Preface

NephSAP® is one of the three major publications of the American Society of Nephrology (ASN). Its primary goals are self-assessment, education, and the provision of Continuing Medical Education (CME) credits and Maintenance of Certification (MOC) credits for individuals certified by the American Board of Internal Medicine. Members of the ASN automatically receive NephSAP with their monthly issue of The Journal of the American Society of Nephrology (JASN).

EDUCATION: Medical and Nephrologic information continually accrues at a rapid pace. Bombarded from all sides with demands on their time, busy practitioners, academicians, and trainees at all levels are increasingly challenged to review and understand all this new material.

Each bimonthly issue of NephSAP is dedicated to a specific theme, i.e., to a specific area of clinical nephrology, hypertension, dialysis, and transplantation, and consists of an Editorial, a Syllabus, a Commentary on the Syllabus, and self-assessment questions. Over the course of 24 months, all clinically relevant and key elements of nephrology will be reviewed and updated. The authors of each issue digest, assimilate, and interpret key publications from the previous issues of other years and integrate this new material with the body of existing information.

SELF-ASSESSMENT: Twenty-five single-best-answer questions will follow the 50 to 75 pages of Syllabus text. The examination is available online with immediate feedback. Those answering >75% correctly will receive CME credit, and receive the answers to all the questions along with brief discussions and an updated bibliography. To help answer the questions, readers may go to the ASN web site, where relevant material from UpToDate in nephrology will be posted. Thus, members will find a new area reviewed every 2 months, and they will be able to test their understanding with our quiz. This format will help readers stay abreast of developing areas of clinical nephrology, hypertension, dialysis, and transplantation, and the review and update will support those taking certification and recertification examinations.

CONTINUING MEDICAL EDUCATION: Most state and local medical agencies as well as hospitals are demanding documentation of requisite CME credits for licensure and for staff appointments. A maximum of 48 credits annually can be obtained by successfully completing the NephSAP examination. In addition, individuals certified by the American Board of Internal Medicine may obtain credits towards Maintenance of Certification (MOC) by successfully completing the self-assessment portion of NephSAP.

BOARD CERTIFICATION AND INSERVICE EXAMINATION PREPARATION: Each issue will also contain 5 questions and answers examining core topics in the particular discipline reviewed in the Syllabus. These questions are designed to provide trainees with challenging questions to test their knowledge of key areas of nephrology.

This paper meets the requirements of ANSI/NISO Z39.48-1921 (Permanence of Paper), effective with July 2002, Vol. 1, No. 1.

NephSAP®
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Fluid, Electrolyte, and Acid-Base Disturbances

Editorial

We Come to Bury “Contraction Alkalosis,” Not to Praise It—John H. Galla, MD, and Robert G. Luke, MD

Syllabus

Fluid, Electrolyte, and Acid-Base Disturbances—Richard H. Sterns, MD, and Michael Emmett, MD

Acid-Base Disorders ................................ 96

Physiology ...................................... 96

Bicarbonate Levels and Chronic Renal Failure ............. 96

Acquired Metabolic Acidosis ............................. 98

Lactic Acidosis and Septic Shock ................ 98

Lactic Acidosis and Hematologic Malignancy .......... 100

Metformin and Lactic Acidosis ...................... 100

Anion Gap Composition ................................ 103

Propofol-Related Infusion Syndrome and Lactic Acidosis 104

Toxic Alcohols ..................................... 105

Asthma: Complex Interaction of Respiratory Alkalosis, Metabolic Acidosis, and Respiratory Acidosis .... 107

Epidemiology of the Anion Gap in “Normal Populations” 109

Topiramate and Hyperchloremic Metabolic Acidosis .... 110

Acquired Forms of Metabolic Alkalosis ................ 110

Metabolic Alkalosis: The Milk Alkali Syndrome (Calcium Alkali Syndrome) ............................. 110

Pseudo-Bartter (or Bartter-Like) Syndrome ............. 112
Mixed Metabolic Alkalosis and Respiratory Acidosis: Role for Acetazolamide? ........................................ 112
Metabolic Alkalosis (Pseudo-Bartter Syndrome) in Cystic Fibrosis .................................................. 114
Pendred Syndrome: Pendrin (SLC26A4) Defects ............. 115
General Principles ........................................ 117
Hypokalemia ........................................ 117
Inherited Forms of Hypokalemia .................................. 117
Familial Hypokalemic Periodic Paralysis ....................... 118
Thyrotoxic Hypokalemic Periodic Paralysis ................. 120
Acquired Forms of Hypokalemia ................................ 121
Acetaminophen Poisoning .................................... 121
High-Dosage Penicillin, Hypokalemia, and Metabolic Alkalosis .................................................. 122
Hypokalemia from Intestinal Pseudo-obstruction Ogilvie Syndrome ........................................ 122
Thiazides, Hypertension, and Hypokalemia ................. 123
Hypokalemia as a Risk Factor in Patients with Chronic Kidney Disease ........................................ 124
Hypokalemia-Induced Hyponatremia and Correction of Hyponatremia with K⁺ Replacement .......... 124
Hyperkalemia ........................................ 125
Physiology ........................................ 125
Pseudohyperkalemia ........................................ 126
Excess K⁺ Intake ........................................ 127
Internal K⁺ Shifts ........................................ 128
Hyperglycemia ........................................ 128
Octreotide ........................................ 128
Hyperkalemic Periodic Paralysis ................................ 128
Succinylcholine ........................................ 128
<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Glycosides</td>
<td>129</td>
</tr>
<tr>
<td>Impaired K⁺ Excretion</td>
<td>130</td>
</tr>
<tr>
<td>Decreased Mineralocorticoid Levels or Activity</td>
<td>130</td>
</tr>
<tr>
<td>Addison Disease</td>
<td>130</td>
</tr>
<tr>
<td>Hypoaldosteronism</td>
<td>130</td>
</tr>
<tr>
<td>Pseudohypoaldosteronism</td>
<td>130</td>
</tr>
<tr>
<td>Drug-Induced Hyperkalemia</td>
<td>130</td>
</tr>
<tr>
<td>Decreased Aldosterone Levels</td>
<td>130</td>
</tr>
<tr>
<td>Aldosterone Receptor Antagonism</td>
<td>131</td>
</tr>
<tr>
<td>Collecting Tubule Sodium Channel Blockade</td>
<td>132</td>
</tr>
<tr>
<td>Consequences of Hyperkalemia</td>
<td>133</td>
</tr>
<tr>
<td>Muscle Weakness</td>
<td>133</td>
</tr>
<tr>
<td>ECG Findings</td>
<td>133</td>
</tr>
<tr>
<td>Mortality</td>
<td>133</td>
</tr>
<tr>
<td>Metabolic Acidosis</td>
<td>133</td>
</tr>
<tr>
<td>Treatment of Hyperkalemia</td>
<td>133</td>
</tr>
<tr>
<td>Sodium Polystyrene Sulfonate</td>
<td>134</td>
</tr>
<tr>
<td>Fludrocortisone and Glycyrrhetinic Acid</td>
<td>136</td>
</tr>
<tr>
<td>Nonhypotonic Hyponatremia</td>
<td>137</td>
</tr>
<tr>
<td>Pseudohyponatremia</td>
<td>137</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>138</td>
</tr>
<tr>
<td>Exogenous Solutes</td>
<td>139</td>
</tr>
<tr>
<td>Intravenous Mannitol</td>
<td>139</td>
</tr>
<tr>
<td>Irrigant Absorption</td>
<td>139</td>
</tr>
<tr>
<td>Hypotonic Hyponatremia: Pathophysiology</td>
<td>140</td>
</tr>
<tr>
<td>Acute Hypotonic Hyponatremia</td>
<td>143</td>
</tr>
<tr>
<td>Psychotic Polydipsia</td>
<td>144</td>
</tr>
</tbody>
</table>
Exercise Hyponatremia ........................................ 144
Obstetric Hyponatremia ........................................ 145
Postoperative Hyponatremia .................................. 145
Neurosurgical Hyponatremia .................................. 146
Treatment of Acute Hyponatremic Emergencies ...... 146
Chronic Hypotonic Hyponatremia .............................. 148
Differential Diagnosis ........................................... 148
Causes of Renal Salt Wasting .................................. 148
  Addison Disease .............................................. 148
  Congenital Adrenal Hyperplasia ............................ 148
  Cisplatin ...................................................... 149
  Cerebral Salt Wasting ........................................ 149
Causes of Euvolemic Hyponatremia ............................ 150
  Tumor-Associated SIADH .................................... 150
  Hyponatremic Hypertensive Syndrome .................... 150
Drug-Induced Euvolemic Hyponatremia ...................... 150
  Cyclophosphamide ......................................... 150
  Carbamazepine .............................................. 151
  Selective Serotonin Reuptake Inhibitors ................ 151
  Other Drugs .................................................. 151
Nephrogenic Syndrome of Inappropriate Antidiuresis ... 152
Clinical Outcomes of Chronic Hyponatremia .............. 153
  Mortality .................................................... 153
  Hospital Costs .............................................. 155
  Falls and Fractures ........................................ 155
  Rhabdomyolysis ............................................. 157
  Osmotic Demyelination Syndrome ......................... 157
Core Knowledge Questions..........................190

Upcoming Issues

Acute Kidney Injury and Critical Care Nephrology—
   Patrick T. Murray, MD, and Kathleen D. Liu, MD . . . . . . . May 2011

Renal Pathology—
   Glen S. Markowitz, MD, Barry Stokes, MD, Neeraja Kambham, MD, Leal
   C. Herlitz, MD, and Vivette D. D’Agati, MD . . . . . . . . July 2011

Chronic Kidney Disease and Progression—
   Linda F. Fried, MD, and Michael J. Choi, MD . . . . . . . September 2011

Transplantation—
   John P. Vella, MD, and David J. Cohen, MD . . . . . . . November 2011
The Editorial Board of *NephSAP* extends its sincere appreciation to the following reviewers. Their efforts and insights have helped to improve the quality of this postgraduate education offering.

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The mission of the Nephrology Self-Assessment Program (NephSAP) is to regularly provide a vehicle that will be useful for clinical nephrologists who seek to renew and refresh their clinical knowledge and diagnostic and therapeutic skills. This Journal consists of a series of challenging, clinically oriented questions based on case vignettes, a detailed Syllabus that reviews recent publications, and an Editorial on an important and evolving topic. Taken together, these parts should assist individual clinicians undertaking a rigorous self-assessment of their strengths and weaknesses in the broad domain of nephrology.

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The ASN designates this journal-based activity for a maximum of 8.0 AMA PRA Category 1 Credits\textsuperscript{TM}. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Continuing Medical Education (CME) Information
CME Credit: 8.0 AMA PRA Category 1 Credits\textsuperscript{TM}
Date of Original Release: March 2011
Examination Available Online: on or before Monday, March 7, 2011
Audio Files Available: On or before Tuesday, March 15, 2011. A notice will be posted on the ASN website when the audio files become available.

CME Credit Eligible Through: February 29, 2012
Answers: Correct answers with explanations will be posted on the ASN website in March 2012 when the issue is archived.
UpToDate Links Active: March and April 2011
Core Nephrology question links active: March, April, and May 2011

Target Audience: Nephrology Board and recertification candidates, practicing nephrologists, and internists.

Method of Participation:
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- Examinations are available online only after the first week of the publication month. There is no fee. Each participant is allowed two attempts to pass the examination (>75% correct) for CME credit.
- Upon completion, review your score and incorrect answers.
- Your CME certificate can be printed immediately after completion.
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- On the ASN home page, double click on the *NephSAP* link (*NephSAP* cover) on the bottom side of the page.
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Agarwal, Rajiv—Research funding: Abbott; Consultant/scientific advisor: Rockwell Medical, Watson Pharma; Honoraria: Abbott, Astra-Zeneca, Merck
Cohen, David J.—Research funding: Life Cycle Pharma, Novartis, Roche, Wyeth; Honoraria: Bristol-Myers-Squibb, Novartis, Roche
Emmett, Michael—Honoraria: Braintree Laboratories Fresenius; Editorial board membership: American Journal of Cardiology, Clinical Nephrology
Fried, Linda F.—Research funding: Merck, Reata; Honoraria: Pfizer
Fuchs, Elissa (Medical Editor)—none
Glassock, Richard J.—Consultant: Bio-Marin (inactive), Eli Lilly (active), FibroGen (inactive), Genentech (active), Lighthouse Learning (active), Novartis (active), QuestCor (active), Wyeth (inactive); Ownership interests: LaJolla Pharmaceutical, Reata Inc.; Honoraria: American Society of Nephrology, various medical schools for lectures and/or visiting professor; Membership board of directors/scientific advisor: American Renal Associates, Los Angeles Biomedical Institute, University Kidney Research Associates (UKRO), Wyeth; Editorial board: UpToDate, American Journal of Nephrology; Royalties: Oxford University Press; Paid expert testimony: Various legal firms regarding product liability
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Murray, Patrick T.—Employment: spouse, Merck, Sharpe, & Dohme (Europe); Consultant/honoraria/research funding/scientific advisor: Abbott Laboratories (USA), Arguts Medical (UK), FAST Diagnostics (USA); NxStage Medical (USA).
Nachman, Patrick H.—Honoraria: QuestCor; Multicenter clinical trial participation: Otsuka
Peixoto, Aldo J.—Consultant: Abbott, Sanofi-Aventis; Research funding: Pulsemetric; Honoraria: Boehringer-Ingelheim, Merck, Novartis, Takeda; Scientific advisor/membership: Associate Editor–Blood Pressure Monitoring; Editorial Board: American Journal of Nephrology, Brazilian Journal of Nephrology
Sterns, Richard H.—Honoraria: Astellas, Otsuka, Merck
Townsend, Raymond R.—Consultant: Daiichi-Sankyo, GlaxoSmithKline, Merck, Nicox, Novartis, Roche; Research funding: Novartis; Honoraria: American Society of Hypertension, National Kidney Foundation
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Commercial Support

There is no commercial support for this issue.
Metabolic alkalosis (MA) has multiple causes, some associated with volume contraction and some with volume expansion (1). Moreover, volume contraction, particularly when severe, is usually associated with lactic acidosis (2). Thus, general clinical observations show that volume contraction does not necessarily lead to MA unless associated with selective chloride (Cl) depletion. MA is associated to variable degrees in sodium, potassium (K), Cl, and fluid volume depending on the nature of the primary stimulus, the availability of corrective factors, and further abnormalities generated by the primary stimulus.

In a seminal article, “contraction” alkalosis by ethacrynic acid described in humans gave rise to the hypothesis that extracellular fluid (ECF) volume contraction produces alkalosis (3). The authors concluded that the abrupt change in ECF volume was the primary event while acknowledging that Cl depletion might influence renal bicarbonate retention.

Our goal is to show that the hypothesis that maintenance of MA that is caused by Cl depletion by the kidney is dependent on ECF or plasma volume contraction is not supported by experimental evidence. We argue that the term “contraction alkalosis” is misleading in both a pathophysiologic and therapeutic sense and suggest that a better term is Cl depletion metabolic alkalosis (CDMA). This concept stresses the use of urinary Cl concentration to categorize the mechanism for MA and the therapeutic need for Cl containing fluids to correct CDMA.

There are basically three important causes of MA: The most common is Cl depletion secondary to vomiting or nasogastric aspiration or chloruretic diuretics; K depletion (not hypokalemia secondary to an intracellular shift of K caused by MA); and, least commonly, base loading in severe chronic renal failure or in ESRD. In true K depletion states, the major mechanism contributing to renal maintenance of MA caused by K depletion is increased reabsorption of HCO in proximal and distal tubules related to intracellular acidosis and H-K-ATPase-induced K conservation in the collecting duct.

The normal kidney rapidly restores HCO levels to normal after oral or intravenous bicarbonate loading. Metabolic alkalosis, regardless of mechanism, is now conveniently divided into three phases: induction, maintenance, and correction. In the steady-state maintenance phase of MA, the kidney, unlike the normal kidney, fails to correct the serum HCO to normal by increased urinary HCO excretion. As noted, some still claim that the maintenance phase in states of MA associated with Cl depletion is maintained by volume contraction. The reasoning behind this follows.

Historically, in the 1960s and 1970s, Cl was regarded as “the mendicant anion,” passively following sodium across epithelial membranes or the paracellular pathway. During transepithelial transport, proton secretion and renal tubular HCO absorption was believed to occur via Na-H exchange throughout the nephron. It was thus logical at that time to believe that maintenance of renal bicarbonate reabsorption in CDMA was driven by enhanced Na-H exchange in states of ECF volume contraction, especially in the presence of reduced Na reabsorption with Cl. It was concluded that the demands of maintenance of ECF volume in the presence of reduced reabsorption of NaCl must enhance Na-H exchange and thus maintain NaHCO absorption and MA.

This now outmoded concept has continued to be the view expressed in NephSAP since at least 2006 and is restated in this issue in discussion of the need for “volume expansion” to correct MA complicating chronic respiratory acidosis in the intensive care unit (page 55). A similar view is expressed...
in regard to the mechanism of generation and maintenance of MA in some patients with cystic fibrosis even though equimolar NaCl (and thus enhanced relative Cl\(^{-}\) depletion) occurs in the sweat glands of such patients (page 58). There are now a plethora of known Cl\(^{-}\)/H\(_2\)CO\(_3\) anion exchangers and Cl\(^{-}\) channels involved in transepithelial solute transport (4). Furthermore, mutations in these account for various congenital electrolyte and acid-base syndromes and renal diseases. These specialized tubule segments, cells, and transport mechanisms in the distal nephron offer attractive explanations of renal adjustments to acid-base perturbations, independent of sodium balance, and are discussed next.

The pathogenesis of CDMA was studied by Schwartz’s group in carefully done balance studies of men and dogs (5). CDMA was produced by gastric aspiration, chloruretic diuretics, NaNO\(_3\) infusion (an effect of “unreabsorbable” anions), and previous hypocapnia (“post-hypocapnic CDMA”). These studies established unequivocally that Cl\(^{-}\) replenishment by NaCl or KCl—but not replacement of Na\(^{+}\) and K losses without Cl\(^{-}\)—fully corrected CDMA in the maintenance phase. The issue of the specific role of ECF volume depletion was assumed but not resolved at this time, although it was established that Na\(^{+}\) replenishment without Cl\(^{-}\) replenishment, regardless of the method of genesis of CDMA, clearly did not correct CDMA during its maintenance phase.

Subsequent studies of men and rats with acute and chronic CDMA, using careful measurement of plasma volume changes during the correction phase, established that correction of Na\(^{+}\) balance and volume deficits was not necessary for correction of CDMA and that Cl\(^{-}\) replenishment was the single, sufficient, and necessary effect to correct CDMA.

CDMA induced by the combination of furosemide; administration of Na\(^{+}\), K\(^{+}\), citrate; and dietary Cl\(^{-}\) restriction in normal men was completely corrected in the maintenance phase of CDMA by oral KCl, with continued restriction of Na\(^{+}\), despite the presence of maintained negative Na\(^{+}\) balance and plasma volume contraction (measured by I\(^{131}\) albumin space and plasma albumin concentrations), and persistently lowered GFR and estimated renal plasma flow (6) (Figure 1).

During correction, net acid excretion decreased with HCO\(_3\)\(^{-}\) diuresis. Sodium phosphate given instead

![Figure 1](image-url)
of KCl replacement was associated with increased serum \(\text{HCO}_3^-\) concentration despite increased plasma volume. In control subjects, furosemide administration without \(\text{Cl}^-\) restriction did not cause CDMA, and serum electrolytes and net acid excretion did not change with the same amount of KCl administration.

In rat studies, using \(\text{Cl}^-\) depletion produced by peritoneal dialysis (PD) against dialysate containing isotonic NaHCO\(_3\) and a K\(^+\) concentration equivalent to a normal serum K\(^+\) level, intravenous infusion of an 80 mM \(\text{Cl}^-\) solution (the same concentration as in the hypochloremic rat) containing several cations excepting Na\(^+\) resulted in the complete correction of CDMA (7). Serial measures of GFR, plasma volume, and Na\(^+\) balance showed that this \(\text{Cl}^-\) infusion, without Na\(^+\) or an increase in plasma volume from its depressed state and likewise for GFR, corrected CDMA promptly and completely. In controls, which received only 5% dextrose intravenously, bicarbonate excretion continued to fall, whereas in the CDMA rats, with maintained plasma volume contraction, negative sodium balance, and low GFR, there was a brisk \(\text{HCO}_3^-\) diuresis (Figure 2).

In other rat studies, we noted that renal \(\text{Cl}^-\) conservation continued during this \(\text{Cl}^-\) infusion until plasma \(\text{Cl}^-\) normalized (8).

In segmental nephron studies of the PD rat model of CDMA, we observed that the change in \(\text{HCO}_3^-\) reabsorption in response to \(\text{Cl}^-\) infusion occurred in the distal nephron during correction without a significant increase in delivery to these sites as compared with rats with maintained CDMA (9). Further support for the importance of adaptation of the distal nephron in maintenance and correction was provided by Wesson (10) and Levine et al. (11).

**In vitro** studies of the cortical collecting duct (CCD) in rats with acute CDMA showed vigorous \(\text{HCO}_3^-\) secretion, abolished by zero \(\text{Cl}^-\) luminal perfusion (12). The degree of \(\text{HCO}_3^-\) secretion **in vitro** was directly proportional to the degree of \(\text{Cl}^-\) depletion and CDMA produced **in vivo**. Proton ATPase was diminished in the apical membrane of the A cell and increased in the basolateral membrane of the B cell (13). The B-intercalated cell in the CCD seemed to be “poised to secrete” \(\text{HCO}_3^-\) as soon as \(\text{Cl}^-\) is provided, and the proton-secreting A cell activity seemed to be inhibited. Further details of our **in vivo** and **in vitro** rat studies are provided in the original publications and are reviewed in detail elsewhere (14).

During our studies, the molecular nature of the luminal neutral \(\text{Cl}^-\)-\(\text{HCO}_3^-\) exchanger in B cells had not been identified. Numerous studies have now shown that it is pendrin, as noted elsewhere in this issue (page 60). Pendrin is rapidly activated in states of renal \(\text{Cl}^-\) conservation and in MA and inhibited by chloruresis and metabolic and respiratory acidosis (15–17). In CDMA, B cells are activated along with the relevant transporters, pendrin and basolateral H\(^+\)-ATPase, and proton secretion by A cells is reduced. Clearly, the increased \(\text{HCO}_3^-\) secretion in the CCD must be accompanied by reduced \(\text{HCO}_3^-\) reabsorption in more distal segments of the CCD for \(\text{HCO}_3^-\) diuresis to occur (18).

That the B cell and the CCD may be important in normal acid-base balance is also supported by the development of MA in rats subject to oral NaHCO\(_3\) loading on a low \(\text{Cl}^-\) diet (11). Feeding babies a low-\(\text{Cl}^-\), high-alkaline diet has also caused MA, again suggesting that collecting duct \(\text{Cl}^-\)-\(\text{HCO}_3^-\) exchange may be important for excreting \(\text{HCO}_3^-\) load (19).

How would the substitution of CDMA for “con- traction alkalosis” contribute to an approach to treatment? First, understanding the true pathophysiology of

**Figure 2.** Urinary \(\text{HCO}_3^-\) excretion in rats with persistent volume depletion, Na\(^+\) depletion, and decreased GFR. Rats receiving \(\text{Cl}^-\) (CC) increased urinary \(\text{HCO}_3^-\) excretion as alkalosis was corrected (data not shown), whereas those receiving only glucose (DX) had a further decrease while alkalosis was maintained (data not shown). Reprinted from Galla JH: Chloride-depletion alkalosis. In: Acid-Base Disorders and Their Treatment, edited by Gennari FJ, Adrogue, Galla JH, Madias NE, Boca Raton, Taylor & Francis, 2005, p 530, with permission.
disease usually helps to improve treatment. Second, it focuses the clinician on the diagnostic value of mechanisms and results of Cl\(^-\) loss in the history, clinical findings, and laboratory data. Third, it emphasizes the replacement of the Cl\(^-\) deficit rather than just expansion of ECF and plasma volume. Volume contraction is commonly an associated finding, and infusion of NaCl is then always appropriate. CDMA often causes shifts of K\(^+\) into cells and enhanced K\(^+\) loss in the distal nephron so that KCl replacement is often also needed. Indeed, in protracted vomiting, continued urinary K\(^+\) losses may eventually lead to true K\(^+\) depletion, which may contribute to maintenance of MA in such circumstances. Volume contraction is not always present in CDMA, and then administration of KCl, HCl, and, especially when KCl or HCl is not feasible, acetazolamide plus KCl as needed should be considered. This is discussed further on page 55 in the consideration of the mixed acid-base disturbance of chronic respiratory acidosis and MA; the latter is usually CDMA because of chloruretic treatment for congestive heart failure. All of these treatments are subject to the limitation as to whether renal function is or becomes adequate to respond to these various therapies. In ESRD or preexisting stage 5 chronic kidney disease, dialysis with a Cl\(^-\)-rich dialysate may be required to correct the CDMA.

Other possible benefits of replacement of Cl\(^-\) in CDMA include an increase in GFR by suppressing tubuloglomerular feedback via the macula densa signal (20). We interpret this reduction of GFR as an attempt to reduce the initial sodium wasting phase of acute CDMA. Renal concentrating ability may also improve because the delivery of Cl\(^-\) is rate limiting for NaCl absorption in the thick ascending limb of the loop of Henle (20). These phenomena, however, have not been studied in humans. Improvement in response to loop diuretics has been shown in humans with correction of CDMA (21).

In summary, CDMA is corrected by selective Cl\(^-\) repletion:

(A) **Desire**

- Maintained or increasingly negative Na\(^+\) or K\(^+\) balance
- Continued HCO\(_3^-\) loading
- Continued high levels of angiotensin II or aldosterone (10,22,23)

(B) And is **not corrected**

- By Na\(^+\) or K\(^+\) repletion without Cl\(^-\) repletion
- By Cl\(^-\) repletion in the absence of renal function (24)
- By plasma volume expansion by as much as 25% or by restoring baseline GFR without Cl\(^-\) repletion

(C) The **adaptive corrective** response is in

- The distal nephron by an integrated response in the CCD to ensure a bicarbonate diuresis in response to Cl replacement

We believe that we have made an adequate rationale to finally bury the term “contraction alkalosis” and replace it with CDMA!

