .....</b>	<b>831</b>

## SECTION 12 ALLERGY, CLINICAL IMMUNOLOGY, AND RHEUMATOLOGY

<b>156</b>	<b>Diseases of Immediate-Type Hypersensitivity .....</b>	<b>835</b>
<b>157</b>	<b>Primary Immune Deficiency Diseases .....</b>	<b>840</b>
<b>158</b>	<b>Systemic Lupus Erythematosus, Rheumatoid Arthritis, and Other Connective Tissue Diseases.....</b>	<b>843</b>
<b>159</b>	<b>Vasculitis .....</b>	<b>850</b>
<b>160</b>	<b>Ankylosing Spondylitis.....</b>	<b>854</b>
<b>161</b>	<b>Psoriatic Arthritis.....</b>	<b>857</b>
<b>162</b>	<b>Reactive Arthritis.....</b>	<b>859</b>
<b>163</b>	<b>Osteoarthritis.....</b>	<b>861</b>
<b>164</b>	<b>Gout, Pseudogout, and Related Diseases .....</b>	<b>863</b>
<b>165</b>	<b>Other Musculoskeletal Disorders.....</b>	<b>867</b>
<b>166</b>	<b>Sarcoidosis .....</b>	<b>870</b>
<b>167</b>	<b>Amyloidosis .....</b>	<b>873</b>

## SECTION 13 ENDOCRINOLOGY AND METABOLISM

<b>168</b>	<b>Disorders of the Anterior Pituitary and Hypothalamus.....</b>	<b>877</b>
<b>169</b>	<b>Diabetes Insipidus and Syndrome of Inappropriate Antidiuretic Hormone .....</b>	<b>883</b>

170	Thyroid Gland Disorders.....	886
171	Adrenal Gland Disorders .....	895
172	Obesity .....	901
173	Diabetes Mellitus.....	904
174	Disorders of the Male Reproductive System.....	912
175	Disorders of the Female Reproductive System .....	917
176	Hypercalcemia and Hypocalcemia.....	924
177	Osteoporosis and Osteomalacia .....	931
178	Hypercholesterolemia and Hypertriglyceridemia.....	936
179	Hemochromatosis, Porphyrrias, and Wilson's Disease .....	942

#### SECTION 14 NEUROLOGY

180	The Neurologic Examination .....	947
181	Seizures and Epilepsy .....	956
182	Dementia.....	968
183	Parkinson's Disease.....	976
184	Ataxic Disorders .....	981
185	ALS and Other Motor Neuron Diseases .....	984
186	Autonomic Nervous System Disorders.....	988
187	Trigeminal Neuralgia, Bell's Palsy, and Other Cranial Nerve Disorders .....	995
188	Spinal Cord Diseases .....	1002
189	Tumors of the Nervous System .....	1008
190	Multiple Sclerosis .....	1012
191	Acute Meningitis and Encephalitis .....	1020
192	Chronic and Recurrent Meningitis .....	1031
193	Peripheral Neuropathies, Including Guillain-Barré Syndrome .....	1040
194	Myasthenia Gravis.....	1050
195	Muscle Diseases .....	1053

#### SECTION 15 PSYCHIATRY AND SUBSTANCE ABUSE

196	Psychiatric Disorders.....	1063
197	Psychiatric Medications .....	1071
198	Eating Disorders .....	1079

199	Alcohol Use Disorder.....	1080
200	Narcotic Abuse.....	1084

#### SECTION 16 DISEASE PREVENTION AND HEALTH MAINTENANCE

201	Routine Disease Screening .....	1087
202	Cardiovascular Disease Prevention .....	1092
203	Prevention and Early Detection of Cancer .....	1094
204	Smoking Cessation .....	1102
205	Women's Health .....	1104

#### SECTION 17 ADVERSE DRUG REACTIONS

206	Adverse Drug Reactions .....	1107
	Index.....	1109

## NOTICE

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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  $[\text{Na}^+]$  result in most cases from abnormalities of  $\text{H}_2\text{O}$  homeostasis, which change the relative ratio of  $\text{Na}^+$  to  $\text{H}_2\text{O}$ . Disorders of  $\text{Na}^+$  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  $\text{H}_2\text{O}$  balance is achieved by changes in both  $\text{H}_2\text{O}$  intake and urinary  $\text{H}_2\text{O}$  excretion (Table 1-1). Confusion can result from the coexistence of defects in both  $\text{H}_2\text{O}$  and  $\text{Na}^+$  balance. For example, a hypovolemic pt may have an appropriately low urinary  $\text{Na}^+$  due to increased renal tubular reabsorption of filtered  $\text{NaCl}$ ; 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  $\text{H}_2\text{O}$  and the development of hyponatremia.