**References**

16. de Seigneur S, Malte H, Dimke H, Fröskjær J, Nielsen S, Frische S: Renal compensation to chronic hypoxic hypercapnia: Downregula-
Learning Objectives:
1. To examine recent scientific advances in our understanding of the pathophysiology of disorders of potassium, acid-base, sodium, and water balance
2. To review how our understanding of pathophysiology can be applied to the care of patients
3. To understand how recent clinical trials related to fluid, electrolyte, and acid-base disorders can be applied to clinical decision-making

Acid-Base Disorders

Physiology
The physiology of acid-base disorders was well reviewed in a previous issue of *NephSAP* (1), and the reader is referred to that review for general information. New discoveries in acid-base physiology in the past few years are discussed in the context of specific, relevant clinical syndromes; more in-depth information about recent advances in the understanding of acid-base physiology is available in recent reviews.

An update of kidney acid-base regulation was published by Koeppen in 2009 (2), and the physiology of kidney ion transport, including acid-base, was reviewed extensively (3).

References

Bicarbonate Levels and Chronic Renal Failure

One of the most important recent developments in the field of metabolic acidosis is the accumulating evidence that the treatment of metabolic acidosis may slow the progressive deterioration of kidney function, often a seemingly inevitable aspect of the chronic renal disease syndrome. More than 25 years ago, Nath *et al.* (1) showed that high ammonia/ammonium concentrations in the kidney could be toxic and that ammonium-related nephrotoxicity is a potential result of the activation of the alternative complement cascade via amidination of C3 (2,3). Although the total daily quantity of excreted urine net acid and ammonium falls as kidney function decreases, the ammonium concentration within each nephron unit increases and systemic acidosis further increases the ammonium concentration in the kidney tissue. Nath *et al.* studied rats subjected to 1 ¾ nephrectomy, which then experienced progressive kidney dysfunction. The administration of sodium bicarbonate supplements to rats with chronic renal failure reduced renal ammonia synthesis, ammonium excretion, and ammonium concentration within the renal tubules. Such findings had been previously described. However, the discovery that sodium bicarbonate supplements also reduced urine protein excretion was unexpected. In addition, other markers of renal tubule dysfunction improved (1). Subsequently, Torres *et al.* (3) studied a strain of rats that developed an inherited form of progressive renal cystic disease. Feeding NH₄Cl to these rats worsened the cystic disease process and accelerated the progression rate of kidney dysfunction, but the administration of sodium bicarbonate supplements decreased urine ammonium excretion and markedly reduced progression of the cystic disease and the severity of interstitial inflammation.

Studies of other rat models of progressive kidney disease have not always been consistent. Some have not confirmed the beneficial effects of sodium bicarbonate supplementation; in some experiments, metabolic acidosis actually seemed to be protective and slowed the progression rate of kidney failure (4,5).
The mechanism of acidosis protection has been hypothesized to be related to increased solubility of calcium phosphate salts in an acid environment. Thus, metabolic acidosis could potentially have both adverse and beneficial effects. Nonetheless, the current consensus is that the adverse effects of metabolic acidosis predominate.

In a recent issue of the *Journal of the American Society of Nephrology*, de Brito-Ashurst *et al.* (6) addressed this question in humans with chronic kidney disease (CKD). They randomly assigned 134 adult patients with CKD (measured creatinine clearance [CrCl] between 15 and 30 ml/min per 1.73 m²) and metabolic acidosis (serum bicarbonate level between 16 and 20 mEq/L) to receive either standard care only or standard care plus oral sodium bicarbonate supplements for a 2-year period. The final dose of oral sodium bicarbonate averaged 1.82 ± 0.80 g/d (approximately 22 mEq/d). Patients who received sodium bicarbonate developed higher serum bicarbonate and lower serum potassium levels. The most important findings were that the bicarbonate-supplemented group had a slower decline in their measured CrCl (1.9 versus 5.9 ml/min/1.73 m²), were less likely to experience a rapid deterioration of GFR (9 versus 45%), and fewer of them developed end-stage kidney disease (6.5 versus 33.0%). A number of nutritional parameters, including dietary protein intake, normalized protein nitrogen appearance, serum albumin, and mid-arm muscle circumference, all were improved in the bicarbonate-supplemented group. The bicarbonate therapy was moderate in dosage and was very well tolerated. It has been known that patients with renal disease and those with hypertension tolerate exogenous sodium bicarbonate much better than equimolar exogenous NaCl supplementation; less weight gain, edema, and BP elevation occur in bicarbonate-supplemented groups, compared with NaCl-supplemented groups (7,8,9).

Similar conclusions were reached in a smaller study by Phisitkul *et al.* (10), in which GFR was not directly measured. Phisitkul *et al.* found that base supplementation (with sodium citrate) slowed the rate of GFR decline as estimated from both the serum creatinine concentrations (with the Modification of Diet in Renal Disease [MDRD] equation) and the cystatin C levels. The yearly decline of the MDRD-derived estimated GFR (eGFR) was 1.60 ± 0.13 ml/min per 1.73 m² in the treated group versus 3.79 ± 0.30 ml/min per 1.73 m² in the control group. The GFR decline rates estimated from the cystatin C level showed similar results: 1.82 ± 0.08 ml/min in the treated group versus 4.38 ± 0.98 in the control. Two markers of tubulointerstitial disease, urine endothelin-1 excretion (a surrogate of kidney endothelin production) and N-acetyl-beta-D-glucosaminidase, were also measured; excretion rates fell in patients who were treated with sodium citrate. Shah *et al.* (11) provided additional evidence for the adverse impact of metabolic acidosis on kidney function deterioration rate, retrospectively analyzing 5422 outpatients with eGFRs of <60 ml/min per 1.73 m². Compared with a reference bicarbonate baseline level of 25 to 26 mEq/L, patients with lower or higher bicarbonate levels were more likely to have a major reduction in kidney function, defined by an eGFR decrease of 30% or a doubling of serum creatinine level.

Independent of the question, “Can oral bicarbonate salts and bicarbonate precursors slow the rate of renal deterioration?” there is ample evidence that alkalinizing salts have multiple beneficial effects on protein metabolism, endocrine function, muscle function, skeletal structure, bone density, and other physiologic parameters in patients with chronic metabolic acidosis of various causes. This is likely to be true for patients with moderate degrees of CKD as well as patients with more severe kidney disease, and for those who require dialysis.

Interpretation of the serum bicarbonate is confounded by multiple factors, some beneficial and others harmful, that affect bicarbonate concentration. These factors can have opposite effects on survival and morbidity. From the research described, it is clear that metabolic acidosis has multiple negative effects, but lower bicarbonate levels could also reflect excellent nutrition because higher protein intake generates larger acid loads. For patients with renal disease and a lower bicarbonate level as a result of higher protein intake, this may actually predict better survival, although lower bicarbonate levels could also reflect systemic inflammation, which would adversely affect morbidity and survival. Conversely, higher bicarbonate levels may have a number of beneficial effects, but in cases in which a higher level reflects poor protein intake or acid loss as a result of vomiting, higher bicarbonate levels may portend a poor outcome. In 2006, Wu *et al.* (12) evaluated baseline predialysis serum bicarbonate levels (averaged over the first 3 months of dialysis treatments) to determine whether they could predict 2-year mortality rates in 56,385
maintenance hemodialysis patients. The study concluded that the “optimal” predialysis serum bicarbonate level associated with the lowest unadjusted mortality rate in these patients was between 17 and 23 mEq/L. After adjustment for the confounding beneficial acidifying impact of nutrition and the adverse impact of inflammation, a bicarbonate level of $\geq 23$ mEq/L predicted the highest survival. A subsequent study directed by the same senior author, Kalantar-Zadeh, evaluated this question in patients with predialysis CKD (13); patients with serum bicarbonate levels in the range of 26 to 29 mEq/L had the lowest mortality rate, whereas those with lower or higher bicarbonate levels had higher mortality rates. In 2010, Kraut and Madias (14) reviewed the consequences of metabolic acidosis in patients with renal disease and the risks and benefits of therapy. They agree with the recommendation of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) that serum HCO$_3$ be increased to $\geq 22$ mEq/L and/or the recommendation of the Caring for Australians with Renal Impairment (CARI) panel that HCO$_3$ be increased to $> 22$ mEq/L. Their report appropriately cautions that HCO$_3$ levels should not be increased above the normal range, at the risk of increased fatality (14).

**References**


**Acquired Metabolic Acidosis**

**Lactic Acidosis and Septic Shock**

In 2001, Rivers *et al.* (1) published a study of “early goal-directive therapy in the treatment of severe sepsis and septic shock.” This study and the subsequent Surviving Sepsis Campaign (2) have had a profound impact on emergency treatment of patients with possible sepsis. The diagnosis of severe sepsis requires evidence of infection and two or more Systemic Inflammatory Response Syndrome (SIRS) criteria:

1. Temperature $> 38$ or $< 36 ^\circ C$
2. Heart rate $> 90$ beats/min
3. Respiratory rate $> 20$ breaths/min or $P_cO_2 < 32$ mmHg
4. WBC greater than 12,000/cc or less than 4,000/cc, or greater than 10% bands.

A diagnosis of septic shock requires either a mean arterial BP $< 65$ or a systolic BP $< 90$ mmHg that persists after IV expansion, or a blood lactate level $\geq 4$ mEq/L regardless of the blood pressure. Although
some controversy has developed regarding the absolute beneficial impact on patient outcomes of treatment based on these guidelines, there is no doubt that this campaign has generated an enormous number of “stat” blood lactic acid measurements.

Chawla et al. (3,4) investigated whether an increased anion gap level could substitute for the direct measurement of lactic acid in critically ill patients, concluding that the inherent variability of the anion gap calculation proved to be too large to predict reliably relatively small lactic acid increases. Critically ill patients often have hypoalbuminemia, which confounds the anion gap calculation. Although the anion gap corrected for albumin is a better lactic acid level predictor, the correction only marginally improved the predictive value of the anion gap. Berkman et al. (5) studied 1419 emergency department patients and reached similar conclusions. An anion gap of >12 mEq/L in a patient who presented to the emergency department with clinically suspected infection had a sensitivity of 80% and a specificity of 69% for predicting a lactate level of >4 mEq/L. They concluded, “This information may be somewhat helpful to emergency physicians to risk-stratify their patients to provide more aggressive early resuscitation” (5). Thus, the anion gap cannot substitute for direct blood lactic acid measurements when relatively small increases are of critical importance (3–6).

After the diagnosis of septic shock has been established, a related issue is whether serial monitoring of lactate levels provides any clinical benefits. Jansen et al. (7) reviewed the literature and concluded that although lactate levels are a helpful risk-stratification tool for critically ill patients, they are not useful as “resuscitation end points.” This question was studied directly by Jones et al. (8), who conducted a multicenter, randomized, noninferiority trial to examine sequential lactate levels as an index of therapeutic adequacy and to determine whether lactate levels may help to direct subsequent therapy. Three hundred patients with early severe sepsis or septic shock were randomly assigned to either (1) a group in which resuscitation efforts were directed at normalization of central venous pressure, mean arterial pressure, and a ScvO₂ of at least 70% or (2) a group that received identical treatments and also used each patient’s “lactate clearance” measurement to direct therapy. Lactate clearance is calculated as 100 × (initial lactate – delayed lactate)/initial lactate, where the initial lactate is the measurement obtained at the start of resuscitation and delayed lactate is a repeat measurement obtained at least 2 hours after the start of resuscitation. The therapeutic goal was a lactate clearance of at least 10%. Lower lactate clearance rates required the addition of sequentially added interventions, including blood transfusions, dobutamine infusion, etc. Efforts directed at improving lactate clearance did not reduce inhospital mortality.

When patients with sepsis syndrome develop lactic acidosis, is lactate the primary or entire cause of the metabolic acidosis and the increased anion gap? In 1991, Mecher et al. (9) evaluated the anion gap elevation in patients with severe sepsis and, after considering the impact of elevated phosphate and urate concentrations and changes in serum protein concentrations on the anion gap, concluded that lactate could account for only approximately 50% of the residual increase. More recently in 2008, Moviat et al. (10) attempted to identify all of the acid anions that accumulated in 31 critically ill patients with metabolic acidosis. They used multiple analytic methods including standard clinical laboratory methods, ion-exchange column chromatography, reverse-phase HPLC, and gas chromatography–mass spectrometry. Again, a large fraction of the anion gap remained unidentified; additional discussion of the “missing component” of the gap is provided in the Anion Gap Composition section.

In addition to anion gap acidosis, which is so prevalent in the patient with severe sepsis and septic shock, the frequency and severity of hyperchloremic metabolic acidosis seems to have increased, probably reflecting therapeutic changes. This acid-base disorder was emphasized in a study of patients with severe sepsis and septic shock at the time they were admitted to the intensive care unit (11). Hyperchloremic acidosis accounted for between 5 and 10 mEq/L of the reduction in bicarbonate and was most likely generated by the aggressive use of intravenous isotonic saline during the patient’s emergency department treatment. As noted, large-volume isotonic saline is now standard of care for most patients with severe sepsis and septic shock. Furthermore, the patients who had sepsis and survived had developed less severe hyperchloremic acidosis than the patients who died. Although it seems likely that these sicker patients would have received more intravenous fluid, differences in the volume of intravenous isotonic saline...
between these groups could not entirely be attributed to the severity of the illness or entirely explain the development of hyperchloremic acidosis (11).

References

Lactic Acidosis and Hematologic Malignancy
Patients with extensive lymphoma and leukemia may develop persistent lactic acidosis that is not readily explained by overt tissue hypoxia. In 2007, Friedenberg *et al.* (1) described this disorder in seven patients, five with lymphomas and two with chronic lymphocytic leukemia; this association has been reported in multiple studies in the past few years (2–8). In some, the liver was extensively infiltrated with tumor, and reduced hepatic lactate uptake probably played a major role. In other studies, however, liver status was normal. It is likely that tumor cells were rapidly synthesizing lactic acid. Tumor cell glycolytic enzyme activity may be increased and high levels of IFG and/or TNF have been implicated. In many of these cases, the lactic acidosis is associated with hyperglycemia that is refractory to glucose infusion (2,4,8). The prognosis of these patients is generally very poor. Thiamine and/or riboflavin deficiency also can contribute to development of lactic acidosis, and Friedenberg *et al.* (1) suggested that these vitamins be administered to patients with this condition.

References

Metformin and Lactic Acidosis
Metformin is an extremely effective drug for type 2 diabetes and has become a cornerstone of therapy for these patients. However, its use is associated with the development of severe and often fatal lactic acidosis, especially when the drug is given to...
patients with renal insufficiency. Under those circumstances, it can accumulate to toxic levels and generate metformin associated lactic acidosis (MALA), an extremely rare condition (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years) (1). When lactic acidosis occurs in a patient who has diabetes and is taking the drug, he or she almost always has multiple comorbidities, is taking multiple medications, and is usually critically ill. Therefore, the exact etiologic role played by metformin in the development of the lactic acidosis often remains uncertain (hence the acronym is MALA and not MILA for “metformin induced lactic acidosis”). Several recent publications have addressed the issue of causality and relative frequency of this complication. Bodner et al. (2) performed a nested case-control analysis using the UK General Practice Research Database and confirmed a lactic acidosis rate of approximately 0.03 cases/1000 patient-years for metformin-treated patients, but they also found an even higher rate of lactic acidosis (0.048 cases/1000 patient-years) among sulfonylurea-treated patients. Salpeter et al. (3) published a Cochrane Database Systematic Review of pooled data from 347 comparative trials and cohort studies, which compared 70,490 patient-years of metformin use with 55,451 patients-years of treatment with non-metformin antidiabetic drugs. No case of lactic acidosis occurred in either group. They concluded that there was no statistical difference in the lactic acidosis rate between the groups. Kamber et al. (4) reported data from the Fremantle Diabetes Study (FDS) in Australia, where 1279 patients with type 2 diabetes were observed over 12,466 patient-years. Five confirmed cases of lactic acidosis were identified, and four of five patients had other derangements that could have caused the acidosis (e.g., cardiogenic shock). Again, there was no significant difference between the occurrence rate of lactic acidosis in patients who were and were not taking metformin. However, the relatively small number of patients followed and the very low rate of lactic acidosis development in this study means that a small increased risk may have been missed. Lalau (5) reviewed the literature through 2009 and came to the same conclusion.

Metformin is very efficiently excreted in the urine of patients with normal kidney function. Its clearance is 300 to 400% of the GFR, and 90% of an oral dose is excreted by the kidneys (1). Consequently, high systemic levels develop only when renal function is impaired or major overdose occurs. Concern about metformin accumulation, and the potential for development of lactic acidosis caused the Food and Drug Administration to mandate a “black box” warning about this complication. The drug is currently contraindicated for men with a serum creatinine level of \( \geq 1.5 \) mg/dl and for women with a serum creatinine level of \( \geq 1.4 \) mg/dl. It also must be stopped for 48 hours whenever an iodinated contrast study is done because of concern that acute renal damage may develop in patients with diabetes. Significant heart failure and/or liver disease are additional strong relative contraindications to use of the drug.

Despite these very clear formal contraindications (which may be too stringent), many patients with unequivocal contraindications are still treated, either because physician and patient believe the benefit of metformin therapy outweighs the risk or because therapeutic errors have occurred. For example, in the FDS (4), up to 38% of patients who were taking the drug had contraindications. The percentage of patients who had contraindications and were treated with metformin was even higher in a recent study from Thailand (6); of patients who had type 2 diabetes and had clear-cut contraindications to metformin, 84% still received the drug. It is worth noting that despite the frequent clear violation of the manufacturer’s recommendations the incidence of lactic acidosis was not increased above the level which was seen in the non-metformin using control patients in the FMS (4). Pongwecharak et al. (6) also could not identify any case of lactic acidosis. These accumulating findings have led to a number of proposals that the strict GFR restrictions on metformin be modified and liberalized. For example, Shaw et al. (7) proposed that metformin prescribing be based on estimated GFR (eGFR) results and not serum creatinine concentration. They further propose that metformin use should be permitted for NKF stage II kidney disease (eGFR between 30 and 59 ml/min/1.73M²) and that the drug should only be contraindicated for patients with an eGFR less than 30 ml/min/1.73M². Herrington and Levy (8) advanced similar recommendations but suggested that the starting and maximal metformin doses be decreased by 50% when the GFR is between 30 and 60 ml/min per 1.73 m² and/or when treating elderly patients. Philbrick et al. (9) also concurred, emphasizing that the benefit of using metformin for any patient must always be balanced with the risk, thereby deeming absolute rules
that are based on creatinine concentration inappropriate and harmful. Tahrani et al. (10) also recommended liberalization of other treatment contraindications, such as heart failure.

Despite all of these data regarding the safety of metformin use and lack of toxicity in patients with normal renal function or modestly reduced renal function, most researchers believe that metformin can produce lactic acidosis when it reaches very high systemic concentrations. High concentrations inhibit mitochondrial uptake and metabolism of pyruvate, bind to mitochondrial membranes, and block oxidative phosphorylation, so the association is scientifically plausible. Very high metformin levels generally occur in one of three settings: The drug is sometimes inappropriately prescribed for patients with severe or end-stage kidney disease (11), patients with relatively normal kidney function may develop acute kidney injury (e.g., volume depletion from nausea and vomiting) and continue to take the drug (12), and there are cases of accidental (13) and intentional overdose (14–18). When massive overdoses of metformin are ingested, measured metformin levels are extremely high; some but not all of these patients develop lactic acidosis, and many develop hemodynamic instability.

When patients present with presumed metformin toxicity, lactic acidosis, and/or hypotension and the metformin levels are believed to be very high, efforts to remove metformin are indicated. The high plasma levels must be presumed because results of measurement will be delayed by many days or more. Usually, renal function is markedly reduced or else high metformin levels would not have developed; therefore, extracorporeal removal modalities are often used. Metformin is minimally bound to proteins and is readily dialyzable, but a prolonged period of dialysis will be required because this drug has a very large distribution volume and is distributed to multiple compartments (17–19). Seidowsky et al. (18) have accumulated a great deal of data on this topic; Table 1 and Figure 1 from their article are shown. Important points from this study are that patients with intentional overdose are younger and have higher metformin levels but less severe lactic acidosis and excellent survival rates. Those who accidentally overdose, by definition have diabetes, and are also older and sicker and have worse kidney, and liver dysfunction. They develop more severe lactic acidosis and are more likely to die (58%), despite aggressive intervention (18). Figure 1 shows that prolonged hemodialysis (≥15 hours) is required to reduce the metformin levels by 90%. A postdialysis rebound will occur. If the patient is too unstable for hemodialysis, then a continuous slow form of hemofiltration or dialysis can be used (15). Although individual cases of treatment with plasma exchange and charcoal hemoperfusion have been published, the efficacy of these modalities is unclear, and hemodialysis continues to be the standard method of extracorporeal removal (15,17).

### Table 1. Comparison between the intentional overdose group (group 1) and the accidental overdose group (group 2)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (n = 13)</th>
<th>Group 2 (n = 29)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>45 (10; 16–81)</td>
<td>69 (19; 49–81)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total LODS score (points)</td>
<td>3 (3; 0–13)</td>
<td>9 (4; 0–14)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Probability of mortality (%)</td>
<td>3 (3; 3–88)</td>
<td>58 (39; 3–92)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>pH</td>
<td>7.34 (0.07; 7.15–7.39)</td>
<td>6.90 (0.22; 6.60–7.35)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Plasma bicarbonate (mmol/L)</td>
<td>18 (6; 8–21)</td>
<td>5 (5; 2–21)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blood arterial lactate (mmol/L)</td>
<td>6 (7; 2–18)</td>
<td>12 (8; 4–30)</td>
<td>0.001</td>
</tr>
<tr>
<td>Plasma anion gap (mmol/L)</td>
<td>20 (5; 13–34)</td>
<td>41 (12; 19–50)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blood urea (mmol/L)</td>
<td>4 (6; 0.5–20.0)</td>
<td>22 (13; 1–83)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>79 (48; 53–500)</td>
<td>523 (366; 35–1126)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Plasma metformin (mg/L)</td>
<td>33 (43; 3–83)</td>
<td>9 (5; 3–16)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Plasma potassium (mmol/L)</td>
<td>4.1 (0.7; 3.4–8.7)</td>
<td>5.8 (1.6; 3.3–7.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prothrombin activity (%)</td>
<td>95 (10; 32–100)</td>
<td>50 (41; 10–109)</td>
<td>&lt;0.0001</td>
</tr>
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Anion Gap Composition

When a patient is found to have anion gap metabolic acidosis, the physician must always seek to identify the “unmeasured” anions. Often, the principal cause is readily apparent, as with lactic acidosis, ketoacidosis, or uremic acidosis. However, in many patients, a large component of the “missing” anions cannot be identified (see previous section). Thirty years ago, Gabow et al. (1,2) intensively searched for the “missing” anions using a variety of chemical analytic techniques including enzymatic analysis for organic acids, gas chromatography–mass spectrometry (GC-MS) of blood and urine, and calculation of the contribution of serum proteins and inorganic phosphate. Despite these multifaceted identification efforts, a large component of “missing” anions remained elusive in many patients. More recently, several groups continued the search for the identity of the “missing anions,” which presumably were added to the blood as acids.

Figure 1. The effect of hemodialysis on plasma metformin levels in 20 patients. The x-axis shows the cumulative dialysis duration. All predialytic metformin levels were considered as the 100% value and the decrease in metformin level was calculated as the percentage of this value. Mean decrease and SD of the mean are depicted. Clinical toxicology by American Academy of Clinical Toxicology. Copyright 2009. Reprinted from reference 18 (Seidowsky A, Nseir S, Houdret N, Fourrier F: Metformin-associated lactic acidosis: A prognostic and therapeutic study. Crit Care Med 37: 2191–2196, 2009), with permission of Lippincott Williams & Wilkins, Inc.

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chromatography coupled to electrospray ionization mass spectrometry. They emphasized the contribution of Kreb’s cycle acids, such as isocitric, alpha keto-butyric, malic, and other acids (5–8). In total, these acids can explain 3 to 5 mEq/L of the anion gap in many patients with metabolic acidosis, but a large component of the anion gap remains missing. Either relatively high concentrations of several anions are still unable to be identified, large numbers of anions in low concentration are not being recognized, or the conceptual framework about these disorders needs revision. For example, Kamel et al. (9) suggested that a component of anion gap changes that occur in a variety of pathologic conditions may be generated by major valence changes of polyvalent anions, including proteins.

References


Propofol-Related Infusion Syndrome and Lactic Acidosis

Propofol is a short-acting, intravenously administered hypnotic agent, unrelated to barbiturates, that is used for induction and maintenance of surgical general anesthesia, outpatient procedures such as colonoscopy, and sedation of mechanically ventilated patients in the intensive care unit. It has many attributes that have made it a very popular drug. Its onset of action and the recovery from its effects are very rapid. Patients do not feel “groggy” after its use and indeed may awake feeling refreshed and with a sense of euphoria. Propofol has neuroprotective effects, including inactivation of GABA receptors and blockade of excitatory neurotransmitters. It reduces cerebral oxygen consumption and intracranial pressure. It also has antioxidant, anti-inflammatory, and bronchodilator properties. However the drug also has a rare but often fatal risk, recently called the propofol related infusion syndrome (PRIS). This was first described in 1992 by Parke et al. (1) in five very critically ill children; all received high doses of the drug. They developed metabolic acidosis (lactic), hyperlipidemia, bradyarrhythmias, and progressive cardiac failure. For several years, it was unclear whether their reaction to propofol marked a truly distinct syndrome because the patients who developed it all were critically ill and there were multiple potential explanations for these findings. However, PRIS is now generally accepted as a true complication of propofol infusion that can occur in both children and adults (2–4). Additional features include rhabdomyolysis, hyperlipidemia, kidney failure, and electrocardiographic (ECG) changes including Brugada symptom—like abnormalities. (Brugada syndrome is an inherited channelopathy that causes a spectrum of ECG abnormalities; the most common characteristic is extreme J-point elevation and a coved ST segment.) Animal studies have shown that propofol may interfere with mitochondrial metabolism, including oxygen utilization, oxidative phosphorylation, fatty acid uptake, and fat oxidation, but the specific defects that cause PRIS in humans remain obscure; some patients may have a genetic predisposition. PRIS is more likely to develop when the drug is used in critically ill patients at doses above 4 mg/kg per hour for longer than 48 hours. When recognized the infusion must be discontinued as soon as possible.

Roberts et al. (5) reported the results of a prospective multicenter study (11 academic medical center intensive care units) of monitoring critically ill adults who were given propofol. In that report, PRIS was defined as metabolic acidosis plus cardiac dysfunction and one or more of the following: rhabdomyolysis, hypertriglyceridemia, or renal failure occurring after initiation of the propofol infusion. Among 1017 patients who received propofol, PRIS developed in 1.1% after an average of 3 days of treatment; 91% of
patients who developed PRIS were receiving vasopressors. Most patients with PRIS in this study survived; the mortality rate of 18% was much lower than reported from previous studies. Children, who have a higher mortality rate with PRIS, were excluded from the study. Fong et al. (6) evaluated presenting characteristics associated with mortality in PRIS. They reviewed all published cases, as well as oral case reports submitted to the Food and Drug Administration’s Medwatch Adverse Event Reporting System Database between 1989 and 2005; information was analyzed using a multivariate logistic regression model. A total of 1139 patients with suspected PRIS were identified, 342 (30%) of whom died. Likelihood of death increased when the patient was male; was ≤18 years of age; required vasopressor use; and/or developed metabolic acidosis, cardiac or renal failure, hypotension, rhabdomyolysis, or dyslipidemia.

References

Toxic Alcohols
Ethylene glycol, the major ingredient in radiator antifreeze, is a widely recognized poison with a well understood pathologic profile and treatment regimen. Recent articles have addressed the effects of two other toxic glycols (glycols are double alcohols, or diols, which contain two hydroxyl groups) that have been underrecognized as causes of metabolic acidosis and reviewed the spectrums of clinical pathology that they generate. Diethylene glycol poisoning was first identified >70 years ago. This clear, colorless, viscous, sweet-tasting solvent has been associated with several major epidemics. The most famous US epidemic occurred in 1937 and is called the “Massengill Incident” (1). The S.E. Massengill Company was one of the early manufacturers of the newly discovered anti-infectious agent sulfanilamide. The company dissolved sulfanilamide in diethylene glycol with raspberry flavoring to create a pleasant-tasting liquid medication that was especially easy to administer to children. During a 2-month period, more than 100 people who ingested this medication died. This episode was the major event leading to the creation of the Federal Food Drug and Cosmetic Act of 1938, a major regulatory, authority-enabling law for the Food and Drug Administration.

Despite documentation of this drug’s lethality, many diethylene glycol poisoning epidemics occurred since the Massengill Incident and continue to occur around the world. In most cases, diethylene glycol has been substituted for glycerin, either accidentally or purposefully by disreputable companies, in the preparation of various medications, toothpastes, etc. A widely publicized epidemic occurred in 2006, when a Chinese pharmaceutical supply company sold diethylene glycol as a “glycerin substitute” to a Panamanian pharmaceutical company that then used the compound to prepare several different cough syrups sold in Panama (2,3). Depending on the source of information, this event caused between 78 and 365 deaths; a much larger number of patients sustained severe and permanent neurologic damage. Of special interest to nephrologists is that many of the victims had underlying diabetes and hypertension and were using the cough syrup to treat a cough related to their use of angiotensin-converting enzyme inhibitors. When an epidemic of severe neurologic dysfunction began, the initial investigation focused on the angiotensin-converting enzyme inhibitors as the possible toxin.

The pathogenic sequence and clinical symptomatic time course generated by diethylene glycol ingestion is similar to what follows ingestion of other, more commonly encountered toxic alcohols. Soon after ingestion, a period of inebriation ensues, with or without gastrointestinal symptoms. Initially, the glycol generates an osmolal gap, but because diethylene glycol is a relatively large molecule, the molar concentration and osmolal gap produced by any given level measured in mg/dl will be less impressive than similar concentrations generated by smaller alcohols, such as methanol. The parent compound is then oxidized, mainly by the enzyme alcohol dehydrogenase, followed by aldehyde dehydrogenase, to a series of highly toxic metabolites.
that include multiple organic acids; the metabolic pathway for diethylene glycol is shown in the Figure 2 from Schep et al. (4).

After oxidation, anion gap metabolic acidosis; acute renal failure; and severe neurologic dysfunction, including peripheral neuropathies, cranial nerve palsies (facial diplegia occurs commonly, in up to 50% of the Panamanian epidemic [5]), and central nervous system dysfunction. Treatment with antagonists of alcohol dehydrogenase, such as fomepizole, should be protective. 

Propylene glycol is a pharmaceutical solvent used to dissolve a variety of intravenous, oral, and topical medications and can be toxic in large doses. It is metabolized to several toxic products including lactic acid (both L- and D-lactate can be generated; see Figure 3). Most cases of propylene glycol poisoning occur when high doses of lorazepam or phenobarbital are used either to treat patients with alcohol withdrawal or to induce a therapeutic coma. Other medications dissolved in this solvent are shown in Table 2 (7). Figure 4 shows the relationship between lorazepam infusion rates and the levels of propylene glycol and the osmolal gap (7). When the osmolal gap exceeds 10 mosmol/L in patients who receive these drugs, toxic propylene glycol levels should be considered (7,8). Propylene glycol is excreted by the kidney, so a reduced GFR will contribute to its accumulation. Case reports of this syndrome continue to appear and recently have emphasized its occurrence in the setting


![Figure 3. The metabolic pathway for propylene glycol.](image)
of therapeutic drug coma (9,10). Zosel et al. (11) recently described the case of an accidental therapeutic overdose with the development of extreme toxicity. The patient was given 2 mg/min lorazepam instead of 2 mg/h. After 10 hours of infusion, the propylene glycol level was 659 mg/dl, the arterial pH was 6.9, serum bicarbonate level was 5 mEq/L, and lactate level was 18.6 mmol/L. Treatment with fomepizole and continuous venovenous hemofiltration led to resolution of the acidosis, and his propylene glycol level fell to 45 mg/dl. Unfortunately, the patient died, but he had sustained severe anoxic brain damage before the medication accident and the fomepizole and continuous venovenous hemofiltration seemed to reverse the metabolic effects of the poisoning effectively. Zar et al. (12) published a review of propylene glycol poisoning, and Kraut and Kurtz (13) published a comprehensive review of the toxic alcohol poisoning syndromes and their treatment.

References

Asthma: Complex Interaction of Respiratory Alkalosis, Metabolic Acidosis, and Respiratory Acidosis

Acute asthma increases respiratory drive and commonly generates respiratory alkalosis. Approximately half of all adult patients hospitalized with severe asthma have respiratory alkalosis (1). If the PCO₂ begins to increase, then this may indicate that
very severe obstruction exists and/or that respiratory muscle fatigue is developing. Overt respiratory acidosis in this setting is an ominous sign that generally indicates that bronchodilator and anti-inflammatory therapy should be intensified and mechanical ventilation considered.

Metabolic acidosis also develops in many patients who are hospitalized for treatment. It is present in 12 to 38% of hospitalized adults and in up to 28% of hospitalized children with asthma (2–4). The metabolic acidosis in these patients is usually due to lactic acidosis (4). There has been increased interest in identifying the cause and clinical significance of this metabolic acidosis (3,4). Multiple factors may contribute to the development of lactic acidosis in these patients, including extreme muscle exertion and fatigue, underperfusion of vascular beds, systemic hypoxia, and reduced hepatic lactate metabolism. Several studies have also proposed that, in some cases, lactic acidosis is caused by overly aggressive treatment with β2-adrenergic agonists and glucocorticoids (3–8). β2-Adrenergic agonists accelerate glycolysis and thereby increase the generation of pyruvic acid. They also increase lipolysis, and the resulting delivery of free fatty acids to hepatic mitochondria reduces mitochondrial uptake and metabolism of the pyruvic acid. These effects combine to increase lactic acid generation and accumulation. Accelerated lipolysis also contributes to ketogenesis, and overt ketoacidosis has been described in some patients who were treated with ketogenesis, and overt ketoacidosis has been described. Accelerated lipolysis also contributes to the development of ketoacidosis in these patients, including extreme muscle exertion and fatigue, underperfusion of vascular beds, systemic hypoxia, and reduced hepatic lactate metabolism. Several studies have also proposed that, in some cases, lactic acidosis is caused by overly aggressive treatment with β2-adrenergic agonists and glucocorticoids (3–8). β2-Adrenergic agonists accelerate glycolysis and thereby increase the generation of pyruvic acid. They also increase lipolysis, and the resulting delivery of free fatty acids to hepatic mitochondria reduces mitochondrial uptake and metabolism of the pyruvic acid. These effects combine to increase lactic acid generation and accumulation. Accelerated lipolysis also contributes to ketogenesis, and overt ketoacidosis has been described in some patients who were treated with β2-adrenergic agonists, especially pregnant women. Glucocorticoids will exacerbate any tendency to hyperglycemia and also contribute to the development of ketoacidosis in some patients.

It is extremely important to recognize the development of metabolic acidosis in these patients because they will compensate with additional hyperventilation and may develop symptomatic air hunger. Sometimes, these findings are mistakenly attributed to worsening reversible airway disease, and this misdiagnosis leads to intensification of the patient’s β2-adrenergic agonist therapy, which is an inappropriate therapeutic response. In fact, the β2-adrenergic agonists may actually be the cause of the metabolic acidosis, and in those cases, the dose should be reduced. Furthermore, Bohn (5) believed that the higher rates of metabolic acidosis that are now recognized in patients with asthma may be the result of overly aggressive therapy with β2-adrenergic agonists and glucocorticoids.

Hyperchloremic metabolic acidosis also occurs in some patients with asthma. Rashid et al. (9) reported that 32 of 109 adults hospitalized with acute asthma exacerbation had an element of hyperchloremic metabolic acidosis. This is more common than anion gap metabolic acidosis, which was seen in only 11 of 109 patients. Why does hyperchloremic acidosis develop in these patients? Most likely, this represents “post hypocapnic” metabolic acidosis. If these patients had been hyperventilating for ≥ 1 day before their admission, as a result of worsening bronchospasm, then they would have compensated for the respiratory alkalosis by reducing their blood HCO3 concentration, simultaneously increasing their blood chloride concentration. In this scenario, after admission and aggressive treatment of their asthma, the respiratory alkalosis would improve or completely resolve, and the patients would be left with a residual “hyperchloremic acidosis.” With time and adequate salt intake, metabolic acidosis would correct as their kidneys excreted NH4Cl. However, it should be noted that in the study by Rashid et al. (9), there is another explanation for the surprisingly high proportion of patients with hyperchloremic acidosis compared with anion gap acidosis. These investigators used a relatively high upper limit of 12 mEq/L for their anion gap normal range; in addition, they did not report albumin levels. If some of the patients had had hypoalbuminemia (and this information were included in the anion gap calculation) and if a lower upper normal limit for the anion gap had been used, then a number of patients with “normal anion gap” metabolic acidosis would instead have been classified as having “elevated anion gap” metabolic acidosis.

Regardless of whether the metabolic acidosis is anion gap (mainly lactic), hyperchloremic, or a combination of both and regardless of the pathophysiologic explanation for the acidosis, another question must be addressed: Does treatment of metabolic acidosis with parenteral sodium bicarbonate have a therapeutic role in these patients with asthma? The benefits of sodium bicarbonate therapy for patients with asthma have been touted for more than 40 years (10). More recently, Buysse et al. (11) published a retrospective, observational study of the use of sodium bicarbonate in 17 children with life-threatening refractory asthma. Virtually all of these patients also had marked respiratory acidosis; the PCO2 was > 70 mmHg in most, and many had PO2 levels > 100 mmHg. A
number of patients who were given sodium bicarbonate demonstrated overall clinical improvement, and most of them showed improvement in PCO2. However, there was no contemporaneous matched control group. The benefit of bicarbonate therapy for patients with severe asthma and metabolic acidosis remains controversial (12).

References

Topiramate and Hyperchloremic Metabolic Acidosis

Topiramate is a drug that is approved to be used as monotherapy or adjunctive therapy for partial-onset seizures and primary generalized tonic-clonic seizures, for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome, and for prophylaxis of migraine headaches. However, it is also very widely used for many “off label” indications. This drug is a carbonic anhydrase inhibitor and therefore produces multiple renal acidification defects, including proximal tubule bicarbonate wasting and impaired distal acidification (carbonic anhydrase inhibition and metabolic acidosis may play a role in the drug’s neurologic therapeutic efficacy as well). Metabolic acidosis reduces urine citrate levels, and this combines with the alkaline urine pH to promote precipitation of calcium phosphate. Soon after acetazolamide was marketed, it was discovered that the drug could lead to calcium phosphate stones and intrarenal calcium phosphate precipitates (1). This adverse effect has been seen with virtually all carbonic anhydrase inhibitors, and topiramate is no exception. The risk for kidney stones is approximately 2 to 4 times that expected in the background population (2). Welch et al. (3) evaluated urine stone risk chemistry profiles of 32 patients who were taking topiramate and also evaluated these parameters before and after treatment with topiramate in seven patients. Serum bicarbonate levels were lower in those on topiramate, and their urinary pH, absolute bicarbonate excretion rate, and fractional excretion of bicarbonate all were higher than in the control group. Urinary citrate excretion was reduced to 278 ± 226 compared with 737 ± 329 mg/d in the control group, and the relative saturation ratio for brushite (calcium phosphate) doubled compared with the control group (3). Certain populations will have even higher risk; for example, nonambulatory patients who take the drug are very likely to form stones because it develops in more than half of these individuals (4). Also, the simultaneous use of a ketogenic diet, which itself is also lithogenic, with topiramate will generate an increased risk for developing urine stones (5). Other recently introduced antiseizure drugs, such as Zonisamide, are also carbonic anhydrase inhibitors and would be expected to have a similar effect on urine calcification tendency (6). Vega et al. (7) reviewed the increased propensity for calcium phosphate kidney stones caused by topiramate.

The hyperchloremic metabolic acidosis generated by topiramate and all carbonic anhydrase inhibitors will cause compensatory hyperventilation. This is usually asymptomatic but sometimes produces a sensation of dyspnea. Some patients will present with this as their chief complaint (8,9), and it is important to remember this possibility when patients who use this drug complain of dyspnea. Massive topiramate overdose also generates severe hyperchloremic metabolic acidosis, which resolves over several days (10,11).

References


Acquired Forms of Metabolic Alkalosis

Metabolic Alkalosis: The Milk Alkali Syndrome (Calcium Alkali Syndrome)

In 1915, Sippy (1) introduced a new regimen, later named for him, to treat peptic ulcer disease that included an hourly diet of milk and cream, as well as eggs and cereals, combined with the ingestion of large amounts of three antacids: Sodium bicarbonate, magnesium carbonate, and bismuth subcarbonate (“Sippy Powders”). The “Sippy Regimen” proved to be very effective, but within a decade, a spectrum of toxic manifestations, which included metabolic alkalosis, were described (2).

In 1936, Cope (3) described what is now called the
acute milk alkali syndrome. The findings included hypercalcemia, hyperphosphatemia, hypermagnesemia, increased bicarbonate levels, and kidney damage; abnormalities usually resolved with discontinuation of the Sippy Regimen. In 1949, Burnett et al. (4) described a more chronic and persistent form of the same disease process.

The introduction of histamine 2 receptor blockers (1976) and proton pump inhibitors (1989) to block acid secretion, as well as treatments directed at eradicating Helicobacter pylori eliminated the use of the Sippy Regimen and its subsequent antacid modifications. It was believed that the milk-alkali syndrome had become a disease of purely historical interest, but a modern variant of this disorder has returned with a vengeance.

Patel and Goldfarb (5) recently reviewed the pathophysiology of the more recent disorder and proposed that we call the current version of milk-alkali syndrome “calcium-alkali syndrome” because it is now rarely associated with the ingestion of large amounts of milk and other dairy products. Instead, it is generated by the ingestion of large amounts of calcium carbonate, sometimes together with vitamin D and occasionally with thiazide diuretics; these drugs are often used for osteoporosis therapy or prevention. The syndrome is now the third leading cause of hypercalcemia in hospitalized patients (after hyperparathyroidism and malignancy) and is often responsible for severe levels of hypercalcemia (6).

There are some important differences between the historical classic varieties of milk-alkali syndrome and the modern form of calcium-alkali syndrome. First, hyperphosphatemia was very common with the original disorders (because kidney dysfunction was combined with large phosphorus loads from dairy products) but is much less common now because of the lower oral phosphorous load and the phosphorous-binding capacity of calcium carbonate. Second, although ingestion of calcium is excessive in all forms of the syndrome, calcium carbonate does not provide nearly as much absorbable base as sodium bicarbonate and perhaps less than the magnesium and bismuth salts used in the past. Consequently, the degree of alkalosis is now moderate unless vomiting has developed. Third, vitamin D supplementation is now common and contributes to the spectrum of pathology, especially hypercalcemia.

Hypercalcemia, metabolic alkalosis, and renal insufficiency have complex interactions that may synergize and reinforce the severity of each disorder. Hypercalcemia causes renal vasoconstriction and interstitial damage, contributing to the renal dysfunction. Hypercalcemia also has complex systemic and renal acid-base effects, likely directly increasing renal proton secretion and, to the extent that parathyroid hormone is suppressed, increasing renal bicarbonate reabsorption. Metabolic alkalosis also has complex effects on calcium metabolism and increases renal tubule calcium reabsorption (7). Reduced renal function will blunt the patient’s ability to excrete both calcium and bicarbonate.

In recent years, our understanding of this complex syndrome has been enhanced by integrating the roles of the calcium-sensing receptor (CaSR) and the calcium selective channel called transport transient receptor potential vanilloid member 5 (TRPV5). In the thick ascending loop of Henle, the CaSR is present primarily on the basolateral cell membrane. When these receptors are activated by high blood calcium levels, they reduce the open state of the renal outer medullary kidney (ROMK) channel on the apical membrane, which acts to blunt activity of the Na-K-Cl co-transporter (NKCC) on the apical membrane (8). CaSR activation may also directly reduce NKCC activity. Therefore, hypercalcemia generates a loop diuretic–like effect that increases sodium and calcium delivery out of the thick limb and blunts the kidney’s concentrating capacity. Further down the length of the tubule, in the distal convolution, activation of apical CaSR by high urine calcium levels increases calcium reabsorption via TRVP5 channels (9). In the collecting duct, high urine calcium levels then activate CaSR on the apical membrane, and in these tubule segments, CaSR activation reduces expression of aquaporin 2 water channels. This reduces water reabsorption and causes excretion of more dilute urine (10). In addition, CaSR activation at this site stimulates proton secretion via H-ATPase (11). In summary, the net effect of hypercalcemia on these various renal CaSRs leads to a loop diuretic–like effect in the thick ascending limb of Henle, which acts to increase urine calcium and sodium excretion. Some moderation of the hypercalciuria occurs in the distal tubule via stimulation of TRVP5-mediated calcium reabsorption and, further down the tubule, dilution and acidification of the urine, should reduce the likelihood of precipitation of calcium salts, especially calcium phosphate. Finally,
all of these renal CaSR effects are enhanced by systemic metabolic alkalosis, which clearly increases the sensitivity of the CaSR and the activity of the TRPV5 channel (12). Much of this new information is derived from animal studies and from cell/tissue preparations. We still must determine its relevance to intact humans with this disease process (13). The fascinating interaction of these complex systems both under physiologic conditions and in response to pathophysiologic disorders such as the milk-alkali (or calcium-alkali) syndrome continue to be elucidated. Figure 5 shows the current understanding of the interplay of blood and urine calcium, systemic alkalosis, and urine bicarbonate on renal tubule calcium transport.

**Pseudo-Bartter (or Bartter-Like) Syndrome**

Many hereditary and acquired disorders bear some similarity to Bartter syndrome. In some cases, the similarities may be very close (e.g., continuous surreptitious loop diuretic use) whereas others may be less so. Treatment with aminoglycosides sometimes generates a renal tubule disorder syndrome that mimics Bartter syndrome. These drugs have many toxic renal effects, but this unusual complication results from the fact that the CaSR can be stimulated by these antibiotics. The result of this stimulation in the thick ascending limb of Henle is inhibition of the ROMK channel on the apical membrane and perhaps the NKCC co-transporter (see previous section - The Milk Alkali Syndrome [Calcium Alkali Syndrome]). As discussed, this generates a furosemide-like effect causing NaCl diuresis, a less positive electrical charge in the lumen and reduced calcium and magnesium reabsorption via the paracellular pathway. The clinical picture is very similar to that seen when inherited Bartter-like syndrome is due to a gain-of-function mutation of the CaSR (14). Chen et al. (15) recently reported a case of pseudo-Bartter syndrome caused by gentamicin and reviewed the literature. Other, similar cases have been previously reported (16). This syndrome was also recently described in a patient receiving another aminoglycoside antibiotic, amikacin (17).

**Mixed Metabolic Alkalosis and Respiratory Acidosis: Role for Acetazolamide?**

When metabolic alkalosis develops in the intensive care unit, it is usually due to nasogastric suction or diuretic therapy. With gastric drainage, the metabolic alkalosis is obviously generated by removal of gastric HCl and is then maintained primarily by intravascular volume contraction with a contribution from the potassium depletion that almost always develops. Gastric alkalosis is usually readily corrected with intravenous saline and potassium salts, which expand effective intravascular volume and allow the kidney to excrete the excess bicarbonate. In other patients, the metabolic alkalosis may be generated by the aggressive use of diuretics, mainly loop diuretics or combinations of loop and thiazide diuretics. In this disorder, the kidney is the site of bicarbonate generation, and, again, effective intra-arterial volume contraction is the reason the metabolic alkalosis is maintained. Volume expansion with intravenous isotonic saline is usually contraindicated (these patients usually have been given the diuretics because of clinical evidence of volume overload) or would be ineffective, as in patients with hepatic cirrhosis, heart failure, etc. It is not uncommon for these forms of metabolic alkalosis to be
superimposed on chronic respiratory acidosis. Patients with chronic respiratory acidosis should already have a high blood bicarbonate concentration as a result of metabolic compensation. This mixed disorder exists when the bicarbonate level is “too high” for the coexistent PCO₂ level; this may occur when patients with chronic respiratory acidosis require gastric drainage or diuresis. The use of steroids, which have some mineralocorticoid effect, can contribute to this mixed disorder. Bicarbonate loads from anticoagulated (with sodium citrate) blood products may be another alkali source. Furthermore, when patients with chronic respiratory acidosis require artificial ventilation, they often develop a “post-hypercapnic” metabolic alkalosis. In these cases, PCO₂ is reduced by the ventilator, but the serum bicarbonate level remains at its previously appropriate high level, which is now too high. Should these various forms of metabolic alkalosis be aggressively corrected, and, if so, does such correction help the patient’s overall clinical status? It has been taught that the development of metabolic alkalosis in patients with chronic respiratory acidosis raises the blood pH to levels that may further depress respiratory drive and thereby promote higher PCO₂ levels. This mixed disorder may also make it more difficult to wean these patients from mechanical ventilation.

Banga and Khilnani (18) recently confirmed this impression in a retrospective study of 84 patients who had chronic obstructive pulmonary disease and required mechanical ventilation. Twenty percent of these patients developed posthypercapnic metabolic alkalosis. Glucocorticoid use for ≥10 days was an independent risk factor for this complication. These patients had increased ventilator dependence (64.7 versus 37.3%) and a longer intensive care unit stay (14.7 ± 6.7 versus 9.5 ± 5.9 days). Consequently, common wisdom is that metabolic alkalosis in this group of critically ill patients should be aggressively corrected. This can most readily be accomplished with volume expansion when that maneuver is indicated and kidney function is adequate. It is also possible to correct the alkalosis by administering strong acid or acid precursors, such as intravenous HCl or enteral NH₄Cl. If additional diuresis is required, then the use of acetazolamide will produce a brisk bicarbonate diuresis (if kidney function is adequate). A number of studies have confirmed many of these clinical impressions (19–23). Those reports suggest that such therapy improves gas exchange, and PCO₂ levels usually fall.

However, Faisy et al. (24) could not confirm this impression. They treated 26 mechanically ventilated patients who had chronic obstructive pulmonary disease and this mixed acid-base disorder (serum bicarbonate >26 mmol/L and arterial pH ≥7.38) with acetazolamide 500 mg intravenously. Unfortunately, they did not have a contemporaneous control group and instead compared their results with a historical control group matched for serum bicarbonate, arterial pH, age, and severity of illness. The bicarbonate concentration fell as expected after acetazolamide treatment. They could not demonstrate any reduction in the length of the weaning period or a statistical improvement in extubation success compared with the historical control. The lack of a contemporaneous control group and the small group size weaken these conclusions. Furthermore, the metabolic alkalosis component of this mixed disorder was mild (blood bicarbonate averaged 34 mEq/L), and this was reduced only to 31.5 mEq/L by the time of extubation. It still seems very reasonable to treat the metabolic component of this mixed disorder, especially when the metabolic alkalosis is severe. If diuresis is required, then acetazolamide is appropriate, although it must be emphasized that this diuretic causes brisk potassium excretion, as well as a sodium bicarbonate diuresis. Usually, aggressive potassium replacement is necessary.