## HYPONATREMIA

This is defined as a serum  $[\text{Na}^+] < 135$  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 Thirst	Sympathetic nervous system Renin-angiotensin-aldosterone system ANP/BNP AVP
What is affected	Urine osmolality $\text{H}_2\text{O}$ 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; 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<sub>2</sub>O. The serum [Na<sup>+</sup>] by itself does not yield diagnostic information regarding total-body Na<sup>+</sup> content; hyponatremia is primarily a disorder of H<sub>2</sub>O 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<sup>+</sup> falls by 1.4 mM for every 100-mg/dL increase in glucose, due to glucose-induced H<sub>2</sub>O efflux from cells. Hyperkalemia may suggest adrenal insufficiency or hypoadosteronism; 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<sup>+</sup> <20 meq/L is consistent with hypovolemic hyponatremia in the clinical absence of a “hypervolemic,” Na<sup>+</sup>-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.

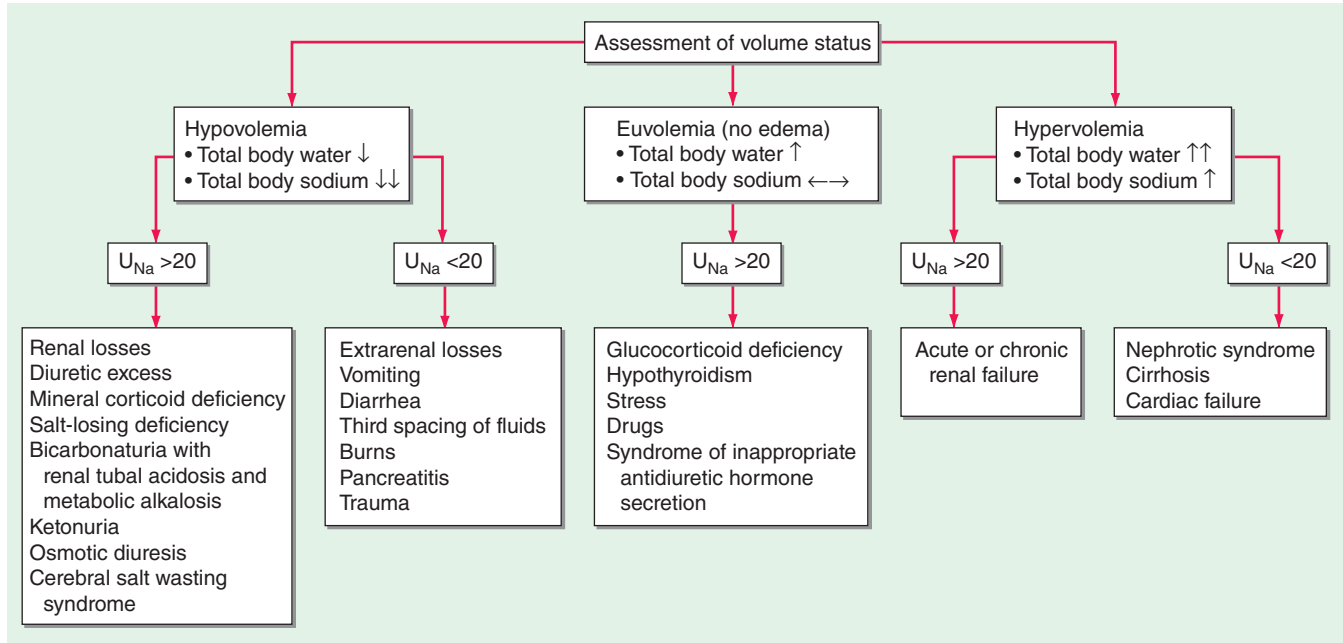
### Hypovolemic Hyponatremia

Hypovolemia from both renal and extrarenal causes is associated with hyponatremia. Renal causes of hypovolemia include primary adrenal insufficiency and hypoadosteronism, salt-losing nephropathies (e.g., reflux nephropathy, non-oliguric acute tubular necrosis), diuretics, and osmotic diuresis. Random “spot” urine Na<sup>+</sup> 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<sup>+</sup> 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<sub>2</sub>O, 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<sup>+</sup>] = 125–135 mmol/L); occasionally, pts with severe CHF or cirrhosis may present with serum [Na<sup>+</sup>] <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),  $\text{Na}^+$  restriction, diuretic therapy, and, in some pts,  $\text{H}_2\text{O}$  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 hypothryroidism 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  $[\text{Na}^+]$  (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.  $\text{H}_2\text{O}$  restriction to  $<1 \text{ L/d}$  is a cornerstone of therapy, but may be ineffective or poorly tolerated. However, vasopressin antagonists are predictably effective in normalizing serum  $[\text{Na}^+]$  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  $[\text{Na}^+]$  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  $\text{H}_2\text{O}$  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  $[\text{Na}^+]$ , 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  $>48 \text{ h}$  ("chronic hyponatremia") are at risk for osmotic demyelination syndrome, typically central pontine myelinolysis, if serum  $\text{Na}^+$  is

corrected by  $>10$ – $12$  mM within the first 24 h and/or by  $>18$  mM 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  $\text{Na}^+$  (initially every 2–4 h) is imperative.