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Metabolic Alkalosis (Pseudo-Bartter Syndrome) in Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive, often fatal disease. In Caucasian populations, it occurs at a rate of approximately one in 3000 live births and is less common in Hispanic, African-American, and Asian populations. The genetic defect results in abnormal synthesis, transport, and/or function of the cystic fibrosis transmembrane regulator (CFTR). This is a regulated chloride channel that also modulates other epithelial ion channels. Although CF is usually diagnosed in childhood, milder forms are increasingly recognized in adult patients who often have nonclas-

cical presentations. It has been known for many decades that children with CF can become severely volume depleted during hot summer months as a result of excessive loss of NaCl in sweat. This early observation was a major clue leading to the development of the sweat chloride test for diagnosis of this disease. Children with known CF may develop what has been called “pseudo-Bartter syndrome” from environmental heat exposure. Yalcino et al. (1) reported that 12% of 241 children with CF developed this disorder. During one particularly hot 2-week period in August, nine such patients were admitted to a pediatric unit in Ankara, Turkey (2). Occasionally, pseudo-Bartter syndrome is the presenting symptom complex in young children.

Adults with known CF can also develop severe hyponatremia, hypokalemia, and metabolic alkalosis when exposed to a hot environment and again these findings may also be their initial presenting symptom complex (3). Smith et al. (4) described this presentation in 1995 but emphasized only the hyponatremia, hypokalemia, and volume contraction. Although it is likely that this patient also had marked metabolic alkalosis, acid-base data were not included in that brief report. Bates et al. (5) described a 17-year-old boy whose presenting findings were metabolic alkalosis, hypokalemia, azotemia, and modest hyponatremia. Several other, similar adult cases have been reported (6,7), and Priou-Guesdon et al. (8) recently reported this presentation in three adults.

It seems obvious why these patients would be predisposed to salt and volume depletion. They lose high concentrations of NaCl in their sweat, so large-volume sweating on a hot day can generate hypovolemia and, when extreme, cardiovascular collapse. The sweat also contains relatively high K⁺ concentrations to account for hypokalemia. If the patients drink water, it will be retained as a result of reduced renal function and high ADH levels and generate hyponatremia. They will also develop secondary hyperaldosteronism. All of these factors will reduce renal excretion of bicarbonate and thereby contribute to maintenance of the metabolic alkalosis. But why do these patients develop metabolic alkalosis? Where is the generation site of the bicarbonate? Although some invoked secondary hyperaldosteronism as the generation mechanism, this cannot be the explanation unless some other factor increases the distal tubule delivery of NaCl in the face of overt extracellular fluid volume contrac-
tion. Bates et al. (5) suggested that the CFTR mutation may impair both proximal and distal renal tubule NaCl reabsorption in some patients. If that occurs, then a renal origin for the alkalosis becomes plausible. However, a gastric origin for bicarbonate generation is much more likely because almost all of the cases reported with this syndrome have vomiting as a prominent feature. To the extent that occurs, it will worsen the volume contraction, generate bicarbonate, and increase renal potassium excretion. Once generated, the metabolic alkalosis would be maintained as a result of the factors described already. Although this syndrome is sometimes called pseudo-Bartter syndrome, the urine chloride concentration should readily distinguish between true Bartter syndrome (high) and this disorder (low).

When adults present with otherwise unexplained metabolic alkalosis and signs and findings consistent with volume contraction, consider the possibility of a mild form of CF. This presentation is much more common during heat waves. Hyponatremia also commonly occurs.

References

Pendred Syndrome: Pendrin (SLC26A4) Defects
The term “pendrin” is derived from a disease described in 1896 by Vaughan Pendred. Pendred observed a relationship among congenital bilateral deafness, goiter, and hypothyroidism, which was later dubbed Pendred syndrome (1). This was subsequently found to be caused by an autosomal recessive disorder linked to mutations on chromosome 7. Next, it was discovered that the affected gene directed the synthesis of the SLC26A4 transporter, later named pendrin. This neutral anion exchanger is present in the cochlea, the thyroid (where it functions mainly as a chloride/iodide exchanger), and the cortical collecting tubule of the kidney (mainly in intercalated cells) (2).

Intercalated cells are a family of proton-secreting cells located in the late distal convoluted tubule, the connecting tubule, and the collecting duct. All intercalated cells use carbonic anhydrase II (CA-II) to catalyze the generation of bicarbonate and protons from CO2 and H2O, and they all express V-type H+–ATPase pumps to secrete the protons. The vectorial directions in which the proton is pumped and the bicarbonate exits determine whether the intercalated cell is acid secreting (a type A intercalated cell), base secreting (a type B intercalated cell), or acid-base neutral (a non–type A/non–type B intercalated cell). See figure 6. The V-type H+–ATPases may be located on either the luminal membrane (in type A cells and in non–type A/non–type B cells) or the basolateral membrane (type B cells). The bicarbonate exit step occurs via one of several anion exchangers. The two best characterized are anion exchanger 1 (AE1), a member of the SLC4 (solute carrier family 4) transporter family, and “pendrin,” which is the common name for SLC26A4 (the A4 member of solute carrier family 26) (3). Although these two anion exchangers seemingly serve the same function in opposite membranes of the intercalated cell (they each exchange one bicarbonate ion for one chloride ion), they are distinctively different proteins. AE1 is present in type A intercalated cells, whereas pendrin is present in both type B intercalated cells and non–type A/non–type B intercalated cells. ATP-energized proton secretion is what drives the bicarbonate/chloride exchangers in each of these cells. Note that the secretion of both the proton and bicarbonate ion into the lumen by the non–type A/non–type B intercalated cells is acid-base neutral. However, a chloride ion is reabsorbed from the lumen. The relative density and activity of each of these intercalated cells are probably modulated by the patient’s acid-base status and avidity of renal chloride reabsorption.
Three types of intercalated cells are shown. They are expressed from the late distal convoluted tubule to the initial third of the inner medullary collecting duct. In all intercalated cells HCO₃⁻ and H⁺ are produced from CO₂ and H₂O catalyzed by the enzyme carbonic anhydrase II. Type A intercalated cells secrete H⁺ across the apical (luminal) membrane mainly via V-type H⁺-ATPase. The apical membrane also expresses H⁺/K⁺-ATPase, which may function mainly to reclaim potassium when potassium deficiency occurs. The basolateral (interstitial) membrane transporters include the anion exchanger AE-1, which is a HCO₃⁻/Cl⁻ exchanger and the KCC4 KCl co-transporters that may have an important role in the maintenance of low intracellular chloride concentrations. Type B intercalated cells express the pendrin HCO₃⁻/Cl⁻ exchanger on the apical membrane and V-type H⁺-ATPase on the basolateral membrane. The net effect of ion transport by these two processes results in HCO₃⁻ secretion and Cl⁻ reabsorption (i.e., HCl addition to the interstitium). Non–type A/non–type B intercalated cells also have the pendrin HCO₃⁻/Cl⁻ exchanger on the apical membrane. However, in these cells, the V-type H⁺-ATPase is also inserted in the apical membrane instead of the basolateral membrane as in the type B intercalated cells. Consequently, both H⁺ and HCO₃⁻ are secreted into the lumen. No net acid-base secretion or absorption occurs, but chloride is reabsorbed from the lumen. The chloride exits the cell into the interstitium through chloride channels consisting of CIC-kb and Barttin subunits. Type-A intercalated cells are found from the late distal convoluted tubule to the initial portion of the inner medullary collecting duct. In contrast, the type B intercalated cells and the non–type-A/non–type-B intercalated cells are mainly expressed in the distal convoluted tubule and the connecting tubule. Adapted from reference 3 (with kind permission from Springer Science+Business Media Wagner, CA, Devuyst O, Bourgeois S, Mohebbi N: Regulated acid-base transport in the collecting duct. Pflugers Arch 458: 137–156, 2009).
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In mice, the abundance of this protein increases with alkalosis and decreases with acidosis (4). In vitro experiments show that the collecting ducts of mice with pendrin gene knockout cannot secrete bicarbonate (5).

Despite this bicarbonate secretory defect, patients with Pendred syndrome generally do not manifest any kidney or acid-base disorder. However, we would expect these patients to be more susceptible to the development of severe metabolic alkalosis. Indeed, Pela et al. (6) described a child who had Pendred syndrome and developed severe metabolic alkalosis when treated with thiazide diuretics. We are just beginning to understand how the pendrin exchanger normally contributes to salt, volume, and BP regulation. Aldosterone probably increases pendrin activity, which increases to the chloride reabsorption that must accompany sodium reabsorption. Pendrin activity is required for up-regulation of epithelial sodium channel (7).

Pendrin is a chloride/bicarbonate exchanger on the luminal membrane of type B and non-type A/non-type B intercalated cells. In type B intercalated cells, it plays an important role in net bicarbonate secretion. In non-type A/non-type B intercalated cells, both protons and bicarbonate are secreted into the lumen. Hence, there is no net acid or base secretion. However, chloride is reabsorbed.

General Principles

Hypokalemia

Hypokalemia, generally defined as plasma potassium (K+) <3.5 mEq/L, is usually caused by the loss of K+ from the body. Less commonly, it is the result of a redistribution of K+ from the extracellular fluid space to the intracellular space. It may have major cardiovascular, neuromuscular, renal, and/or metabolic consequences.

The physiology of K+ transport and its implications in hypokalemic disorders has been well reviewed in a previous issue of NephSAP devoted to fluid, electrolyte, and acid-base disturbances (1), so the reader is referred to that review for general information. Regarding new discoveries in K+ physiology that have occurred in the past few years, they are discussed in the context of specific clinical syndromes when relevant; more in-depth information is available in several excellent recent reviews (2–5).

Inherited Forms of Hypokalemia

A number of transport mechanisms are responsible for maintaining the distribution of potassium (K+) between the intracellular fluid and extracellular fluid (ECF) spaces and for regulating K+ excretion via the kidney and gastrointestinal tract. Of greatest importance is energy utilizing Na+–K+–ATPase, a transport protein that moves K+ into cells and Na+ out of cells. Also of critical importance are several families of K+ channels. K+ channels are membrane-spanning proteins that create water-filled permeation pores through which K+ can be selectively transferred across the cell membrane; K+ always flows through these channels down its electrochemical gradient. Many different K+ channels have been identified and characterized; they have various gating mechanisms that switch the channels into open or closed confor-
mations and different rates of $K^+$ transit. The open versus closed probability of various $K^+$ channels is a critically important determinant of a cell’s resting transmembrane voltage. Sometimes, even when an identical electrochemical gradient for $K^+$ is artificially created, the ion can flow more readily in one direction versus the other. Channels with this property are called “rectified.” The rectification can be either inward or outward, depending on whether the flow of the ion, in this case $K^+$, is more rapid going into or out of the cell. One of the best characterized rectified $K^+$ channels is the renal outer medullary kidney channel (ROMK channel). The physiology and pathophysiology of renal $K^+$ channels were reviewed by the Yale group (1,2).

**Familial Hypokalemic Periodic Paralysis**

Hypokalemic periodic paralysis (HypoKPP) is an autosomal dominant disorder that is transmitted with incomplete penetrance. Patients with this disease develop episodes of flaccid paralysis associated with marked hypokalemia. The prevalence of HypoKPP is thought to be approximately one in 100,000. Although inherited as an autosomal dominant genetic disease, it occurs more frequently and is more severe in men, in whom the symptoms often develop during the first 2 decades of life. When symptoms of the disease develop in women, they are generally milder and usually begin later in life. The paralytic attacks often occur during the night or in the early morning hours but can also be precipitated by strenuous exercise (in this case, developing after the actual period of exercise); the ingestion of carbohydrate-rich meals; cold exposure; or the administration of glucose, insulin, or glucocorticoids. Each of these stimuli or factors may generate an intracellular $K^+$ shift. Paraparesis or tetraparesis may develop. Although respiratory and cardiac muscles are generally spared, profound hypokalemia may result in respiratory muscle weakness and cardiac arrhythmias. A discrete attack may last hours to days. In addition, a chronic myopathic form of HypoKPP develops in approximately one quarter of affected individuals and can result in progressive fixed muscle weakness.

The initial search for the genetic molecular mechanism responsible for this disease obviously focused on $K^+$ channels and other $K^+$ transport mutations. Therefore, it was surprising when familial genetic analyses instead identified the most common mutation to be in a gene coding for a muscle calcium channel. This is found in 50 to 70% of patients with HypoKPP. The second most common mutation, occurring in approximately 10% of patients with HypoKPP, is in a gene coding for a muscle sodium channel. The affected calcium channel gene, CACNA1S (more specifically, the affected gene codes for the $\alpha_1$ subunit of the dihydropyridine-sensitive voltage-gated $Ca^{2+}$ channel), and affected sodium channel gene, SCN4A (more specifically the affected gene codes for the $\alpha$ subunit of the tetrodotoxin-sensitive voltage-gated $Na^+$ channel), direct the synthesis of critical components of their respective sarcolemmal ion channels. These two channels (Cav1.1 and Nav1.4 is the nomenclature used to identify the channel proteins) have a great deal of molecular homology and may have evolved from a common precursor gene. Each of these channels is “voltage gated,” meaning that they open and close in response to changes in the intracellular electrical charge generated by cellular polarization or depolarization events. How does a change in a cell’s internal electrical charge affect the permeation characteristics of a channel, and how does the mutation alter the channel properties? The answers to these questions were explored in a recent article by Matthews et al. (3); Figures 7 and 8 shows the proposed...
structure of the two implicated ion channels. The α1
subunits of each of these channels have four repeated
discrete domains, and each of the domains is com-
posed of six helical transmembrane segments. The
fourth segment (S4) of each domain is comprised of
many charged amino acids with every third one being an
arginine or lysine. These multiple arginine or lysine
moieties will either release or accept a proton in response
to changes in cell charge and/or pH. These ionic alter-
ations cause the S4 segments to physically change
shape and move in response to the cell voltage
changes. These movements and shape changes mod-
ify the permeability characteristics of the channel.
Therefore, these S4 segments are now considered
the “voltage sensors” of these channels.

It has been determined that virtually all of the
mutations responsible for HypoKPP result in the re-
placement of one of the arginine molecules in the S4
segment by a less charged, or neutral, amino acid.
Consequently, these mutations alter the way these
muscle cell Ca\(^\text{2+}\) (or Na\(^\text{+}\)) voltage gated channels
respond to muscle cell depolarization–repolarization
cycles. This new information affords a better under-
standing of how the gene defects discovered in pa-
tients with this disorder result in the characteristic
paralytic episodes. Although we now have a much
better understanding of why the muscles become par-
alyzed, it remains unknown why the paralytic attacks
are associated with profound hypokalemia.

Acetazolamide is a carbonic anhydrase inhibitor
that generates metabolic acidosis and hypokalemia as
a result of NaHCO\(_3\) diuresis and secondary hyperal-
dosteronism. This drug was first empirically used to
treat patients with hyperkalemic periodic paralysis,
and it was found to be effective in these patients (4).
Because it generates hypokalemia, its potential effi-
cacy for hyperkalemic conditions seems apparent.
Similarly, its use in patients with HypoKPP seems to
be counterintuitive. Nonetheless, it was tried in these
patients and again found to be extremely effective; acetazolamide is now recognized as one of the most
effective prophylactic drugs for patients with Hypo-
KPP. Not only does it reduce the frequency and
severity of acute paralytic attacks, but it also improves
the muscle strength of these patients between attacks
(5,6). However, not all patients with HypoKPP re-
spond. How does acetazolamide work in this disease?
Do the recent genetic/molecular discoveries help ex-
plain this drug’s efficacy in some patients but not
others? It is likely that acetazolamide’s efficacy is
primarily related to the chronic metabolic acidosis
generated by the drug. Acidosis causes movement of
protons into muscle cells, and this seems to ameliorate
the disease process; inhibition of carbonic anhydrase
within the muscle cells may also play a role (7). What
is clear is that patients with calcium channel mutations
respond to acetazolamide therapy much more reliably
than do those with a mutated sodium channel (7).
Indeed, some patients with the sodium channel muta-
tions become worse when treated with acetazolamide.

It has been suggested that a high-K\(^{+}\), low-Na\(^{+}\),
and low-carbohydrate diet may alleviate the symptoms
of HypoKPP and reduce the frequency of attacks. If
attacks occur at a specific time, such as during sleep or
early morning, then bedtime prophylactic doses of oral
KCl may prove helpful. The acute paralytic attacks are
treated with oral or parenteral potassium salts. This
certainly increases the plasma K\(^{+}\) concentration but
often may improve the muscle weakness only to a
small degree. The recommended oral K\(^{+}\) dosage for
acute attacks is approximately 0.2 to 0.4 mmol/kg
every 15 to 30 minutes over several hours. If the
patient cannot be treated with oral potassium, then
KCl can be given intravenously. It is recommended
that 20 to 40 mEq of KCl be diluted in 1 L of 5%
mannitol but not in 5% dextrose (8). Infusion of dextrose can shift additional K⁺ into cells and presumably worsen the paralytic attack. In addition, it is critical to remember that the hypokalemia in HypoKPP is entirely generated by a shift of K⁺ from the ECF into cells. Therefore, significant risk is associated with the administration of large amounts of exogenous potassium because there is no true total body potassium deficit. The administration of KCl must be stopped when the serum potassium concentration approaches normal, even if muscle weakness persists. Cases of fatal hyperkalemia after treatment of hypokalemic periodic paralysis continue to be reported both with this disease and with the related disorder of thyrotoxic hypokalemic periodic paralysis (9).

The most common cause of familial hypokalemic periodic paralysis is a mutation in the α1-subunit of the dihydropyridine-sensitive voltage-gated Ca²⁺ channel Cav1.1. The mutations reduce the number of positively charged (arginine or lysine) amino acids which are critically important for response to voltage changes – they are part of the channel’s “voltage sensor.”

**Thyrotoxic Hypokalemic Periodic Paralysis**

Thyrotoxic hypokalemic periodic paralysis is much more common than the inherited forms of HypoKPP. By definition, this form of hypokalemic periodic flaccid paralysis always occurs in patients with hyperthyroidism and is eliminated (cured) when the thyroid disease is effectively treated. It is a very common disorder in Asian men who develop hyperthyroidism (approximately 10% of Asian men with hyperthyroidism are thus affected) and is also relatively common in hyperthyroid Latin American men. It occurs in approximately 0.1% of American Caucasian men with hyperthyroidism. A genetic component has been strongly suspected in view of the differential incidence in these various ethnic groups. The emergency treatment of the acute paralytic attacks is identical to that described for HypoKPP, plus β-adrenergic blockade is used to antagonize the sympathetic drive generated by hyperthyroidism. Of course, definitive therapy requires reestablishment of a euthyroid state. In view of the strong clinical similarity with HypoKPP, once investigators recognized the molecular etiology of that disease, they evaluated the calcium channel gene CACNA1S and sodium channel gene SCN4A of patients with thyrotoxic hypokalemic periodic paralysis for mutations (10); however, none were identified.

Recently, Ryan et al. (11) reported mutations in a gene that codes for a newly described muscle K⁺ channel. This muscle cell K⁺ channel is another inwardly rectifying channel (Kir 2.6) that, very interestingly, has a thyroid hormone response element in its promoter region. Therefore, thyroid hormone would normally be expected to “turn on” this gene. Ryan et al. discovered that this gene was mutated in approximately one third of Caucasian patients with thyrotoxic hypokalemic periodic paralysis. A variety of different missense, frameshift, and stop codon mutations of this gene were identified in various patients. When this gene was probed in Asian patients with thyrotoxic hypokalemic periodic paralysis, mutations were identified in seven of 27 patients from Singapore but in only one of 83 patients from Hong Kong and none of 31 patients from Thailand. Clearly, a variety of mutations and genes must be involved in this disorder, and their frequency must vary in different ethnic populations. Venance et al. (12) reviewed the diagnosis, pathogenesis, and treatment of all of the periodic paralysis syndromes.

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Acquired Forms of Hypokalemia

Acetaminophen Poisoning

Several recent reports have described a very high frequency of hypokalemia among patients who are admitted for treatment of acute acetaminophen poisoning (1–5). The fall in serum K⁺ is clearly related to the severity of the acetaminophen poisoning and to the presenting acetaminophen level (1,5). Hypokalemia develops in up to 80% of those with severe poisoning. Of note, the K⁺ concentration is often normal or only slightly reduced at the time of admission and then falls during the first day of hospitalization. This sequence was highlighted by a recent report of two teenage girls who attempted suicide with acetaminophen poisoning. Their K⁺ concentrations were 3.9 and 3.2 mEq/L at admission and fell to 2.3 and 2.6 mEq/L, respectively, within the first 30 hours of hospitalization (3). Although multiple factors may contribute, including vomiting, the administration of intravenous dextrose and hyperpertention, none of them can completely account for the development of hypokalemia. Pakravan et al. (5) reported that the change in serum K⁺ at 4 hours and the severity of hypokalemia at 24 hours both were correlated with the serum acetaminophen level at 4 hours after admission. In addition, they found that the renal fractional excretion of K⁺ was increased at 4 and 12 hours to approximately 16% despite the sharp fall in serum K⁺ and that the renal K⁺ excretion fell sharply by 24 hours. The transtubular potassium gradient (TTKG) was also increased at 4 and 12 hours and correlated with the initial acetaminophen level; it fell sharply at 24 hours after admission. Increased renal fractional K⁺ excretion, with a similar time course, has been reported in a rat model of acetaminophen toxicity (6).

Increased renal fractional excretion of K⁺ has also been reported in patients on the day of admission for ibuprofen poisoning (7). In that study, the admission ibuprofen level also correlated with increased fractional K⁺ excretion (7). It remains unclear whether inappropriate renal potassium loss after these drugs is the result of renal tubule toxicity or is hormonally driven. In many aspects, these findings of inappropriate kaliuresis parallel those of inappropriate phosphaturia and hypophosphatemia after acetaminophen poisoning (8). The study by Pakravan et al. also reported that acetaminophen levels 4 hours after admission correlated with a fall in the renal tubular maximum reabsorption of phosphate, or TmPO₄/GFR.

Of note, phosphaturia and hypophosphatemia have been shown to be associated with a better prognosis after acetaminophen poisoning (9). Perhaps the sickest patients present to hospital with lactic acidosis and/or an acute fall in GFR. These complications could raise serum phosphate levels and reduce phosphate excretion. Impressive, self-resolving hypophosphatemia as a result of renal phosphate excretion has also been well described in the immediate postoperative period after patients undergo partial hepatic resection (10,11). Although it would be attractive to invoke increased levels of a phosphatonin or parathyroid hormone as the cause, recent studies were not consistent with that hypothesis (11). The possible mechanism responsible for phosphaturia after acetaminophen poisoning has not been defined.

Hypokalemia occurs commonly after severe acetaminophen poisoning and is in large part the result of inappropriate kaliuresis. This may be the result of acetaminophen-related tubule toxicity.

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High-Dosage Penicillin, Hypokalemia, and Metabolic Alkalosis

The use of massive doses of penicillin in the 1960s led to the recognition that sodium penicillin delivers a large sodium load and that the penicillin molecule can act as a “poorly absorbed” anion in the distal renal tubule. Under certain conditions, this can generate inappropriate kaliuresis and renal acid excretion as well as an osmotic diuresis. Brunner and Frick (1) reported a series of such patients who developed hypernatremia, hypokalemia, and metabolic alkalosis (the most extreme case developed Na of 165, K of 2.0, and HCO₃ of 37). These patients were receiving 100 “mega” units (100 million units) of penicillin each day, which delivered 170 mEq of sodium. Subsequentlv, similar electrolyte abnormalities were re-
ported in patients who were given high-dosage car-
benicillin (2,3). Again, the sodium and penicillin-like anion loads were enormous. For example, 30 to 60 g/d carbenicillin provides 4.7 mEq Na/g = 141 to 282 mEq/d Na and carbenicillin. Lippner et al. (4) published in vivo and in vitro animal studies (rats and toad bladders) that were entirely consistent with the “poorly absorbed anion” mechanism. In subsequent years, hypokalemia and metabolic alkalosis have been reported in patients who were given a number of other penicil-
lin derivatives, including ticarcillin, oxacillin, dicloxa-
cillin, flucloxacillin, and, most recently, meropenem (5–11).

Although the same mechanisms are sometimes invoked, it is unlikely that this explanation is correct. Meropenem, for example, delivers approximately 4 mEq Na/g of antibiotic. Therefore, even a large meropenem dose of 3 g/d will provide only 12 mEq of Na-Meropenem, probably far too little to generate hypokalemia via the mechanism described above. Other mechanisms must contribute when hypokalemia and/or metabolic alkalosis develops in patients who are treated with the lower doses generally used with current penicillin derivatives. This point is further emphasized in the case reported by Hoorn and Zietse (7). Their patient received 12 g/d ticarcillin (approximately 26 mEq/d sodium ticarcillin). Although she developed inappropriate kaliuresis, there was no evidence of volume contraction; her urine chloride concentra-
tion was high; her renin and aldosterone levels were low; and she did not improve with triamterene administration, which should have blocked the “clas-
 sic” mechanism described in the past. Therefore, the hypokalemia and metabolic alkalosis that develop with currently used penicillin-class antibiotics may be caused by some form of direct tubule damage, which leads to obligatory renal potassium wasting. Zietse et al. (11) recently published a very nice review of the fluid, electrolyte, and acid-base disorders associated with antibiotics.

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Hypokalemia from Intestinal Pseudo-obstruction Ogilvie Syndrome

It is generally accepted that patients with chronic kidney failure develop adaptive mechanisms that markedly increase stool K⁺ secretion. However, the original reports by Hayes et al. (1,2) that described stool K⁺ excretion in the >50-mEq/d range in multiple patients have never been confirmed. Although
stool K⁺ excretion does increase in comparison with normal individuals, the increment is generally very modest; stool K⁺ excretion with advanced kidney disease is usually in the 10- to 15-mEq/d range (3,4). Agarwal et al. (5) reviewed the literature and concluded that colon adaptation in chronic kidney failure was not a major contributor to total K⁺ balance. Another common assumption is that watery diarrhea generates major K⁺ loss as a result of high stool K⁺ concentration. The K⁺ concentration in the water phase of normal stool is very high—on the order of 85 to 95 mEq/L. However, when diarrhea develops, the stool K⁺ concentration falls markedly and with voluminous watery diarrhea often barely exceeds the plasma K⁺ concentration (6). Consequently, the major cation lost in patients with secretory diarrhea is Na⁺. Against this background, the discovery of a colonic secretory condition in which K⁺ was the overwhelming predominant cation was a great surprise. In the last issue of*NephSAP*(7), the case of a 78-year-old woman who developed colonic pseudo-obstruction (Ogilvie syndrome) after surgical repair of a hip fracture was discussed (6). The colonic fluid K⁺ concentration ranged between 130 and 170 mEq/L, whereas the Na⁺ concentration was between 4 and 15 mEq/L. The electrochemical data (colon lumen PD was −13 mV) was entirely consistent with active K⁺ secretion.