Treatment of acute symptomatic hyponatremia should include hypertonic saline to acutely increase serum  $\text{Na}^+$  by 1–2 mM/h to a total increase of 4–6 mM; 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 “ $\text{Na}^+$  deficit,” where the  $\text{Na}^+$  deficit =  $0.6 \times \text{body weight} \times (\text{target } [\text{Na}^+] - \text{starting } [\text{Na}^+])$ . Regardless of the method used to determine the rate of administered hypertonic saline, the increase in serum  $[\text{Na}^+]$  can be highly unpredictable, due to rapid changes in the underlying physiology; serum  $[\text{Na}^+]$  should be monitored every 2–4 h during and after treatment with hypertonic saline. The administration of supplemental  $\text{O}_2$  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  $\text{H}_2\text{O}$  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 ( $<10$ – $12$  mM in the first 24 h and  $<18$  mM 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  $[\text{Na}^+]$  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  $\text{H}_2\text{O}$ , typically IV  $\text{D}_5\text{W}$ ; again, close monitoring of the response of serum  $[\text{Na}^+]$  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  $[\text{Na}^+]$  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  $\text{H}_2\text{O}$  and volume deficit, with losses of  $\text{H}_2\text{O}$  in excess of  $\text{Na}^+$ . Elderly individuals with reduced thirst and/or diminished access to fluids are at the highest risk of hypernatremia due to decreased free  $\text{H}_2\text{O}$  intake. Common causes of renal  $\text{H}_2\text{O}$  loss are osmotic diuresis secondary to hyperglycemia, postobstructive diuresis, or drugs (radiocontrast, mannitol, etc.);  $\text{H}_2\text{O}$  diuresis occurs in central or nephrogenic diabetes insipidus (DI) ([Chap. 168](#)). In pts with hypernatremia due to renal loss of  $\text{H}_2\text{O}$ , it is critical to quantify *ongoing* daily losses in addition to calculation of the baseline  $\text{H}_2\text{O}$  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  $\text{H}_2\text{O}$  deficit slowly to avoid neurologic compromise, decreasing the serum  $[\text{Na}^+]$  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<sub>2</sub>O Deficit**

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

**Ongoing H<sub>2</sub>O Losses**

4. Calculate free-water clearance,  $C_e \text{H}_2\text{O}$ :

$$C_e \text{H}_2\text{O} = V \left( 1 - \frac{U_{\text{Na}} + U_{\text{K}}}{S_{\text{Na}}} \right)$$

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

**Insensible Losses**

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

**Total**

6. Add components to determine H<sub>2</sub>O deficit and ongoing H<sub>2</sub>O loss; correct the H<sub>2</sub>O deficit over 48–72 h and replace daily H<sub>2</sub>O 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<sub>5</sub>W, should hyperglycemia ensue. Calculation of urinary electrolyte-free H<sub>2</sub>O clearance is helpful to estimate daily, ongoing loss of free H<sub>2</sub>O 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<sub>2</sub>O 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<sub>2</sub>O 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 ( $\text{K}^+$ ) is the major intracellular cation, discussion of disorders of  $\text{K}^+$  balance must take into consideration changes in the exchange of intra- and extracellular  $\text{K}^+$  stores. (Extracellular  $\text{K}^+$  constitutes <2% of total-body  $\text{K}^+$  content.) Insulin,  $\beta_2$ -adrenergic agonists, and alkalosis tend to promote  $\text{K}^+$  uptake by cells; acidosis, insulinopenia, or acute hyperosmolality (e.g., after treatment with mannitol or D<sub>50</sub>W) promotes the efflux or reduced uptake of  $\text{K}^+$ . A corollary is that tissue necrosis and the attendant release of  $\text{K}^+$  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  $\text{K}^+$  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  $\beta_2$ -adrenergic sympathetic activity: post-myocardial infarction, head injury, theophylline
    3.  $\beta_2$ -Adrenergic agonists: bronchodilators, tocolytics
    4.  $\alpha$ -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<sup>+</sup> 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 11 $\beta$ -dehydrogenase-2 (syndrome of apparent mineralocorticoid excess), inhibition of 11 $\beta$ -dehydrogenase-2 (glycyrrhetic/glycyrrhizic 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<sup>+</sup> 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<sup>2+</sup>, and Ca<sup>2+</sup>, a complete blood count, and urinary pH, osmolality, creatinine, and electrolytes. Serum and urine osmolality are required for calculation of the transtubular K<sup>+</sup> gradient (TTKG), which should be <3 in the presence of hypokalemia (see also Hyperkalemia). Alternatively, a urinary K<sup>+</sup>-to-creatinine ratio of >13-mmol/g creatinine (>1.5-mmol/mmol creatinine) is compatible with excessive K<sup>+</sup> excretion. Further tests such as urinary Mg<sup>2+</sup> and Ca<sup>2+</sup> 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<sup>+</sup> 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<sup>+</sup>. 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  $<2.5$  mM) 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  $\beta$ -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 mM 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).

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## 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  $K^+ \geq 6.0$  mM). 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;