Active K⁺ secretion had not previously been described as a mechanism for secretory diarrhea. More recently, extremely high colon K⁺ concentration in patients with colonic pseudo-obstruction was confirmed in five consecutive patients with this disorder (8). It is likely that high-conductance K⁺ channels (BK channels) play an important role in this disorder and other, related colon pathologies. The physiology and pathophysiology of these channels was recently reviewed by Sandle et al. (9). Of great interest and potential clinical importance is the discovery that these BK channels were overexpressed in the colon of a patient who developed pseudo-obstruction and secretory diarrhea after an episode of hemorrhagic shock (10). Her stool Na⁺ concentration was only 11 mEq/L, and her stool K⁺ concentration was 143 mEq/L. Overexpressed BK channels may also account for colon K⁺ losses in some patients with ulcerative colitis (11). The open state of these K channels is increased by stretch, so this may play an important role in disorders with extreme colon dilation. Sorensen et al. (12) recently reviewed the topic of colonic potassium secretion.

References

Thiazides, Hypertension, and Hypokalemia

The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) states that “thiazide-type diuretics should be used in drug treatment for most patients with uncomplicated hypertension, either alone or combined with drugs from other classes” (1). This recommendation was in part based on the Systolic Hypertension in the Elderly Program (SHEP) and the Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT) studies, which demonstrated the efficacy of these drugs (2,3).

However, thiazide diuretics are associated with the development of hypokalemia, hyperuricemia, and diabetes. Although reducing BP certainly has a major impact on cardiovascular risk, the benefit of the BP reduction may be blunted in some patients by these metabolic complications of therapy. Shafi et al. (4) reviewed and discussed these issues and the relationship between developing hypokalemia and diabetes in...
two previous trials. The risk of incident diabetes was 50% higher compared with placebo in SHEP and between 39 and 48% higher than with amlodipine or lisinopril, respectively, in ALLHAT. The diabetes risk increases early (generally in the first year) and during this period is closely linked to the development of hypokalemia.

Agarwal (5) discussed these results in an editorial entitled “Hypertension, Hypokalemia, and Thiazide-Induced Diabetes: A 3-Way Connection.” Figure 9 from this editorial shows how these three factors may interact. Although it is not yet proved that a combination of potassium (K⁺) loss and hypokalemia is the initiating derangement that leads to the development of diabetes and the worsening of BP control, there is much indirect evidence that this is the case. High K⁺ intake may reduce BP as a result of salt excretion and beneficial neurohumoral effects, but not all studies are consistent (6,7). Diuretic-induced hypokalemia is also associated with reduced β cell response to glucose. Agarwal (5) hypothesized that K⁺ depletion might have an adverse impact on glucose metabolism by reducing the perfusion of skeletal muscle. If diuretic-related K⁺ losses do contribute to the development of diabetes, then treatment with K⁺ supplements, K⁺-sparing diuretics, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers may not only prevent hypokalemia but also decrease the risk for developing diabetes and also improve BP control.

**Hypokalemia as a Risk Factor in Patients with Chronic Kidney Disease.** The U-shaped relationship between mortality or morbidity and many physiologic and biochemical parameters is not surprising or new. Humans evolved to maintain these parameters within a certain range, and extremes on either side usually cause physiologic malfunction, morbidity, and a greater risk for death. This U-shaped relationship was recently confirmed for serum K⁺ concentration in patients with chronic kidney disease. In a prospective, observational study of adult patients with stages 3 through 5 chronic kidney disease, conducted at four US outpatient nephrology clinics, 834 patients were followed for an average of 2.6 years each (8). Their average age was 60.5 years, average GFR was 25.4 ml/min per 1.73 m², and average K⁺ concentration was 4.6 mmol/L. Mortality was significantly greater when the serum K⁺ was ≤4 mmol/l, and serum K⁺ ≥5.5 mmol/l increased the risk for reaching the compound end point of “death or cardiovascular event.” Although the risk for death as an isolated end point did not reach significance for the group with hyperkalemia, this may be explained by the fact there were very few patients in this group; only 65 patients had hyperkalemia at enrollment. In addition, the use of dialysis as “rescue” therapy for severe hyperkalemia probably blunted its mortality impact.

Chan et al. (9) evaluated the safety of digoxin therapy in patients with ESRD. In an observational cohort analysis, digoxin use among 120,864 incident hemodialysis patients increased the risk for death by 28%. This risk was greatest in patients with lower predialysis serum K⁺ concentrations (<4.3 mEq/L), in whom the hazard ratio for death was 2.53 compared with patients who had higher predialysis serum K⁺ concentrations. The hazard ratio for death among patients with predialysis K⁺ concentration >4.6 mEq/L was not statistically different from 1.0.

**Hypokalemia-Induced Hyponatremia and Correction of Hyponatremia with K⁺ Replacement.** Berl and Rastegar (10) recently discussed the case of a woman who was taking thiazide diuretics and nonsteroidal anti-inflammatory drugs long term and then became ill with a cough and sinusitis. At presentation to the hospital, she had severe hyponatremia (96 mEq/L), hypokalemia (1.6 mEq/L), and metabolic alkalosis (38 mEq/L). After what her physicians believed was very conservative treatment of her hyponatremia, her sodium (Na⁺) concentration increased 18 mEq/L over 20 hours, and she developed a “locked-in syndrome” with radiologic evidence of the osmotic demyelination
hours, which by itself should not have raised the Na
and only 300 ml of isotonic saline over the first 24
will increase the plasma osmolality and the Na
concentration as much as equimolar quantities of retained
Na salts (11). The physicians ordered water restriction
and a 3-L electrolyte-free water diuresis that ensued resulted in her Na concentration increasing from 96 to 114 mEq/L, or 18 mEq/L, over 20 hours. The other issue relates to the impact on brain cell swelling or shrinking when hyponatremia is caused mainly by water gain, by Na⁺ loss, or by K⁺ loss. In general, acute hyponatremia means that brain cells have swollen. The degree of swelling gradually decreases as the brain cells adapt with time. Conversely, when the serum Na⁺ concentration increases as a result of the hypertonic saline infusion or a water diuresis water moves out of the brain cells and they shrink. If the Na⁺ concentration increases too rapidly and/or too much, osmotic demyelination syndrome may occur. The exact mechanism of the demyelinating damage remains obscure but too-rapid cell shrinkage is thought to contribute. However, these generalizations may not apply when the mechanism for the hyponatremia is mainly K⁺ depletion. Analogously, they may not apply when the increase in Na⁺ concentration is largely due to K⁺ repletion. Under these circumstances, the development of hyponatremia would be associated with brain cell shrinkage as a result of brain cell K⁺ depletion. A fall in intracellular osmotic solute will cause water to move from the cells into the extracellular fluid (ECF). Expansion of the ECF dilutes the Na⁺ concentration while the intracellular space simultaneously contracts. Analogously, to the extent that correction of hyponatremia is the result of K⁺ repletion, it occurs because water moves from the ECF into cells and they should therefore swell. If these changes had occurred in the patient described in the article, it would be difficult to attribute the development of demyelination to shrinking of her brain cells. Nonetheless, despite these considerations, epidemiologic studies have found repeatedly that hypokalemia is a risk factor for the development of the
osmotic demyelination syndrome in patients with hyponatremia with treatment (12,13). Undoubtedly, the brain cell swelling/shrinking hypothesis for the demyelination process is an oversimplification. It is suggested that the interested reader carefully review the Berl and Rastegar (10) publication as well as an in depth discussion of these issues by Nguyen and Kurtz (11).

References

Hyperkalemia

Physiology
Aldosterone plays an important role in the defense against hyperkalemia. Aldosterone stimulates electrogenic sodium (Na⁺) reabsorption through the
epithelial Na⁺ channel (ENaC), creating a lumen-negative potential that serves as a driving force for Cl⁻ reabsorption through the paracellular pathway and secretion of potassium (K⁺) and hydrogen (H⁺) into the collecting duct lumen.

Aldosterone secretion is mediated by a direct stimulatory effect of angiotensin II on cells in the zona glomerulosa of the adrenal gland and through a direct effect of K⁺ on the zona glomerulosa. As extensively reviewed in the last fluid and electrolyte issue of Neph-SAP, two members of the “with-no-lysine” (WNK) family of kinases (a name derived from the atypical placement of the catalytic lysine as compared with other types of kinases) play an important role in modulating K⁺ secretion, and mutations of these proteins are responsible for congenital abnormalities that result in hyperkalemia.

In adults, dietary K⁺ intake is matched by K⁺ excretion primarily by the kidney, with a lesser contribution by the gastrointestinal tract. K⁺ is freely filtered by the glomerulus and then reabsorbed in the proximal tubule and loop of Henle such that only 10% of the filtered load reaches the distal nephron. K⁺ delivery to the distal nephron is usually small and is fairly constant. Most of the K⁺ in the final urine derives from K⁺ secreted by the distal nephron (primarily the cortical collecting duct) in response to physiologic need.

K⁺ enters the tubular lumen of the collecting duct through K⁺ channels. The ROMK channel, which has a low conductance and a high probability of being open under physiologic conditions, is the major K⁺-secretory pathway. The maxi-K⁺ channel, found mostly in intercalated cells, is relatively quiescent in the basal state but plays a major role in flow-stimulated K⁺ secretion. A high K⁺ intake stimulates K⁺ secretion mediated by both aldosterone-dependent and aldosterone-independent mechanisms that are summarized in a recent review (1).

A typical Western meal provides a K⁺ load that equals the total K⁺ content of extracellular fluid. Thus, every meal represents a life-threatening K⁺ challenge, and the organism must quickly adapt to it. Aldosterone is an unlikely candidate to mediate this adaptation because the effects of the hormone require transcription, requiring too much time, and because aldosterone also effects sodium and acid-base balance. The serine protease tissue kallikrein (TK) was recently identified as an aldosterone-independent mechanism that protects against postfeeding hyperkalemia by promoting increased renal K⁺ excretion (2). TK is synthesized in large amounts by connecting tubule cells and secreted into the tubular lumen; its secretion is promoted by K⁺ intake. TK activates the ENaC, which promotes K⁺ secretion and inhibits K⁺ reabsorption by H⁺-K⁺-ATPase. Knockout mice lacking TK become more hyperkalemic than wild-type mice after a large feeding, and cortical collecting ducts isolated from TK null mice absorb potassium rather than secrete it; K⁺ absorption is associated with increased H⁺-K⁺-ATPase.

Pseudohyperkalemia

Pseudohyperkalemia is an in vitro phenomenon that results from mechanical release of K⁺ from cells during phlebotomy or specimen handling. Common causes include fist clenching, use of small-bore needles during phlebotomy, and exposure of blood samples to lower ambient temperatures either during transport or by placing the sample on ice.

Inappropriate phlebotomy techniques in which patients are requested to fist clench to facilitate blood draws is known to cause pseudohyperkalemia, but the incidence of the problem is difficult to determine. A program to retrain phlebotomists to eliminate this practice in a primary care population in the United Kingdom reduced the percentage of K⁺ values above the reference range (≥5.2 mmol/L) from 9 to 6% and reduced the percentage of K⁺ values >5.8 mmol/L from 0.9 to 0.5% (3). Similarly, when a standard protocol was introduced in a university hospital in Japan that mandated avoidance of fist clenching during phlebotomy and nonuse of the first blood sample for electrolyte measurements when multiple specimens were obtained from a single patient, the number of cases of pseudohyperkalemia fell from eight to one per year (4).

A spurious increase in plasma K⁺ concentration caused by in vitro contamination with K-EDTA, sometimes used as an anticoagulant in sampling tubes, should be considered when unsuspected hyperkalemia is accompanied by a very low plasma Ca²⁺ concentration (5). Most other cases of pseudohyperkalemia are seen in patients with thrombocytosis and pronounced leukocytosis (6,7).

In vitro elevation of the serum K⁺ caused by release of K⁺ from platelets during clot formation in the specimen tube was first reported in 1955 by Hart-
mann and Mellinkoff in patients with thrombocytosis; plasma K⁺ level (sampled from anticoagulated blood in heparinized tubes) was normal. To determine the incidence of pseudohyperkalemia in myeloproliferative disorders, a 6-year retrospective audit was conducted on all patients who had thrombocytosis and were referred to the hematology department of a large district general hospital in Ireland (8). Ninety patients with thrombocytosis (platelet count range of 413,000 to 2,997,000) as a result of reactive thrombocytosis, primary thrombocytopenia, polycythemia vera, and myelofibrosis were studied. The median serum K⁺ during the peak of thrombocytosis was 5.3 mmol/L (range 3.3 to 8.7 mmol/L). Pseudohyperkalemia was most frequent among patients with primary thrombocytopenia (75.7%) and polycythemia rubra vera (75%), followed by myelofibrosis (50%) and reactive thrombocytosis (34.5%). Among the 90 patients, a highly significant positive correlation was found between the platelet count and the serum K⁺ level (r = 0.998). Above a platelet count of 870,000, the highest recorded serum K⁺ levels always exceeded 5.5 mmol/L, and all patients with a platelet count of ≥1,192,000 had at least one serum K⁺ level of ≥6 mmol/L; serum K⁺ levels as high as 8.7 with plasma K⁺ in the normal range were recorded. Pseudohyperkalemia led to unnecessary admissions, repeated venipunctures, and inappropriate therapy with intravenous calcium and insulin, and administration of K⁺-binding resins. Investigators suggested that clinical laboratories could help clinicians avoid these errors by checking platelet counts in patients with unexplained serum K⁺ levels of ≥5.5 mmol/L; a platelet count >800,000 should prompt a request for a plasma K⁺ in the appropriate heparinized tube.

Patients with high platelet counts and coexistent K⁺ depletion may not exhibit the expected difference between serum and plasma K⁺ values (9). Presumably, K⁺ that has been released by platelets into the serum during clotting is subsequently taken up by K⁺-depleted erythrocytes, masking the pseudohyperkalemia phenomenon; for example, one K⁺-depleted patient with a myeloproliferative disorder and thrombocytosis redeveloped pseudohyperkalemia after his K⁺ deficit was replaced (9).

In patients with isolated erythrocytosis from chronic obstructive pulmonary disease and congestive cyanotic heart disease, the difference between serum and plasma K⁺ level exceeded that in normal control subjects, but it was less than the discrepancy found in patients with thrombocytosis or mixed-type disorders (9). In patients with erythrocytosis, K⁺ released from platelets during the clotting process enters a smaller volume of serum than in patients with a normal hematocrit level; however, even with extreme isolated erythrocytosis, serum K⁺ is no more than 0.7 mmol/L higher than plasma K⁺.

High white blood cell (WBC) counts (>120,000) caused by chronic lymphocytic leukemia can also lead to falsely increased K⁺ concentrations, prompting unnecessary therapeutic interventions (6,7,10). However, unlike thrombocytosis, spurious hyperkalemia occurs in both serum and plasma samples and may actually be more prominent when blood is sampled in heparinized tubes (10). For plasma collection, the blood specimen is centrifuged immediately, and this may lead to in vitro cell destruction and release of K⁺ as these cells are freely suspended in the plasma. WBCs in patients with chronic lymphocytic leukemia are fragile, and coupled with higher WBC counts, more cells are destroyed during the direct centrifugation process, leading to a falsely increased K⁺ value. This phenomenon can be visualized by the presence of a thin layer of cells above the gel in the plasma tube after centrifugation in patients with a very high WBC count. In contrast, this layer of cells is not visibly present in a serum tube after centrifugation. Serum (plasma without the clotting factors) is collected by first incubating a blood sample at room temperature to allow clotting to separate the serum from the cells before centrifugation. During the clotting process, a fibrin clot is formed, generating a matrix that entraps and protects fragile leukemic WBCs, minimizing cell lysis and in vitro release of K⁺ into the serum. Measurement of whole-blood K⁺ in an uncentrifuged specimen using direct potentiometry is another option, and this agrees well with values obtained in serum (10). Pseudohyperkalemia has also been reported after mechanical disruption of leukocytes during the transport of blood samples by pneumatic tube systems; in one reported case, spurious hyperkalemia led to unnecessary dialysis, which resulted in hypokalemia (11).

**Excess K⁺ Intake**

With normal renal function, it is difficult to ingest enough K⁺ to cause hyperkalemia. However, excess K⁺ intake is an important contributing cause of hyperkalemia in patients with impaired kidney function. Melons, citrus juice, and salt substitutes are
Internal K⁺ Shifts

Cellular redistribution of K⁺ is an important cause of hyperkalemia; a shift of as little as 2% of body K⁺ stores can increase the plasma K⁺ concentration to 8 mmol/L. When renal function is intact, K⁺ shifts cause only transient hyperkalemia because the excess K⁺ is normally excreted in the urine.

Hyperglycemia. Hyperglycemia has multiple effects on internal K⁺ balance. Low insulin levels provoke translocation of intracellular K⁺ to the extracellular compartment. In addition, hypertonicity and the catabolic state associated with hyperglycemia cause egress of K⁺ from cells. In patients with anuria, changes in the serum K⁺ concentration caused by hyperglycemia and its correction are reflections of internal K⁺ balance. Serum K⁺ values of ≥5.5 mmol/L were encountered in one third of episodes of nonketotic hyperglycemia and three fourths of episodes of diabetic ketoacidosis in hemodialysis patients. Insulin corrects the hyperkalemia of dialysis-associated hyperkalemia and is usually the only treatment needed. Lethal hyperkalemia has been reported, and emergency dialysis is often considered for patients with severe hyperkalemia accompanied by electrocardiographic (ECG) abnormalities; it is unknown whether this intervention is really needed. In a recent case report, a 33-year-old woman who had ESRD and poorly controlled diabetes and presented with hypertension, blood sugar level of 1884 mg/dl, K⁺ level of 7.2 mmol/L, serum bicarbonate level of 4 mmol/L, and T-wave elevation on electrocardiogram was treated with an insulin drip for 2.5 hours before starting on dialysis because of concerns that the rapid fall in tonicity could cause cerebral edema.

Octreotide. Octreotide, a long-acting synthetic octapeptide analog of the human hormone somatostatin, has been reported to be useful in the treatment of sulfonlurea-induced hypoglycemia that is refractory to conventional therapy, especially in patients with renal disease. Similar to somatostatin, octreotide directly inhibits the release of insulin from the pancreas, and it also suppresses the secretion of glucagon, growth hormone, vasoactive intestinal peptide, and gastrin. Suppression of insulin release impairs cellular uptake of K⁺ and can result in hyperkalemia if K⁺ excretion is impaired. A 48-year-old patient who had ESRD and was on maintenance hemodialysis was treated with octreotide for sulfonlurea-induced hypoglycemia and developed severe hyperkalemia (7.3 mEq/L) after three doses (14). There have only been three other reports of the use of octreotide in patients with ESRD, and one of these patients developed hyperkalemia; there have been two other reported cases of octreotide-induced hyperkalemia in patients without ESRD (14).

Hyperkalemic Periodic Paralysis. Hyperkalemic periodic paralysis is an inherited disorder caused by mutations in SCN4A encoding the voltage-gated skeletal muscle sodium channel; an extensive review of the disorder, including the various allelic variants associated with the disease, is available online (www.ncbi.nlm.nih.gov/omim/17-500). The disease is characterized by attacks of flaccid limb weakness and sometimes weakness of the muscles of the eyes, throat, and trunk; hyperkalemia (>5 mmol/L or an increase of at least 1.5 mmol/L in plasma K⁺); and provoked attacks by K⁺-rich food or K⁺ supplements. Spontaneous attacks typically begin before breakfast, last for 15 minutes to 1 hour, and then resolve. Serum K⁺ concentrations are normal between attacks. Attacks can be aborted by intake of carbohydrates, inhalation of β2-adrenergic agents, or intravenous calcium gluconate. Continuous use of thiazide diuretics or acetazolamide and avoidance of fasting and K⁺-rich foods can prevent attacks.

Succinylcholine. Hyperkalemia from succinylcholine was first recognized by Gronert in burn units in the 1960s and was studied in a controlled trial that compared serial electrocardiograms and arterial K⁺ values in 89 burn victims who were given anesthetic agents, as compared with 16 normal control subjects. Subsequent studies have shown that in addition to patients with burns, succinylcholine-induced hyperkalemia occurs in patients with muscle trauma and in patients with neurologic disorders that result in motor muscle defects. Hyperkalemia results from extrajunc-
tional acetylcholine receptor spread along the muscle membrane in conditions that undergo prolonged depolarization in response to succinylcholine with release of K⁺. In addition, myopathies that weaken skeletal muscle membranes are subject to rhabdomyolysis with stress. Gronert (15) recently published a fascinating biographical recounting of his studies related to the epidemiology and pathophysiology of succinylcholine-induced hyperkalemia that includes ECG recordings of a burn patient whose serum K⁺ increased from 4.7 to 9.1, accompanied by a widened QRS complex and loss of P waves within 5 minutes of receiving succinylcholine under close observation. Remarkably, no patient experienced a cardiac arrest in these studies despite the extreme hyperkalemia that was observed. Rebound hyperkalemia may occur after K⁺ chloride treatment of thyrotoxic hypokalemic periodic paralysis (TPP) beginning 2 to 3 hours after recovery (16). During the recovery phase, K⁺ release from muscle occurs at rates up to 15 mmol/L per h. Rebound hyperkalemia has been reported to occur in 40 to 70% of patients who are treated with intravenous K⁺. A fatal case of iatrogenic hyperkalemia was recently reported in a 40-year-old Hispanic woman who had TPP and was treated with 240 mmol of KCl (at 30 mmol/L per h) for a serum K⁺ level of 1.9 mmol/L (16). K⁺ therapy was stopped 8 hours after the start of therapy, when the serum potassium rose to 6.6 mmol/L. However, despite the administration of 50 ml of 50% dextrose and 10 U of insulin, serum K⁺ continued to increase, reaching 10.1 mmol/L at the time of death. Oral and intravenous propranolol have been effective in reversing TPP hypokalemia without risk for rebound hyperkalemia. A similar phenomenon has been described in patients with drug-induced internal shifts of K⁺. Barbiturates, which are often used as a neuroprotective agent in patients with head trauma and other neurosurgical interventions, cause hypokalemia by shifting K⁺ into cells. Once the administration of barbiturate is stopped, a rebound hyperkalemia may ensue, which has been fatal in several reported cases (17). K⁺ replacement to correct severe barbiturate-induced hypokalemia is likely to increase the severity of hyperkalemia once the drug is stopped. In a recent case report, dramatic, severe fluctuations of the serum K⁺ every few hours between 1.8 and 8.3 mmol/L developed in a patient who had head trauma and was treated with therapeutic hypothermia (34.5°C) and norepinephrine (0.1 μg/kg per min) to maintain BP but no barbiturates (17). He was treated with parenteral K⁺ supplements when hypokalemic and then, hours later, with K⁺-lowering agents (insulin, furosemide, and Kayexalate) when his K⁺ rose too high. The serum potassium ultimately increased abruptly to 8.9 mmol/L, resulting in cardiac arrest and treatment with venovenous hemofiltration. Presumably, endogenous catecholamine discharge after head trauma resulted in a transient β2-adrenergically mediated shift of K⁺ into cells augmented by exogenous norepinephrine and hypothermia. Cardiac Glycosides. Inhibition of Na-K-ATPase by cardiac glycosides results in migration of K⁺ out of cells, and digitalis poisoning can cause clinically significant hyperkalemia. The stems, leaves, flowers, roots, and seeds of two common species of Oleander (Nerium oleander, or common oleander, and Thevetia peruviana, or yellow oleander) contain high concentrations of cardiac glycosides, and they have become a common cause of poisoning in tropical and subtropical parts of the world (18,19). Deliberate self-harm through ingestion of yellow oleander is very popular in South Asia, and several thousand cases have been reported each year with a fatality rate ranging between 4 and 10%. Symptoms are those of digitalis intoxication and include nausea, vomiting, abdominal pain, diarrhea, cardiac arrhythmias, and hyperkalemia. The management of serum K⁺ is difficult because hypokalemia can worsen digitalis toxicity and predispose to dangerous arrhythmias, but severe toxicity results in hyperkalemia. The treatment of hyperkalemia and other complications of oleander poisoning was recently reviewed (19). Intravenous calcium is generally avoided because intracellular calcium concentrations are already high in the setting of digoxin toxicity and calcium administration may worsen arrhythmias. Insulin-dextrose infusion was shown to be cardioprotective in an animal model; in addition to the K⁺-lowering effect of insulin, which drives K⁺ back into cells, insulin may modify access of digoxin to the Na-K-ATPase–binding site, reducing its toxicity. Treatment with digoxin-specific Fab antibody fragments is very effective in the correction of hyperkalemia and is the preferred therapy; however, their high cost and lack of availability limit their use in countries where yellow oleander poisoning is common. Treatment with K⁺-binding resins or other measures aimed at eliminating potassium is ill advised because the cause of hyperkalemia is a shift of K⁺ out of cells.
rather than excess body $K^+$; $K^+$-depleting therapies may precipitate hypokalemia when given with digoxin-specific antibody fragments.

**Impaired $K^+$ Excretion**

Although redistribution of $K^+$ can cause hyperkalemia, a sustained increase in the plasma $K^+$ concentration is indicative of defective $K^+$ excretion caused by oliguric renal failure, low aldosterone levels, or aldosterone resistance. Calculation of the transtubular $K^+$ concentration (TTKG) may be helpful in distinguishing between these two possibilities:

$$\text{TTKG} = \frac{\text{urine} [K^+]/\text{plasma} [K^+]}{\text{urine osmolality/plasma osmolality}}$$

The TTKG is intended to estimate the tubular fluid $K^+$ concentration in the cortical collecting duct, the site responsible for most excreted $K^+$, where the luminal fluid is isosmotic to the plasma. The calculation assumes that changes in the $K^+$ concentration between that point and the final urine result from water reabsorption, which raises urine osmolality above plasma and increases the concentration of $K^+$ in the final urine above that in the collecting duct lumen. Impaired $K^+$ excretion as a result of defects in tubular $K^+$ secretion results in a low TTKG, whereas impaired excretion attributable to decreased delivery of fluid to the secretory site results in a higher TTKG. There is a positive correlation between mineralocorticoid activity and the TTKG, but values have varied greatly in the various published studies (20). The greatest clinical utility of the TTKG may be to differentiate between hyperkalemia caused by low aldosterone levels and hyperkalemia caused by aldosterone resistance and to gauge the effectiveness of mineralocorticoid replacement therapy. Administration of physiologic doses of mineralocorticoid (0.05 mg of fludrocortisone) to patients with adrenal insufficiency increases the TTKG to >6 within 4 hours, whereas in patients with aldosterone resistance, the TTKG remained <6 with a variable or delayed response after 24 hours to pharmacologic doses (0.2 mg) (20).

**Decreased Mineralocorticoid Levels or Activity.** Decreased mineralocorticoid activity can be caused by disturbances anywhere along the renin-angiotensin-aldosterone system (RAAS) arising from disease or drug effects.

**Addison Disease.** When Addison disease was first reported in 1855, most of the cases were caused by disseminated tuberculosis. Today, autoimmune adrenitis counts for 70 to 90% of the cases; tuberculosis is responsible for 7 to 20%; and the remaining cases are caused by adrenal hemorrhage or infarction, drugs, and malignancy (21,22). Infiltration of the adrenal glands by metastatic cancer is found at autopsy in 40 to 60% of patients with disseminated lung or breast cancer, probably because of their rich blood supply. Although most adrenal metastases are thought to be functionally unimportant, adrenal insufficiency can be missed in patients with cancer because hyperkalemia can be ascribed to other comorbidities such as impaired renal function and $K^+$-sparing diuretics. Hyperkalemia can be the first sign of adrenal metastases, as was the case in a patient who had adenocarcinoma of the lung and presented with tetraparesis and widened QRS complexes on electrocardiogram caused by a serum $K^+$ of 8.8 mmol/L (22).

**Hypoaldosteronism.** Functional hypoaldosteronism with hyperkalemia may occur after successful resection of aldosterone-producing adenomas (23). Long-term suppression of contralateral aldosterone synthesis by the adenoma or by chronic untreated hypokalemia can result in hyperkalemia with serum $K^+$ concentrations of >6 mmol/L and postural hypotension for several weeks after surgery; administration of fludrocortisones may be necessary.

**Pseudohypoaldosteronism.** Pseudohypoaldosteronism type 2, also known as Gordon syndrome, is a dominantly inherited hyperkalemic hypertension with an associated (usually mild) acidosis, in which removal of the distal NaCl co-transporter from the distal convoluted tubule apical surface and insertion of ROMK into the collecting duct membrane is impaired because of mutation in one of their regulators, WNK1 or WNK4 (with-no-lysine kinases). The pathogenesis of this disorder was discussed in the previous fluid and electrolyte issue of NephSAP. Patients with the WNK4 mutation have hypercalciuria, whereas patients with the WNK1 mutation do not (24).

**Drug-Induced Hyperkalemia**

Inhibition of the RAAS is a key strategy in treating hypertension and cardiovascular and renal diseases. However, RAAS inhibitors (angiotensin-converting enzyme inhibitors [ACEIs], angiotensin receptor blockers [ARBs], aldosterone receptor antagonists, and direct renin inhibitors) increase the risk for hyperkalemia, particularly when they are prescribed in combination (25). Common drugs that are associated
with hyperkalemia and their mechanisms of action are listed in Table 3.

### Decreased Aldosterone Levels

Several studies have shown that ACEIs can cause hyperkalemia by interfering with the production and/or secretion of aldosterone. An analysis of the African American Study of Kidney Disease and Hypertension (AASK) database showed that the incidence of severe hyperkalemia (defined as a serum potassium $>5.5$ mmol/L) was significantly higher among 1094 African American patients who did not have diabetes, had hypertension, had a GFR of 20 to 65 ml/min, and were randomly assigned to treatment with ACEIs compared with patients who were treated with calcium channel blockers or a β blocker (26). However, there was no increased risk for hyperkalemia when the GFR was $>40$ ml/min. Diuretic use decreased the risk for hyperkalemia by 59%. Patients with a body mass index (BMI) of $\leq 25$ were more likely to develop hyperkalemia on an ACEI, possibly because the low-BMI group might have had a lower GFR than what was estimated. The results of the study suggest that more frequent monitoring of the serum $K^+$ is necessary for patients who are treated with an ACEI and whose GFR is $<40$ ml/min; patients who have a low BMI; all patients with a GFR $<30$ ml/min, regardless of BMI; older patients; patients with higher levels of microalbuminuria; and patients who are not receiving concurrent treatment with diuretics.

A review of the PubMed database of clinical trials published through December 2008 found that the risk for developing a serum potassium $>6$ mmol/L is $<2\%$ with RAAS inhibitor monotherapy. The risk for hyperkalemia with monotherapy remains low in patients who have chronic kidney disease (CKD) and a GFR of 30 to 60 ml/min. The risk for hyperkalemia with ACEI/ARB combination therapy is higher than with monotherapy; however, the number of patients who experience “hyperkalemia events” (discontinuation or adverse event of hyperkalemia or serum $K^+$ $\geq 6.0$ mmol/L) was similar for combination therapy and lisinopril monotherapy. The addition of an aldosterone receptor antagonist is associated with a small but statistically significant 0.3-mmol/L increase in serum $K^+$ levels, and the incidence of severe hyperkalemia (serum $K^+$ $\geq 6.0$ mmol/L) is also greater.

### Aldosterone Receptor Antagonism

Spironolactone blocks the effect of aldosterone on the mineralocorticoid receptor. The Randomized Aldactone Evaluation Study (RALES) showed benefit in treating with spironolactone patients who had heart failure. In Canada, an increase in hospital admissions and deaths from hyperkalemia occurred concurrently with the publication of RALES. A study of a stable population in a town in Scotland (population 400,000) found that the number of prescriptions for spironolactone and the number of ordered laboratory tests for creatinine and serum $K^+$ doubled after the release of the RALES results in 1999 (27). Similarly, among patients who were taking ACEIs and had been recently admitted to the hospital for heart failure, use of spironolactone increased from 19.8% before the publication of RALES to 70.1% after the trial. Although the rate of mild hyperkalemia ($>5$ mmol/L but $\leq 6$ mmol) increased as the number of spironolactone prescriptions and laboratory $K^+$ determinations increased, the rate of severe hyperkalemia ($>6$ mmol/L) did not. The number of hospital admissions for hyperkalemia remained at three or less per quarter before and after RALES. During the 6-year study, a total of 578 patients with spironolactone-associated severe hyperkalemia ($K^+ >6$ mmol/L) were identified, including 172

### Table 3. Drugs that cause hyperkalemia

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exogenous potassium</td>
<td>Potassium supplements, Salt substitutes, Herbal medicines (e.g., alfalfa, dandelion)</td>
</tr>
<tr>
<td>Redistribution of intracellular potassium</td>
<td>Hypertonic mannitol, β blockers, Succinylcholine, Somatoctatin, Octreotide, Digitalis glycosides</td>
</tr>
<tr>
<td>Decreased aldosterone levels</td>
<td>ACEIs, ARBs, Heparin, NSAIDs, Tacrolimus, Eplerenone, Trimethoprim, Amiloride, Triamterene</td>
</tr>
<tr>
<td>Aldosterone receptor antagonism</td>
<td>Spironolactone, Eplerenone</td>
</tr>
<tr>
<td>Collecting tubule sodium channel blockade</td>
<td>Trimethoprim, Pentamidine, Amiloride, Triamterene, Cyclosporine, Tacrolimusx</td>
</tr>
<tr>
<td>Collecting tubule Na+-K+-ATPase blockade</td>
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patients with heart failure, 45 with cirrhosis, and 361 with hypertension. Among those with hyperkalemia, 75% were older than 65 years. A serum creatinine >2.5 mg/dl (≥220 μmol/L) preceded hyperkalemia in 76% of patients with heart failure, 71% of patients with cirrhosis, and 53% of patients with hypertension. The authors took this to mean that spironolactone is a safe drug when it is used with appropriate monitoring (presumably more diligent in Scotland than it was in Canada!) and that closer monitoring is indicated for older patients and for patients with impaired renal function.

There is growing evidence that aldosterone contributes to hypertension and insulin resistance in obesity (28,29). Adipokines released by the adipocyte induce aldosterone secretion from human adrenocortical cells and sensitize the cells to stimulation by angiotensin II. The resulting hyperaldosteronism promotes insulin resistance, inflammation, oxidative stress, and sodium retention, which contribute to the development of resistant hypertension. Mineralocorticoid receptor blockade seems to be useful in treating patients who have both the metabolic syndrome and resistant hypertension (30,31). Use of spironolactone for the treatment of hypertension in patients with coexistent renal disease carries a risk for hyperkalemia. An observational study conducted in two university-based hypertension clinics identified 46 patients (38 of them African Americans) with resistant hypertension and stage 2 or 3 CKD and evaluated the safety and efficacy of addition of aldosterone blockade to preexisting BP-lowering therapy that included a diuretic and a renin-angiotensin system (RAS) blocker (31). Addition of an aldosterone receptor antagonist further decreased systolic BP by an average of 14.7 mmHg. The mean increase in serum K⁺ was 0.4 mEq/L, with 17% of the patients having a serum K⁺ of >5.5 mEq/L. Of the eight patients with hyperkalemia, only one had a serum K⁺ of >6 mEq/L. The odds ratio for developing hyperkalemia was significantly increased when the baseline estimated GFR (eGFR) was ≤45 ml/min, baseline serum K⁺ was ≥4.5 mEq/L, or the eGFR fell by >30% after the introduction of the aldosterone antagonist. The study suggests that patients who are given aldosterone antagonists for resistant hypertension should have their serum creatinine and K⁺ checked within 1 to 2 weeks after initiation of therapy (similar to the monitoring after the initiation of RAS blockade). Hyperkalemia seems to be a manageable risk when it is limited to patients with an eGFR of >45 ml/min and a baseline serum K⁺ of <4.5 mEq/L while on optimal diuretic and RAS-blocker therapy.

The non–testosterone-derived progestin drospirenone, used as an oral contraceptive agent, blocks the mineralocorticoid receptor and in the dosage used for contraception is roughly equivalent to 25 mg of spironolactone (32). Monitoring of the serum K⁺ concentration has been recommended when these drugs are prescribed to patients who are treated with K⁺ supplements, ACEIs, angiotensin receptor antagonists, or nonsteroidal anti-inflammatory drugs (12). However, a study of a drospirenone-containing contraceptive identified only one case of hyperkalemia among 22,429 women who began ethinyl estradiol 0.03 mg/drospirenone and none among women who were identified as having preexisting adrenal, renal, or hepatic insufficiency (32).

**Collecting Tubule Sodium Channel Blockade.** Treatment of *Pneumocystis jiroveci* pneumonia (PCP) with trimethoprim-sulfamethoxazole results in hyperkalemia in as many as 53% of patients with HIV infection because of an amiloride-like effect of trimethoprim on sodium channels in the distal nephron. Corticosteroids are often used as adjunctive therapy in patients with moderate to severe PCP, and they might be expected to ameliorate trimethoprim-associated hyperkalemia by increasing GFR and by exerting a mineralocorticoid effect. However, a single-center study of 30 patients who had PCP and were treated with trimethoprim-sulfamethoxazole found that the addition of glucocorticoids potentiates the risk for hyperkalemia (33). Patients with serum creatinine >1.5 mg/dl and those who were taking medications that are known to influence serum K⁺ levels were excluded from the study. Hyperkalemia developed in seven of the 18 patients who were treated with trimethoprim-sulfamethoxazole plus prednisolone and none of the 12 patients treated with trimethoprim-sulfamethoxazole without prednisolone; release of K⁺ caused by steroid-induced catabolism was thought to be the best explanation for this finding because each gram of nitrogen released from muscle is accompanied by 2.7 mEq of K⁺. Although the investigators did not measure urinary K⁺ losses in the two groups, the blood urea nitrogen concentration on the eighth day of therapy was significantly higher in patients who were receiving steroids (30.0 versus 11.8 mg/dl).

Treatment with trimethoprim-sulfamethoxazole...
is a potential risk factor for hyperkalemia in ambulatory patients who are treated with ACEIs or ARBs. The risk of trimethoprim-sulfamethoxazole in these patients was explored in a population-based nested control study of elderly patients who were aged ≥66 years and resided in Ontario, Canada (34). Compared with amoxicillin, the use of trimethoprim-sulfamethoxazole was associated with nearly a sevenfold increased risk for hospitalization for hyperkalemia. No increased risk was seen with any of the comparator antibiotics that are used to treat urinary tract infections. The investigators could not identify outpatient hyperkalemia (and they did not have access to serum K⁺ values), so the study probably underestimates the clinical consequences of the drug interaction between RAS blockade and trimethoprim. The findings suggest that the drug should be avoided in elderly patients who receive RAS blockade and/or aldosterone antagonists when other options exist.

Consequences of Hyperkalemia

Muscle Weakness. Neuromuscular manifestations of hyperkalemia range from paresthesias, mild motor paralysis, para paresis, ascending paraplegia, and eventually quadriplegia. Paralysis usually begins distally with an ascending course that may mimic Guillain-Barré syndrome. The diaphragm, cranial nerves, and sensory functions are usually unaffected; muscle weakness from hyperkalemia usually reflects a serum K⁺ >7 mmol/L (35).

ECG Findings. In experimental settings, hyperkalemia has been associated with a defined series of ECG findings: Shortening of the QT interval, peaking of T waves, QRS prolongation, shortening of the PR interval, reduction in P wave amplitude, loss of sinoatrial conduction with onset of a wide-complex “sine-wave” ventricular rhythm, and ultimately asystole. The most severe cardiac manifestations have been shown to occur with serum K⁺ concentrations >9 mEq/L (36). As discussed in the previous fluid and electrolyte issue of NephSAP, clinical studies have shown a poor correlation between the serum K⁺ concentration and cardiac manifestations; in a recent series, abnormal ECG findings were documented for only 12% of patients with serum K⁺ values of 6.0 to 7.1 and in 39% of patients with values of 7.2 to 9.3 (37).

Mortality. A prospective, observational study of adult patients with stages 3 to 5 CKD conducted at four outpatient nephrology clinics in the United States identified 86 deaths before reaching ESRD among 820 patients (38). The investigators found that pre-ESRD mortality was significantly higher for a serum K⁺ ≤4.0 mmol/L compared with K⁺ values >4.0 and <5.5 mmol/L, but surprisingly a higher serum K⁺ (≥5.5 mmol/L) was not associated with elevated mortality. A multivariable analysis showed that the lowest risk for mortality was in patients with serum K⁺ values of 4.1 to 5.5 mmol/L. Even at serum potassium levels of 5.5 to 5.9 mmol/L, a range that often provokes therapeutic intervention, no increase in mortality was observed. This modest level of hyperkalemia seemed to be well tolerated in this patient population from the perspective of predicting mortality risk.

Metabolic Acidosis. Normal men fed a high-K⁺ diet decrease their urine pH and ammonium and net acid excretion; in experimental animals, K⁺ loading has been shown to decrease ammonia generation in the proximal tubule. The precise mechanism is not firmly established, but presumably hyperkalemia raises the intracellular pH of the tubular cell by exchanging with protons, impairing enzymes that promote the deamination of filtered or secreted glutamine (39). In humans, despite reduced renal ammonia production, administration of K⁺ does not cause acidosis when adrenal and renal functions are intact because upregulation of aldosterone accelerates hydrogen ion secretion. When aldosterone is deficient or in the presence of genetic or acquired defects in function of the epithelial sodium channel, hyperkalemia is accompanied by acidosis.

Treatment of Hyperkalemia

Guidelines for the treatment of hyperkalemia are based on consensus or expert opinion because of a lack of controlled clinical trials; most sources recommend emergency interventions for serum K⁺ concentrations >6 mmol/L if there are ECG changes and for K⁺ values >6.5 mmol/L regardless of the electrocardiogram (40). Severe ECG findings can be reversed by infusion of calcium gluconate in a volume of 10 ml of 10% solution infused over 3 to 5 minutes; calcium infusion does not affect the serum K⁺ level, but improvement in the electrocardiogram can be seen within 1 to 3 minutes and its effect can last 30 to 60 minutes. Calcium is contraindicated for patients who are taking digoxin because it potentiates digoxin tox-
icity. A shift of $K^+$ into cells can be achieved with administration of insulin or a $\beta_2$-adrenergic agonist. Insulin is given as an intravenous bolus with enough glucose to prevent hyperglycemia; the most commonly recommended regimen is a bolus injection of 10 U of insulin combined with 50 ml of 50% glucose given over 5 minutes. Insulin’s hypokalemic effect can be seen within 20 minutes, peaking between 30 and 60 minutes, and lasting for 6 hours. Salbutamol (the international nonproprietary name), known as albuterol in the United States, is the most commonly used $\beta_2$-adrenergic agonist for hyperkalemia, either as a single agent or in combination with insulin. It can be given by nebulizer (10 to 20 mg in 4 ml of saline); its effect may be seen in 30 minutes, with maximum effect at 90 to 120 minutes. Patients with acidosis can be given isotonic bicarbonate, but the benefit is uncertain and routine use of bicarbonate for the treatment of hyperkalemia is controversial. With the exception of patients with hyperkalemia caused by a shift of $K^+$ out of cells, definitive therapy of hyperkalemia requires that excess $K^+$ be eliminated. $K^+$ intake should be restricted, and medications that impair $K^+$ excretion should be discontinued. Loop diuretics are often recommended to enhance $K^+$ excretion (12,40) because of the known effect of flow in the distal nephron, but, surprisingly, no studies have documented their effectiveness in the acute treatment of hyperkalemia. Dialysis is the most effective means to remove $K^+$ from patients with compromised renal function, but cation exchange resins, which are intended to eliminate $K^+$ from the colon in exchange for $K^+$, are often used as a temporizing maneuver; as discussed next, their safety and effectiveness have recently been challenged (41,42).

**Sodium Polystyrene Sulfonate.** Sodium polystyrene sulfonate (SPS; also known by its trade name, Kayexalate) has been used for 40 years to treat hyperkalemia. In its early use, SPS was given suspended in water, but constipation and fecal impactions associated with the drug led to the recommendation that it be given in a suspension with hypertonic sorbitol, an osmotic cathartic. Several reports of intestinal necrosis caused by SPS in sorbitol ensued, initially in the renal transplant literature. Most of the cases occurred in a postoperative setting or in critically ill patients with ESRD. Until recently, bowel necrosis was thought to be an extremely rare complication affecting very sick patients who were given $K^+$-binding resin enemas. McGowan *et al.* (43) conducted a 9-year retrospective, single-center study at a university hospital and found 29 patients with reports of SPS crystals in surgical specimens. Of these, 11 patients were identified with confirmed intestinal ischemia (four of them fatal) temporally related to the oral administration of SPS-sorbitol (mean dosage 92 g, range 30 to 170 g). Only two of these patients had been admitted for surgical procedures (both of them orthopedic); four (36%) of the 11 patients had ESRD that required dialysis, and three had been treated with SPS-sorbitol despite normal renal function. Three of the four patients with fatal bowel necrosis associated with SPS-sorbitol had been admitted to the hospital for noncritical illness, including one with normal renal function. Since McGowan’s study, there have been additional reports of bowel necrosis associated with $K^+$-binding resins. A 64-year-old woman with severe heart disease and renal failure developed severe abdominal cramping, abdominal distention, and colonic dilatation a few hours after receiving the first of three doses of SPS (30 g) in sorbitol; 2 weeks later, massive hematochezia developed and a colonic biopsy showed ulcerated mucosa and prominent granulation tissue with eosinophilic, angulated crystals embedded in mucosal ulcers (44). A 56-year-old woman with stage 3 renal disease was given a single dose of 15 g of SPS orally for a serum $K^+$ of 5.8 mmol/L (45). She developed a large sessile mass in the midtransverse colon; when examined on biopsy, the mass was shown to contain crystals, consistent with SPS-induced colonic injury. The authors noted that she really did not need the SPS that was given to her because she had no changes on her electrocardiogram and her mild hyperkalemia was already resolving in response to intravenous fluids. A 24-year-old woman who had acute renal failure and a $K^+$ of 6.8 mmol/L and was treated with 30 g of the premixed SPS-sorbitol preparation and a 50-g SPS-sorbitol enema developed patchy transmural small bowel necrosis 12 days after exposure to the binding agents, resulting in purulent peritonitis that required bowel resection; SPS crystal deposition was found within the intestinal mucosa. The patient had been receiving thiopental to induce barbituric coma for epilepsy before SPS-sorbitol, and the resulting ileus may have increased her susceptibility to this complication, and norepinephrine, given to counteract the hypotensive effects of thiopental for 10 days before the recognition of peritonitis, was likely to have reduced splanchnic blood flow.
flow (46). On the basis of experiments on rats, sorbitol is thought to be the offending agent in this complication. However, there has been one report of colonic mucosal necrosis with ulceration but not infarction of the bowel after administration of calcium polystyrene sulfonate, an analog of sodium polystyrene sulfonate without sorbitol; the patient had been given the drug both orally and as an enema suspended in 20% dextrose (47). Colonic biopsies showed the crystals within the ulcer bed tissue and within the necroinflammatory debris.

In response to reports of these complications, in September 2009, the US Food and Drug Administration issued an advisory against concomitant administration of Kayexalate powder with sorbitol. Because it was believed at the time that toxicity was related to 70% but not 30% sorbitol, a premixed preparation of SPS in 30% sorbitol was allowed to remain on the market. However, several of the more recent reports of colon necrosis followed use of the premixed preparation containing 30% sorbitol (43, 44, 46). These disturbing reports prompted an invited commentary in the American Society of Nephrology’s official journal to review the evidence showing that K+-binding resins are safe and effective in the treatment of hyperkalemia (42). Synthetic cation-exchange resins are insoluble polymers with a molecular structure resembling a crystal lattice to which reactive carboxylic or sulfonic groups are attached. When placed in a solvent, the resin’s reactive groups, which can be preloaded to form sodium, K+, calcium, or ammonium salts, exchange their bound cations with cations dissolved in the solvent. However, although hydrogen-cycled resins markedly increase fecal K+ losses (albeit, at the expense of acidosis from absorption of hydrogen ions in exchange for K+), administration of a sodium-cycled carboxylic acid resin to experimental animals showed no increase K+ excretion. This is not surprising given both the limited amount of K+ available for exchange in the colon and the competition with the high concentrations of ammonium in the colonic lumen, which compete with K+ for binding (41). There are no published data showing increased K+ elimination in the stool after administration of SPS to animals; the only evidence that it increases K+ elimination comes from uncontrolled data showing K+ binding in the stool and a hypokalemic effect in four patients with renal failure and a single normal volunteer. The best evidence available that SPS lowers the serum K+ concentration is an uncontrolled study in 1961 showing that in 23 of 30 patients with hyperkalemia and renal failure, the plasma K+ fell by at least 0.4 mEq/L in the first 24 hours after treatment with SPS suspended in water. Because of concurrent treatment with extremely low-K+ diets and administration of large quantities of dextrose, it is uncertain that the hypokalemic effect was actually due to the resin. Because most K+ enters the bowel in the rectum, speeding delivery of the oral resin to the distal colon with cathartics would be expected to enhance its effectiveness, but adding sorbitol to SPS does not seem to make it more effective in correcting hyperkalemia. Studies of patients with normokalemia and mild hyperkalemia and with ESRD found that the serum K+ concentration rose slightly (0.4 mEq/L) on placebo and did not change during the course of 12 hours in response to a single dose of 30 g of resin in water, 30 g of resin in 60 g of sorbitol, or 60 g of sorbitol alone. The JASN commentary concluded that “clinicians must weigh uncontrolled studies showing benefit against uncontrolled studies showing harm” as well as stating that it “would be wise to exhaust other alternatives for managing hyperkalemia before turning to these largely unproven and potentially harmful therapies” (42). An editorial in the society’s clinical journal (CJASN) called these conclusions “immoderate,” arguing that “the majority clinical consensus is that they do work,” a conclusion supported by preliminary findings from an observational study demonstrating a dose-dependent decrease in plasma K+ within 8 hours of treatment with SPS/sorbitol (48); (2) “the only other ‘excretory’ modalities available are dialysis and loop diuretics, both of which have limitations and potential side effects, and like SPS, may take hours to have an effect”; (3) “kaliuresis induced by loop diuretics (which have not, per se, been studied for the treatment of hyperkalemia) requires adequate kidney function, which is often not present, and at high doses may cause azotemia and ototoxicity”; (4) “the estimated incidence of colonic necrosis would be less than 0.1% per dose”; and (5) “demonstrating SPS crystals in the necrotic lesion does not prove causality.” The authors also cited settings such as the Haitian earthquake and other disasters in which dialysis availability is limited and SPS may be the only option for K+ removal.

No one would argue that treatment with SPS in sorbitol is the best available choice for patients with ESRD in a disaster area. However, it is doubtful that
the 5 million doses of premixed SPS in sorbitol sold each year are reserved for such patients. Most patients who are given SPS have some renal function and serum K\(^+\) values <6 mmol/L (48); it is difficult to justify even a small risk for a drug that is probably unnecessary. We clearly need more data on both the benefit and the harm associated with SPS and sorbitol. We also need data on alternative therapies: Diuretics alone and in combination with bicarbonate and high-dose mineralocorticoids and cartharctics other than sorbitol.

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**Fludrocortisone and Glycyrrhetic Acid.** Serum K\(^+\) levels >6 mmol/L have been reported to occur in up to 12% of patients who receive long-term hemodialysis and is a frequent reason for emergency dialysis. Because of concerns about the efficacy and safety of cation exchange resins, alternative agents to enhance K\(^+\) elimination in the colon have been sought for this population. Because K\(^+\) secretion in the distal colon is regulated by the mineralocorticoid receptor, mineralocorticoids might be expected to be effective in managing hyperkalemia. In uncontrolled studies, the synthetic mineralocorticoid fludrocortisone has been reported to lower the plasma K\(^+\) concentration in patients on hemodialysis. However, not all studies have confirmed the effectiveness of fludrocortisone, possibly because of differences in dosing. High doses of fludrocortisone may be more effective, but because the drug is eliminated in the urine and has a higher glucocorticoid potency than cortisol, there is concern that accumulation of fludrocortisone may cause adverse effects (49). In a 2-week preliminary proof-of-principle study, inhibition of 11\(\beta\)-hydroxysteroid dehydrogenase (11\(\beta\)-HSD2), by glycyrrhetic acid, the active ingredient of licorice, was shown to decrease the serum K\(^+\) concentration in dialysis patients (49). The enzyme 11\(\beta\)-HSD2, which is present in mineralocorticoid target tissues including colonic epithelial cells, converts endogenous cortisol into cortisone, which has a much lower affinity for the receptor; endogenous cortisol can activate the mineralocorticoid receptor. The efficacy and safety of glycyrrhetic acid was subsequently studied in 20 patients who were on maintenance hemodialysis in a prospective, placebo-controlled 6-month crossover study. Glycyrrhetic acid reduced the frequency of severe hyperkalemia (>6 mmol/L) when compared with placebo (0.6 versus 9.0%; \(P < 0.001\)), and within days, it produced a sustained decline in predialysis K\(^+\) concentrations, prompting the use of higher dialysate K\(^+\) concentrations during treatment with glycyrrhetic acid than during treatment with placebo (3.2 ± 0.4 versus 2.8 ± 0.4 mmol/L) to avoid hypokalemia. During treatment with glycyrrhetic acid, the ratio of plasma cortisol/cortisone increased in all patients and plasma aldosterone and the aldosterone/renin ratio decreased. Treatment with glycyrrhetic acid was well tolerated and no differences in BP or interdialytic weight gain occurred, but there was a modest increase in liver enzymes during treatment. The study indicates that glycyrrhetic acid is effective as a K\(^+\)-lowering agent in patients whose ability to excrete K\(^+\) in the urine is limited, but more data on pharmacokinetics and on toxicity are needed before the drug can be adopted for long-term use.

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Pseudohyponatremia

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Nonhypotonic Hyponatremia

Pseudohyponatremia

“True hyponatremia,” or “hyponatremia hypotonic,” is characterized by a decreased concentration of
sodium in the aqueous phase of plasma. Plasma is normally 93% water and 7% proteins and lipids. Hyperproteinemia or hyperlipidemia decreases the aqueous fraction of the plasma sample and causes an artificially low plasma sodium concentration despite a normal sodium concentration in plasma water—a phenomenon called “pseudohyponatremia.” Autoanalyzers for routine chemical analysis dilute the plasma sample before the actual measurement is obtained; correction for the dilution factor (which assumes that plasma water equals 93% of the total sample volume) results in an artificially low result when the plasma water content is actually <93%. Instruments for measuring arterial blood gases use direct ion-specific electrodes (ISE) without any dilution and measure the activity of sodium in the water phase only. Thus, pseudohyponatremia does not occur when the measurement is made with direct ISE (sometimes called “direct potentiometry”). Although many autoanalyzers use ISE to measure the sodium concentration, the dilution step (sometimes called “indirect potentiometry”) allows pseudohyponatremia to occur. These differences in methodology should be taken into account to explain discrepancies between results obtained with classical biochemistry analyzers and with blood gas apparatus, and they can be exploited in evaluating patients in whom pseudohyponatremia is suspected.

Hyperlipemia that causes hyponatremia is usually due to the presence of triglyceride-rich chylomicrons, which cause specimen turbidity. When lipemia is observed, the laboratory can avoid spurious results by either measuring the sodium by a direct potentiometric method or by ultracentrifuging the specimen before using an indirect sodium method. However, specimen turbidity, even when objectively determined, has a poor correlation with actual triglyceride levels and the subsequent potential for various interferences. It is commonly believed, incorrectly, that pseudohyponatremia that is attributable to hyperlipemia is seen only in specimens that show obvious lacticence. Unlike hypertriglyceridemia, high cholesterol levels do not cause the blood to be visibly lipemic, and, in some cases, hypercholesterolemia can be associated with pseudohyponatremia. High concentrations of lipoprotein X (Lp-X), found in patients with intrahepatic and extrahepatic cholestasis and in the plasma of patients with lecithin cholesterol acyltransferase (LCAT) deficiency, cause pseudohyponatremia with little or no specimen turbidity (1). Lp-X is an abnormal lipoprotein that has a density in the LDL fraction. In cholestasis, it is thought to form from reflux of unesterified cholesterol and phospholipids into the circulation from cholestatic bile ductules. In LCAT deficiency, a condition in which cholestasis is not a feature, Lp-X may form in the plasma from the accumulation of phospholipids and free cholesterol. Unlike LDL, HDL, and VLDL, the particles of Lp-X cholesterol are not soluble in plasma water and thus increase the solid fraction of plasma (and decrease its water content). Levels of Lp-X can be as high as several thousand milligrams per deciliter of cholesterol.

**Hyperglycemia**

Hyperglycemia is the most common cause of nonhypotonic hyponatremia. In patients with diabetes, accumulation of glucose in the extracellular space draws water out of cells, lowering the serum sodium concentration. On theoretical grounds, Katz (2) predicted that serum sodium concentration would be expected to decrease by 1.6 mmol/L for every 100 mg/dl in blood glucose. Similarly, as blood sugar decreases, serum sodium would be expected to increase by 1.6 mmol/L for every 100-mg/dl fall in blood glucose. On the basis of data from acute somatatostatin-induced hyperglycemia in six healthy subjects, Hillier et al. (3) concluded that the mean decrease in serum sodium concentration averaged 2.5 mmol/L for every 100-mg/dl increase in glucose concentration and that the association between sodium and glucose concentrations was nonlinear; up to 400 mg/dl, Katz’s correction factor of 1.6 worked well, but if the glucose concentration was >400 mg/dl, then a correction factor of 4.0 was better. However, neither of these predictions can be applied to patients with intact renal function because serum sodium concentration increases during therapy for two reasons: (1) Water shifts back from the extracellular space to cells as the plasma glucose concentration falls, and (2) glucose acts as an osmotic diuretic eliminating electrolyte-free water in the urine, which also raises the serum sodium concentration. In patients with oligoanuria and ESRD, hyperglycemia is corrected by metabolism rather than excretion. A review of six published cases of dialysis-associated hyperglycemia found that the average change in serum sodium concentration during correction of hyperglycemia was almost identical to Katz’s predicted correction factor of −1.6 mmol/L per 100
mg/dl; however, the $\Delta[\text{Na}] / \Delta[\text{glucose}]$ values in individual studies ranged between $-2.48$ and $-1.44$ (4). The data did not support Hillier’s observation that a higher correction factor is necessary when the blood glucose concentration is $>400$ mg/dl. Edematous states would be expected to blunt the effect of glucose on the serum sodium concentration because the extracellular volume is larger than that assumed in the calculation. The mean value of $\Delta[\text{Na}] / \Delta[\text{glucose}]$ was $-1.04 \pm 0.23$ mmol/L per 100 mg/dl in four dialysis patients with severe edema and was $-1.65 \pm 0.08$ mmol/L per 100 mg/dl in five patients who were close to their dry weight (4).

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**Exogenous Solutes**

**Intravenous Mannitol.** Similar to hyperglycemia, infusion of hypertonic mannitol draws water out of cells, transiently lowering the extracellular sodium concentration. Mannitol acts as an osmotic diuretic, and its eventual excretion in the urine results in free water losses that raise the serum sodium concentration causing hypernatremia when water losses are not replaced. However, high doses of mannitol can cause renal tubular injury and acute renal failure. In this case, accumulation of mannitol results in sustained hypertonic hypernatremia that can be distinguished from true or hypo-osmotic hypernatremia by demonstrating the presence of an osmolar gap (5), a discrepancy between the measured plasma osmolality and the osmolality calculated by multiplying the serum sodium by 2 (to include accompanying anions) and adding the osmotic contributions of glucose and urea in mmol/L (values reported in mg/dl can be converted to mmol/L by dividing the glucose concentration by 18 and the blood urea nitrogen by 2.8).

**Irrigant Absorption.** Many endoscopic surgical procedures require an irrigating fluid to dilate the operating field and to wash away debris and blood. Systemic absorption of the irrigating fluid can lower the serum sodium concentration by expanding the extracellular space with sodium-free irrigant. Systemic absorption of isosmotic or hypo-osmotic irrigants during endoscopic prostate, bladder, or intrauterine surgery lowers the plasma sodium concentration with little or no change in plasma osmolality. In contrast to hypernatremia that is caused by hyperglycemia or hypertonic mannitol infusion, no shift of water from cells occurs; rather, serum sodium concentration falls because the extracellular volume is expanded with fluid containing nonelectrolyte solutes: Glycine, mannitol, sorbitol, or glucose. Immediately upon absorption, regardless of the solution used, serum sodium concentration falls to very low levels because the solute is confined to the extracellular fluid, but plasma osmolality remains constant or, if a hypo-osmotic solution is used, falls slightly. Shortly after surgery, regardless of the solution, serum sodium concentration begins to increase but for different reasons depending on which solute is used. If isosmotic (and isotonic) mannitol is absorbed, then the absorbed solute remains confined to the extracellular fluid and the plasma osmolality is unaltered; the serum sodium concentration increases as mannitol, an osmotic diuretic, is excreted in the urine with water. Changes in serum sodium concentration after absorption of isosmotic (5%) dextrose or sorbitol are more complex than those produced by mannitol. Serum sodium concentration increases as these sugars, also osmotic diuretics, are excreted in the urine, but, in addition, some of the absorbed solute is metabolized to carbon dioxide and water, allowing the plasma osmolality to fall over time. Some of the postabsorptive increase in serum sodium occurs as water leaves the extracellular fluid and enters cells. After initially distributing in the extracellular space, absorbed glycine, an amino acid, is able to enter muscle cells, which increases serum sodium above its nadir level. However, the absorbed glycine, along with serine and other osmotically active metabolites, persists in both the circulation and intracellular fluid for many hours. The amino acids are metabolized gradually to urea, another solute that is measured by the osmometer; therefore, the plasma osmolality remains stable as the serum sodium concentration rises to reflect distribution of the absorbed solution in total body water. Only a few studies have reported both serum sodium concentration and osmolarity after irrigant absorption. In a series of 72 patients who underwent transurethral resection of the prostate (TURP),
serum sodium concentrations decreased in 26% of the patients, with a decrement ranging from 10 to 54 mmol/L, whereas plasma osmolarity changed in only two (3%) cases (6).

Several irrigating fluids are available commercially, and the choice among them tends to be governed by price, stickiness and transparency, personal preference, and tradition. Solutions of glycine, an endogenous amino acid that is transparent and reasonably inexpensive, have become the most popular, but systemic absorption of the solution commonly results in nausea, vomiting, confusion, arterial hypotension, and, more rarely, coma and death. Hyperammonemic encephalopathy may develop because ammonia is an intermediate product in glycine metabolism. Laboratory studies of animals showed that glycine has direct and indirect cardiotoxic effects, and high plasma levels of glycine have been associated with echocardiographic abnormalities and increased troponin levels (7). More physiologic alternatives to glycine have been associated with less collateral and penetrative tissue damage, lower incidence of TURP syndrome, shorter catheter indwelling times, and earlier hospital discharge. New bipolar resection systems permit normal saline to be used as irrigant during endoscopic surgical procedures. A single-center, randomized, controlled trial compared monopolar cautery using 1.5% glycine as an irrigant (n = 30) with bipolar cautery using 0.9% saline as irrigant (n = 30). Serum sodium concentration fell by 1.3 mmol/L in the saline bipolar group and by 4.12 mmol/L in the glycine monopolar group, but these differences did not reach statistical significance in this small study.

References

Hypotonic Hyponatremia: Pathophysiology

In 1959, Edelman described a relationship among the plasma sodium (Na) concentration (PNa), isotopically measured exchangeable sodium (Nae), exchangeable potassium (Ke), and total body water (TBW) in 98 heterogeneous patients with stable PNaNs:

\[ \text{PNa} = \frac{\alpha \times (\text{Nae} + \text{Ke})}{\text{TBW}} + \beta \]

Edelman’s equation has been applied to clinical situations in which the PNa is changing, assuming that changes in the PNa can be predicted or explained by external balances of Na, K, and water (1). However, although this “tonicity balance” calculation has worked well in individual cases (2–4), its assumptions have not been rigorously tested. A study of acute hyponatremia in pigs (with plasma Na reduced from 136 to 120 mmol/L over 480 minutes) found that plasma Na values calculated from external balances of
cations and water on the basis of Edelman’s equation fit the observed plasma Na values extremely well \( (r = 0.98) \) with a significantly better fit than Na values calculated from water retention alone (Figure 10) (5). The calculated values for the slope of the equation \( (\alpha) \) and its intercept \( (\beta) \) in pigs were quite close to those derived from Edelman’s original data.

The findings of this experiment have important implications. Individual cells and some tissues (most notably the brain) are known to volume regulate when subjected to a hypotonic environment; for example, minimizing cell swelling by extruding K and chloride within minutes and organic osmolytes over several hours (6). If muscles, containing 80% of body water in pigs, were to respond rapidly to acute water retention with a volume regulatory response, then the decrease in PNa would be much greater (more of the retained water would be confined to extracellular space) and hyperkalemia would result from the efflux of K from muscle cells. External K losses did not exceed control levels during the experiment, and the plasma K did not increase, suggesting that there is no global volume regulatory response to acute water intoxication. Furthermore, muscle water content, as measured in vivo by magnetic resonance imaging and validated by direct measurements of tissue water content, increased as would be expected for perfect osmotic behavior, and there was no change in tissue K content (7).

The observation that changes in plasma Na are determined by external balances of Na, K, and water is consistent with our classic understandings of Na and water balance. In this traditional model, Na and its accompanying anions are the principal extracellular effective osmoles, and K salts account for almost all of the intracellular effective osmoles. These ions act as effective osmoles maintaining the volume of the extracellular and intracellular spaces because they remain osmotically active regardless of external balances and because they are restricted to their respective compartments by the activity of the Na\(^{+}\)-K\(^{+}\)-ATPase pump in the cell membrane. The PNa is thus considered to be an accurate measure of the concentration of Na throughout body fluid because concentration gradients cannot exist between the intravascular, interstitial space, and the cellular fluid compartments beyond the very small differences explained by the Gibbs-Donnan equilibrium. However, several observations in humans have challenged the traditional model and have increased interest in the possibility that pools of osmotically inactive Na are able to store or release Na: (1) Balance studies have shown that large amounts of Na can accumulate on a high-salt diet without accompanying water retention; (2) marked discrepancies have been found between changes in water and Na balance during weight loss induced by dieting; and (3) discrepancies between changes in body weight and changes in plasma Na have been reported after intense exercise (8,9). Mixed connective tissues are known to contain large amounts of Na, and in contrast to most animal cells, chondrocytes are surrounded by an extracellular fluid with an ionic composition that is altered by the negative charge density of glycosaminoglycans in the extracellular matrix. Glycosaminoglycans (GAGs) are negatively charged polyanions that attract cations and repel anions, resulting in extracellular cartilage Na concentration of 250 to 350 mmol/L and extracellular osmolality of 350 to 450 mmol/L. This osmotic strength maintains a high water content in
cartilage, which provides its biomechanical properties. Conversely, the high electrolyte concentrations of cartilage indicate “osmotically inactive” Na storage. Studies in rats subjected to very-high- or very-low-salt diets for several weeks showed that skin behaves in a similar manner acting as an adaptable pool for osmotically inactive Na storage (8). Increases in the polyanionic character of the extracellular matrix on a high-salt diet were accompanied by Na storage in skin, whereas reduced GAG polymerization and GAG sulfation and a subsequent reduction in the polyanionic character of the extracellular matrix were associated with the mobilization of Na from the skin reservoir with dietary salt scarcity. The previously mentioned pig studies suggested that, at least in the short term, osmotically inactive Na storage pools do not alter the traditionally expected relationships between Na, K, and water.

In contrast to skeletal muscle, the brain does not swell as much as would be expected for perfect osmotic behavior, even in acute hyponatremia; an extensive review of the response of the brain to hyponatremia was recently published (10). Previous studies have relied on measurements of water and solute contents in the whole brain. In the pig model described already, magnetic resonance imaging was used to measure brain water content in vivo at 70-minute intervals during the induction of hyponatremia (plasma Na 123 mmol/L) over 7 hours. These measurements were then validated with direct measurements of water content as determined by tissue drying and deuterium dilution. Major regional differences in the brain were found. Surprisingly, brain water content in the region of the cell-rich thalamus increased as would be expected for perfect osmotic behavior, swelling by 12%. In white matter, brain water content increased by only 3%, possibly reflecting a regulatory volume decrease as a result of extrusion of solutes or, alternatively, slow water equilibrium in hydrophobic regions of the brain. Consistent with these findings, measurements of tissue Na content showed that brain Na content decreased significantly, but, in contrast to rodents subjected to hyponatremia over a similar time course, brain K content did not change. The decrease in Na content can be explained by a decrease in extracellular Na-rich fluid as interstitial fluid, cerebrospinal fluid, and blood are squeezed out of the skull (11).

In rats with hyponatremia, intracerebroventricular administration of benzamil, a specific Na channel blocker, completely abolished brain swelling in response to acute hyponatremia (a decrease in plasma Na from 146 to 110 mmol/L over 2 hours); conversely, intracerebroventricular administration of arginine vasopressin (AVP) exacerbated osmotic brain swelling (12). There is some evidence that AVP stimulates Na uptake by the brain by activating V1B receptors, which are widely distributed in the central nervous system, and the authors speculated that an early cellular Na uptake through benzamil-sensitive activated Na channels may play a role in brain swelling that is caused by hyponatremia. However, the mechanism for these intriguing observations is not entirely clear. Brain tissue Na content (likely reflecting extrusion of extracellular fluid from the brain) decreased in response to hyponatremia to a similar degree in all groups with hyponatremia, including those with exacerbated brain swelling induced by AVP and those with ameliorated brain swelling induced by benzamil.

Hyponatremia occurs when water intake exceeds water losses. Discussions of the pathogenesis of hyponatremia have focused on the regulation of water excretion, but we should ask why patients who are unable to eliminate water normally do not compensate for that abnormality. Similar to how patients with diabetes insipidus–related defective water conservation avoid hypernatremia by drinking more, patients who cannot eliminate water normally might avoid hyponatremia by decreasing water intake. The transient receptor potential vanilloid 4 (TRPV4) channel, expressed in the osmosensing nuclei of the brain, is activated by hypotonic stress. Targeted deletion of the TRPV4 gene causes aberrant osmoregulation in murine...
models, causing them to drink more and to become more hyponatremic than wild-type mice when given exogenous vasopressin. A polymorphism in the TRPV4 gene resulting in a proline-to-serine substitution at residue 19 (TRPV4P194) was found to be significantly associated with the serum Na concentration in two male non-Hispanic Caucasian healthy aging cohorts (one cohort participating in a study on the genetic determinants of Alzheimer disease and one participating in a study to assess the genetic determinants of osteoporotic fractures) (13). Male participants with the allele were 2.30 to 6.45 times as likely to exhibit hyponatremia as male participants without the allele. It was inferred that the presence of the TRPV4P194 allele may act synergistically with conditions of vasopressin excess, making participants drink more than those without the allele, thereby promoting hyponatremia. Consistent with this hypothesis, cells transfected with the mutated TRPV4P194 channel exhibited diminished whole-cell cationic currents when exposed to mild hypotonic shock (corresponding to a 15% reduction in osmolality), as compared with cells transfected with the wild-type TRPV4 gene.

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Acute Hypotonic Hyponatremia

Since the 1920s and 1930s, it has been understood that “acute water intoxication” can cause fatal cerebral edema and that brain swelling and death can be prevented by administering hypertonic saline. There should be no doubt that when the plasma sodium concentration decreases more rapidly than the brain can adapt to it, patients are at risk for serious neurologic complications. Very rapid onset of hyponatremia is most likely to occur in only a few settings: (1) Self-induced water intoxication, in psychotic patients with marked polydipsia; (2) excess water consumption by marathon runners; (3) use of the illicit drug “ecstasy” (3,4-methylenedioxymethamphetamine), which provokes both thirst and vasopressin release; and (4) excessive hypotonic fluid administration to patients with an impaired ability to excrete an acute water load, most commonly in the postoperative period (1). However, there are occasional reports of acute water intoxication in other settings. For example, a 34-year-old man developed seizures, requiring mechanical ventilation, associated with a serum sodium of 123 mmol/L after drinking approximately 40 glasses of water (approximately 8 L) over a few hours, during a domino game that required the loser of each match to drink a full glass of water (2). Two previously healthy young women developed acute hyponatremic encephalopathy (serum sodium 122 and 126 mmol/L) after drinking 3 to 6 L of water in preparation for a pelvic ultrasound (in response to advice to drink “as much as possible” because “the more you drink, the better the test results”); both survived without sequelae (3).

Brain edema has seldom been documented before death in patients with acute hyponatremia. In a recent report, an elderly woman developed acute symptomatic hyponatremia (vomiting, stupor, Babinski signs and mydriasis of one pupil) after experiencing a decrease in plasma sodium from 133 to 109 mmol/L over 26 hours in the hospital. A computed tomography (CT) scan showed near absence of cere-
bral sulci, compression of the ventricles and sylvian fissures, and decreased cerebrospinal fluid in the basal cisterns and the cerebral sulci (4). Despite a 4-hour delay, during which her plasma sodium fell to 108 mmol/L, she survived the experience without neurologic sequelae. A repeat CT scan obtained 36 hours later, when plasma sodium was 120 mmol/L, showed improvement in cerebral edema; however, there was no improvement in a scan done at 12 hours, when the plasma sodium was 116 mmol/L. In the two young women who developed hyponatremia preparing for their pelvic ultrasounds, CT scans 2 and 8 hours after symptom onset showed diffuse sulcal effacement and compression of lateral ventricles consistent with brain edema. Magnetic resonance imaging (MRI) obtained 10 and 14 hours after onset revealed cortical sulcal narrowing and restricted diffusion; findings suggested diffuse cerebral cortical cytotoxic edema and blood-brain barrier breakdown, although a repeat scan in one of these cases showed the findings to be reversible (3). The authors noted that with T1- and T2-weighted MRI modalities, detection of mild to moderate cerebral edema is difficult because the mass effect is faint and can be overlooked. Diffusion-weighted images show easily noticeable findings analogous to the cerebral edema found in ischemic stroke. It is not clear whether the evidence of blood-brain barrier breakdown observed in these MR images reflect the acute cerebral edema or rapid correction of hyponatremia.

**Psychotic Polydipsia**

Polydipsia is very common among chronic psychiatric patients, although the actual prevalence of the disorder is still unclear. Objective measures to identify patients, such as urine specific gravity and diurnal weight gains, have not been applied in a consistent manner. A study of psychiatric inpatients from Cuba used the same criteria that were used in two previously published studies from the United States and Spain (5). Urine specific gravity <1.009 in an afternoon urine sample was used to define polydipsia, and a 4% diurnal weight gain was taken to identify the population at serious risk for water intoxication. In the Cuban patients, the risk for primary polydipsia and water intoxication were 47% (n = 189) and 6.7% (n = 27), respectively. These results are similar to those reported for patients in the United States (34.0 and 3.7%) and Spain (25 and 7%) for the total population of psychiatric inpatients. Pooling findings from studies in the United States, Spain, and Cuba using the same criteria showed that the prevalence of polydipsia is twice as high in institutionalized psychiatric patients with other diagnoses (41.5 versus 25.1%, respectively; odd ratio 2.12; P < 0.001).

The anterior hippocampal volume is smaller in patients with schizophrenia and a history of hyponatremia compared with similar patients with schizophrenia and polydipsia but without a history of hyponatremia, patients without polydipsia, and healthy control subjects (6,7). There is evidence that this brain region normally constrains hypothalamic-pituitary-adrenal and vasopressin responses to psychological stressors, and some authors have hypothesized that abnormalities of vasopressin release are central to pathogenesis of water intoxication. However, pathologic antidiuresis is not a prerequisite for self-induced water intoxication because patients with severe polydipsia have been observed to develop hyponatremia despite excretion of maximally dilute urine. Thus, it is unclear whether the reset osmostat that has been found in the recovery phase of acute water intoxication represents the cause or consequence of water retention. Similarly, cognitive defects have been shown in patients with schizophrenia and a history of water intoxication; although these findings could reflect primary pathology within the anterior hippocampus and associated prefrontal/limbic brain regions, they could also represent neurologic morbidity from repeated episodes of water intoxication (8).

Hyponatremia is sometimes attributed to the use of antipsychotic drugs, but a cause-and-effect relationship is not as well established as that of antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs). Using a standard drug reaction probability rating system, Meulendijks et al. (9) reviewed all published reports of hyponatremia attributed to antipsychotic drugs and identified 91 published case reports and case series describing 120 patients with one or more hyponatremic events; 19% of these were rated as showing a “probable” relationship, and in 7% of cases, hyponatremia recurred on rechallenge with the drug. In the majority of cases, it was not possible to exclude reliably other possible causes for hyponatremia including psychosis itself.

**Exercise Hyponatremia**

Exercise-associated hyponatremia (EAH) has emerged as a serious problem among endurance athletes, affecting as many as 7% of participants. Hyponatremia develops primarily because of excess water or hypotonic
fluid intake, causing athletes to gain weight despite loss of tissue glycogen. Ingested water is retained because of the nonosmotic release of vasopressin, and hyponatremia is augmented by sweat losses of sodium. Since 1993, at least four otherwise healthy women and one male runner have died from EAH after following advice to consume as much fluid as possible during exercise; the subject was discussed extensively in previous fluid and electrolyte issues of NephSAP, and a review was published recently (10). On-site whole-blood sodium testing was introduced at the finish-line tent of the Boston marathon beginning in 2001 to provide diagnosis and to facilitate triage for appropriate treatment (11). Hyponatremia was identified in 27.7% of collapsed runners and was treated with 0.9% saline when runners were unable to drink fluids. Hyponatremia was found in 63 (4.8%) runners, including 26 (2.0%) with values <130 mmol/L; those with seizures or coma received intravenous 3% saline, and 16 runners who were able to drink were given a concentrated oral solution composed of 4 bouillon cubes in 4 oz of water. The treatment increased the serum sodium by 6 to 7 mmol/L within 16 to 26 minutes in three patients with delirium, resulting in complete resolution of symptoms.

Obstetric Hyponatremia

Rare cases of water intoxication have been reported during labor. In a recent case report, a 37-year-old primigravida with a history of habitual water drinking developed multiple seizures associated with a serum sodium of 111 mmol/L (12); her newborn had a serum sodium of 108 mmol/L. The patient’s serum sodium was increased to 123 mmol/L on the second hospital day, and she was treated with 3% saline but likely autocorrected because urine osolalities of 67 and 80 were documented in the first 2 days. Infusion of oxytocin, which acts as an antidiuretic hormone, in the peripartum period may result in hyponatremia if the drug is administered in hypotonic fluids. In a recent case report, a young woman who received oxytocin in 5% dextrose water experienced seizures 24 hours postpartum when her serum sodium concentration fell to 113 mmol/L; she recovered consciousness 12 hours later, when her serum sodium had increased to 119 mmol/L (13).

Postoperative Hyponatremia

The first reported case of fatal cerebral edema caused by water intoxication occurred in a postoperative patient. Surgery almost invariably results in the nonosmotic release of vasopressin, and administration of hypotonic fluid in the postoperative period predictably causes hyponatremia. Many deaths have been recorded, mostly in young women and children (1,14). Children exhibit more symptoms than adults in response to abnormal sodium levels because there is less room for brain cells to swell (the brain reaches its adult size by the time the child is 6 years old, but the skull does not reach adult size until a person is 16 years old). Four pediatric deaths from cerebral edema with brain herniation as a result of acute hyponatremia associated with intravenous administration of hypotonic solutions—three in a postsurgical setting, one in a medical setting—were voluntarily reported (two to the Institute for Safe Medication Practices Canada and two to the Institute for Safe Medication Practices in the United States) (15). Details of the clinical course of these patients is provided in a published report: (1) A 4-year-old who was given 3.3% dextrose and 0.3% sodium chloride solution (“2/3 and 1/3,” containing 50 mmol/L NaCl) at 55 ml/h and 200 ml of oral fluids after a routine tonsillectomy developed vomiting and seizures; when the serum sodium was found to be “less than 120 mmol/L,” 3% saline was begun, but the patient died of herniation; and (2) a previously healthy 3-year-old who was admitted for vomiting and diarrhea and was given “2/3 and 1/3” at 130 ml/h intravenously for a total of >1.5 L; less than 24 hours later, the serum sodium fell from 138 to “less than 120 mmol/L,” and the child became rigid, developed seizures and oxygen desaturation, and then cardiac arrest despite the administration of hypertonic saline; (3) a 6-year-old child who was given 5% dextrose at 200 ml/h after an outpatient tonsillectomy because of a prescription error died after her serum sodium concentration fell to 107 mmol/L over 12 hours; death was preceded by several hours of vomiting, jerking motions, rigid extremities, and rolled back eyes, erroneously attributed to a dystonic reaction to promethazine; and (4) a child of unspecified age who became somnolent, with vomiting and seizure-like activity for several hours after the serum sodium fell to an unspecified level and after unspecified fluids 2 days after surgery for coarctation of the aorta. The National Patient Safety Agency in the United Kingdom has identified hospital-acquired hyponatremia in children as a major patient safety issue. Safety alerts
and guidelines for the administration of fluids to children have been published as a result, including the requirement for sodium chloride 0.18% with glucose 4% intravenous solution to be removed from hospitals. A provincial coroner identified six pediatric deaths related to acute hyponatremia in hospital settings in a 10-year period and provided a guideline for practitioners who administer parenteral fluids to children.

These tragic experiences have caused many investigators to question the widespread use of hypotonic solutions for parenteral fluid maintenance therapy in children, a practice based on a formula that was developed more than 50 years ago (16). The formula is derived from minimum free water requirements based on caloric expenditure per kilogram of body weight in normal children. These estimates are unlikely to be valid during fasting and without physical activity; more important, the formula presumes normal excretion of free water by the kidneys because it was developed before release of ADH in response to nonosmotic stimuli was widely appreciated. A study of 124 children who were admitted for elective surgery documented vasopressin levels at or above the range of maximal antidiuresis (3 to 5 pg/ml), before the induction of anesthesia (presumably reflecting the effects of pain, anxiety, or nausea); during and after surgery, most patients had vasopressin levels of >3 pg/ml that remained in many patients 24 hours after surgery (17). A number of studies, including randomized trials, have shown that fluid replacement with isotonic saline carries a lower risk for hyponatremia without causing hypernatremia (17–19).

Neurosurgical Hyponatremia

Hyponatremia is common in patients with acute neurologic and neurosurgical conditions. Although the onset of the electrolyte disturbance is variable in these conditions, patients with hyponatremia and intracranial pathology are at serious risk because even mild degrees of brain swelling are poorly tolerated. Hyponatremia is particularly common in subarachnoid hemorrhage (SAH), and it augers a poor prognosis. Thus, there is general agreement that hyponatremia in patients with intracranial pathology regardless of the duration of the disturbance should be treated when the serum sodium level is <131 mmol/L (20) and, if symptomatic, aggressively with hypertonic saline (21,22). A sliding-scale hypertonic saline infusion protocol, to be started once the serum sodium falls to ≤133 mmol/L or after a serum fall in serum sodium concentration by ≥6 mmol/L over 24 to 48 hours, was found to be effective in avoiding progression of mild acute hyponatremia in critically ill patients with neurologic and neurosurgical diseases (23). The protocol calls for administration of NaCl tablets 3 g every 6 hours orally or per nasogatric tube combined with intravenous 3% NaCl, starting at an initial dosage of 20 ml/h. The dosage of 3% NaCl is then escalated every 6 hours by 10 to 20 ml/h, depending on the serum sodium concentration, to a maximum dosage of 80 ml/h; the rate is held constant for serum sodium values of 136 to 140 mmol/L and held for 6 hours for serum sodium concentrations >140 mmol/L. In contrast to use of hypertonic saline maintenance fluid without sliding-scale adjustment, which has been reported to result in a 52% incidence of serum sodium concentrations >155 mmol/L and 34% >160 mmol/L (24), <1% of the sodium values exceeded 145 mmol/L with the sliding-scale approach, whereas 0.06% of the time was spent with sodium values <130 mmol/L and 84% of the time was spent in the goal range (Na 136 to 145 mol/L). The regimen was well tolerated with no neurologic adverse effects and no incidents of heart failure.

A sliding-scale hypertonic saline infusion protocol, to be started once the serum sodium falls to ≤133 mmol/L or after a serum fall in serum sodium concentration by ≥6 mmol/L over 24 to 48 hours, was found to be effective in avoiding progression of mild acute hyponatremia in critically ill patients with neurologic and neurosurgical diseases.

Treatment of Acute Hyponatremic Emergencies

Self-induced water intoxication and symptomatic hospital-acquired hyponatremia are true emergencies that demand prompt and aggressive intervention with hypertonic saline. In these conditions, the risks of cerebral edema caused by hyponatremia exceed the risks of excess therapy. Similar recommendations apply to patients who have hyponatremia and intracranial pathology and develop neurologic symptoms and to patients who have hyponatremia and active seizures regardless of the duration of the electrolyte disturbance. If hypertonic saline is withheld from patients who have self-induced water intoxication and whose urine is not maximally dilute, there is a risk that serum concentration may decrease spontaneously because of delayed
absorption of water from the gastrointestinal tract. If hypertonic saline therapy is delayed or if isotonic saline is given instead to patients with acute postoperative hyponatremia, then excretion of concentrated urine can further reduce the serum sodium concentration with disastrous results. A review of the literature to identify reports of patients with hyponatremia and seizures or coma concluded that a 4- to 6-mEq/L increase in the serum sodium concentration was enough correction to rescue the most severely affected patients from complications of acute hyponatremia (1). A consensus has emerged that this goal is best achieved with 100 ml or 2-ml/kg bolus infusions of 3% saline, repeated up to two times if necessary (1,25). Use of hypertonic saline to treat life-threatening intracranial hypertension in patients with normonatremia and neurosurgical emergencies has shown that an increase in serum sodium concentration of this magnitude can successfully reduce intracranial pressure and reverse impending herniation (1,26,27). Some clinicians may be reluctant to prescribe bolus infusions of 3% saline, in the erroneous belief that this violates an old in recom-

A consensus has emerged that treatment goals for patients with seizures and coma as a result of acute hyponatremia are best achieved with 100 ml or 2-ml/kg bolus infusions of 3% saline, repeated up to two times if necessary.

Confusion was created when a proposed limit of 12 mEq/L per day was expressed as an hourly rate. In fact, there is no evidence that a rapid hourly rate of correction is harmful as long as the total increase in serum sodium concentration over a 24-hour period is not excessive.

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Chronic Hypotonic Hyponatremia

Differential Diagnosis

Chronic hyponatremia is usually caused by vasopressin (AVP)-mediated water retention. Because AVP levels should normally be undetectable when the plasma sodium concentration falls below 135 mmol/L, secretion of AVP in the presence of hyponatremia represents a nonosmotic stimulus for AVP release or ectopic secretion of the hormone. The most common cause for nonosmotic release of AVP is an inadequate circulating blood volume caused by true hypovolemia, heart failure, or hepatic cirrhosis and sensed by pressure and volume receptors that relay signals to AVP-secreting cells in the hypothalamus. These conditions also activate the sympathetic nervous system and result in increased levels of renin, angiotensin, and aldosterone, factors that cause sodium retention and are reflected in a low urine sodium concentration.

Hyponatremia caused by heart failure or hepatic cirrhosis is clinically obvious because it occurs in patients with advanced disease. Hypovolemic hyponatremia may be equally obvious, with orthostatic hypotension, tachycardia, and prerenal azotemia, but, in many cases, these features are absent and the clinician must turn to laboratory clues to distinguish between hypovolemic hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH).

The use of fractional excretion of sodium and fractional excretion of urea in the differential diagnosis of chronic hyponatremia were discussed in the last fluid and electrolyte issue of *NephSAP* and in a recently published review (1). However, these diagnostic tools are useful only in identifying patients who have developed hyponatremia from extrarenal fluid losses. Patients with renal salt-wasting syndromes pose a greater diagnostic challenge because urine osmolality and urine sodium both are high and cannot be distinguished from urine chemistries in patients with SIADH.

Causes of Renal Salt Wasting

Addison Disease. In patients with unexplained hyponatremia, adrenal insufficiency must be excluded before making a diagnosis of SIADH (2). Addison disease often presents insidiously, and symptoms of postural hypotension are late manifestations. In developed countries, Addison disease is usually caused by autoimmune adrenalitis, which can occur in isolation or as a part of autoimmune polyendocrinopathy syndromes: (1) autoimmune polyendocrinopathy syndrome type 1, including autoimmune hypoparathyroidism, chronic mucocutaneous candidiasis, and other autoimmune disorders (e.g., type 1 diabetes, chronic active hepatitis, primary gonadal failure, autoimmune thyroid disease) and (2) autoimmune polyendocrinopathy syndrome type 2, primarily including type 1 diabetes or autoimmune thyroid disease and sometimes primary gonadal failure, pernicious anemia, and vitiligo. Tuberculosis remains the most common cause of Addison disease worldwide, and fungal infections and cytomegalovirus adrenalitis may be complications of immunodeficiency. Adrenoleukodystrophy, caused by accumulation of long-chain fatty acids in the adrenal gland and central and peripheral nervous system, is an important cause of Addison disease in men. A morning serum cortisol level >18 µg/dl (500 nmol/L) generally excludes Addison disease, whereas a level <6 µg/dl is suggestive of the disease. The response to injection of a synthetic analog of ACTH is the definitive diagnostic test.

Addison disease can often go unrecognized for months or years. A German study of 270 patients who had adrenal insufficiency (99 with Addison disease and 117 with hypopituitarism) and agreed to complete a questionnaire found that <30% of women and 50% of men received a diagnosis within the first 6 months after the onset of symptoms; in 20% of patients, diagnosis was delayed for >5 years (3). Fatigue and lack of energy were complaints in 74% of women and 88% of men. Symptoms of nausea and vomiting occurred in 50% of women and 25% of men with Addison disease; weight loss, anorexia, abdominal pain, and diarrhea were also common. These symp-
toms often led to erroneous diagnoses of psychiatric or gastrointestinal disorders.

**Congenital Adrenal Hyperplasia.** Congenital adrenal hyperplasia (CAH) from 21-hydroxylase deficiency is an autosomal recessive disorder that causes cortisol deficiency and androgen excess, with or without aldosterone deficiency. Severe life-threatening, salt-wasting hyponatremia, often with serum sodium values <125 mmol/L, and hyperkalemia are common features that can result in death in early infancy; these abnormalities respond to cortisol and mineralocorticoid replacement with fludrocortisone (4,5). The disease is most obvious in girls because of ambiguous genitalia, but boys appear normal. Advances in the recognition and care of the disease have enabled many children to reach adulthood. Because of the unfamiliarity of internists with the disease, young adults with CAH are often lost to follow-up and may stop taking corticosteroid replacement (6,7). Salt-wasting crises appear less often in adults but can emerge during concurrent illnesses.

**Cisplatin.** Cisplatin has been used effectively in the treatment of a variety of solid tumors. However, without adequate hydration, 50% of patients develop a usually reversible decline in GFR and, less commonly, a renal salt-wasting syndrome as a result of proximal tubular injury that may result in hyponatremia; a comprehensive review of this condition was published recently (8). Renal salt wasting has been detected from 12 hours up to 1 month after cisplatin administration after doses ranging from >200 to 600 mg/m². Signs of volume depletion including orthostatic hypotension and weight loss (as much as 12 lb in 3 days in one reported case) have been present in most reports of cisplatin-induced hyponatremia. Hyponatremia caused by cisplatin is often treated as SIADH because both conditions are characterized by hypotonic hyponatremia and increased urinary sodium concentrations (8,9). Clinical signs of hypovolemia, including weight loss, symptomatic orthostatic hypotension, and tachycardia, are responsive to volume replacement and distinguish cisplatin-induced renal salt wasting from SIADH. Orthostatic hypotension also occurs in patients with SIADH caused by small cell lung cancer, but, in these cases, it is caused by autonomic insufficiency and not volume depletion, and it does not respond to intravenous fluids. It is important not to treat cisplatin-induced salt wasting with water restriction, diuretics, or AVP antagonists because this may lead to more volume depletion and hemodynamic collapse. Treatment should be aimed at restoring intravascular volume with oral fluids and salt tablets or intravenous isotonic saline.

**Cerebral Salt Wasting.** Hyponatremia is a common complication of central nervous system disease. High urine sodium concentrations despite a low serum sodium concentration led to the term “cerebral salt wasting” in the early 1950s, before the pathophysiology of SIADH was understood. The term has reappeared in recent years and is now considered by many neurointensivists to be a common cause of hyponatremia in patients with intracranial pathology (10–13). As discussed in the last fluid and electrolyte issue of NephSAP, there is controversy in the literature as to whether hyponatremia in patients with intracranial disease should be ascribed to SIADH or to “cerebral salt wasting.” Some have questioned whether cerebral salt wasting actually exists and, if it does, whether it is possible to diagnose the condition reliably. A valid diagnosis of cerebral salt wasting requires the demonstration that urinary salt losses persist despite hypovolemia. In the neurosurgical literature describing purported cases of cerebral salt wasting, hypovolemia is defined clinically as a central venous pressure (CVP) <5 mmHg. However, CVP is not a reliable measure of volume depletion. Marik et al. (14) reviewed the literature to identify studies that compared CVP measurements with other objective measures of intravascular volume. The only study they could find demonstrating the utility of CVP in predicting volume status was performed in seven standing, awake mares undergoing controlled hemorrhage. Of the 24 studies of humans included in their analysis, five compared CVP with the measured circulating blood volume, whereas 19 studies determined the relationship between CVP and change in cardiac performance after a fluid challenge (generally defined as a >10 to 15% increase in stroke index/cardiac index). In all, 830 patients across a spectrum of medical and surgical disciplines were studied; the pooled correlation coefficients between the CVP or ΔCVP and measured blood volume or change in stroke index/cardiac index were <0.18 for all of these comparisons. The baseline CVP (reported in 11 studies) was 8.7 ± 2.3 mmHg in patients who responded to fluid challenge, as compared with 9.7 ± 2.2 mmHg in nonresponders (NS; P = 0.3). The receiver operating charac-
teristic curve for the CVP, a statistical tool that helps assess the likelihood of a result being a true positive versus a false positive, was 0.56; thus, at any CVP value, the likelihood that CVP can accurately predict fluid responsiveness was only 56%.

Maesaka et al. (15) have advocated for the use of the fractional excretion of urate (FEurate) and fractional excretion of phosphate (FEphosphate) to distinguish between SIADH and hyponatremia caused by salt wasting. Data supporting this distinction are summarized in a recent review and a small series by these authors (16). SIADH is associated with hypouricemia, largely as a result of increased FEurate, and the FEurate typically improves with correction of hyponatremia. On the basis of a number of individual cases they have studied, these investigators argued that a subset of patients with hyponatremia, some with cerebral disease and some without, have “appropriate” ADH secretion in response to hypovolemia caused by volume depletion. These patients, unlike those with SIADH, had a persistently elevated FEurate and hypouricemia after correction of hyponatremia, and this has been associated with increased levels of renin and aldosterone, increased FEphosphate (paired in some cases with a reduction in measured blood volume), and a response to saline. One of these patients had a urine sodium concentration of 6 mmol/L after a hip fracture, which many would attribute to hypovolemia as a result of extrarenal fluid losses. Despite a low urine sodium concentration, the investigators attributed hypovolemia to previous salt wasting by the proximal tubule because the persistently high FEuric acid and FEphosphate were thought to reflect a proximal tubular abnormality. This argument would be more convincing if recurrent hyponatremia associated with negative sodium balance, weight loss, and clinical signs of hypovolemia had been demonstrated after discontinuation of saline therapy.

Causes of Euvolemic Hyponatremia

Tumor-Associated SIADH. The first cases of the SIADH were reported in patients with small cell lung cancer (SCLC). This disease continues to be one of the most common causes of chronic SIADH. Among 455 patients with a diagnosis of SCLC in a single University hospital in Denmark, 44% had hyponatremia; the plasma sodium concentration was <125 mmol/L in 11% of patients and 126 to 135 mmol/L in 33% (17). By comparison, only 1.6% of patients with non-SCLC had hyponatremia at the time of diagnosis. Only 25% of patients who had serum sodium concentrations <130 mmol/L and were treated with water restriction had fully normalized their serum sodium to 135 mmol/L by the time of the second cycle of chemotherapy, 3 to 4 weeks after the first cycle. Patients who did not fully normalize their serum sodium had a significantly worse prognosis than patients who did. Atrial natriuretic peptide (ANP) is produced by most SCLC cell lines, and ectopic secretion of ANP as well as SIADH may play a role in the pathogenesis of hyponatremia. Patients with ectopic secretion of ANP have been reported to respond less positively to water restriction, and lack of response to water restriction has been suggested as a screening test for this abnormality.

Hyponatremic Hypertensive Syndrome. Some patients with unilateral renal artery stenosis develop hypertension, hyponatremia, polyuria, hypokalemia, and marked polydipsia. Most patients are elderly, asthenic women with renal artery stenosis as a result of atherosclerosis; the disease has also been described occasionally in children with fibromuscular dysplasia (18). Renin secretion induced by renal ischemia results in high circulating levels of angiotensin II, a potent dipsogen; high doses of angiotensin-converting enzyme inhibitors to block the conversion from angiotensin I to angiotensin II have been suggested. Hypertension in patients with Wilms’ tumor is relatively common and usually due to intrarenal ischemia, secondary to compression of the normal renal vasculature, which increases renin production. A recent report described two children who had Wilms’ tumor and first presented with severe hypertension, hyponatremia, hypokalemia, polyuria, and polydipsia; preoperative treatment with an angiotensin-converting enzyme inhibitor (captopril) caused a remission of the clinical syndrome, thereby allowing a safer curative nephrectomy (19).

Drug-Induced Euvolemic Hyponatremia

Cyclophosphamide. Cyclophosphamide is an alkylating agent used extensively in the treatment of malignant and rheumatologic diseases. Because one of its adverse effects is hemorrhagic cystitis, it is routinely administered with forced hydration. Although hyponatremia was once a common complication when high dosages (>50 mg/kg) of cyclophosphamide were used to treat neoplastic diseases, there have been only a few case reports of hyponatremia complicating more cur-
rent low-dosage (<20 mg/kg) regimens. A retrospective analysis of 84 patients who were given intravenous pulse cyclophosphamide (500 to 750 mg/m²) with half-isotonic saline for prophylactic hydration identified hyponatremia (<135 mmol/L) in 15 treatment episodes (13.4%) in 12 patients (14.3%) (20). Hyponatremia was generally mild and largely asymptomatic, with serum sodium concentrations <130 mmol/L (123 to 129 mmol/L) in only five patients. Urinary data from eight patients with hyponatremia were consistent with SIADH with urine osmolality 327 ± 195 mOsm/kg H₂O (range 182 to 790 mOsm/kg H₂O) and urine sodium 68 ± 47 mmol/L (range 31 to 176 mmol/L). However, as shown in two recent case reports, hyponatremia after low-dosage cyclophosphamide can be more serious (21,22). For example, a 49-year-old woman with diffuse systemic sclerosis presented with a serum sodium of 106 mmol/L and urine osmolality of 620 mOsm/kg 1 day after receiving a 500-mg intravenous pulse of cyclophosphamide (21). She developed seizures 12 hours after presentation, prompting treatment with 3% saline, and subsequently (with an unreported increase in serum sodium concentration) a biphasic neurologic course associated with magnetic resonance imaging–documented central pontine myelinolysis. The cause of cyclophosphamide-induced hyponatremia is unknown, but because it was reported to cause an antidiuresis in a patient with diabetes insipidus (DI), there is speculation that the drug may enhance AVP’s effect on the collecting duct (20,23). The antidiuresis caused by cyclophosphamide is temporally related to the appearance of its metabolites in the urine. Cyclophosphamide metabolites (mofosfamide and 4-hydroperoxy-cyclophosphamide) decrease the production of IL-1 and TNF-α in a dosage-dependent manner (23), and these cytokines have been shown to downregulate expression of the vasopressin 2 receptor (V2R) and aquaporin 2 (AQP2) (24); cyclophosphamide could potentially cause hyponatremia by upregulating expression of V2R and AQP2 through suppression of IL-1 and TNF-α, which are effector molecules in the downregulation of VR2 (23).

**Carbamazepine.** Carbamazepine is an anticonvulsant and psychotropic medication commonly used in the treatment of patients with epilepsy or intellectual disability. The drug has an antidiuretic effect that commonly results in hyponatremia with clinical features of SIADH; this side effect has been exploited to decrease the urinary volume in DI. Oxcarbazepine, which differs from carbamazepine only by the addition of one oxygen molecule, is also a recognized cause of hyponatremia. The antidiuretic effect of carbamazepine is not well characterized; direct stimulation of AVP release from the pituitary gland has been suggested, but there has also been evidence of a possible effect directly on the renal tubule. Bragança et al. (25) investigated the mechanism using in vitro and in vivo experiments that support the latter hypothesis. Microperfusion studies showed that in the absence of ADH, carbamazepine was able to increase water absorption fourfold in the isolated rat inner medullary collecting duct (IMCD); administration of specific inhibitors suggested that carbamazepine acts on the V2R–protein G complex and that its effect on water flow is cAMP dependent. Administration of carbamazepine in vivo to rats with nephrogenic DI significantly blunted the water diuresis induced by lithium, decreasing urine volume and increasing urine osmolality; consistent with this effect, AQP2 expression in IMCD obtained from rats given lithium and carbamazepine was significantly increased in comparison with that in rats given lithium alone.

**Selective Serotonin Reuptake Inhibitors.** Selective serotonin reuptake inhibitors (SSRIs), the most popular antidepressants in use, have become one of the most common causes of hyponatremia, particularly in the elderly during the first 2 weeks of treatment. Patients with SSRI-induced hyponatremia present with a clinical SIADH, but increased plasma levels of AVP have not been demonstrated. Moyses et al. (26) treated rats with fluoxetine, one of the most popular SSRIs, and found that the plasma sodium decreased from 139.3 ± 0.78 to 134.9 ± 0.5 mmol/L (P < 0.01), whereas plasma AVP levels remained unchanged. IMCDs from fluoxetine-treated rats showed a 40% increase in AQP2 protein abundance, and incubation of IMCDs with fluoxetine resulted in a similar increase in AQP2. In addition, microperfusion studies of IMCDs showed that in the absence of ADH, carbamazepine doubled water absorption. These results are consistent with the conclusion that SSRIs stimulate water absorption by a non-ADH modulation of AQP2 in the kidney. In addition to carbamazepine and fluoxetine, hydrochlorothiazide, chlorpropamide, angiotensin I, and rosiglitazone all seem to have AVP-independent effects on water reabsorption in the collecting duct (26).
Other Drugs. Hyperkalemia is a common complication of trimethoprim, which inhibits sodium influx via the epithelial sodium channel (ENaC) in the collecting duct. Much more rarely, the drug has been associated with hyponatremia, presumed to result from renal sodium wasting and hypovolemia-induced AVP release (27). Hyponatremia has also been occasionally associated with ciprofloxacin neurotoxicity (27).

Nephrogenic Syndrome of Inappropriate Antidiuresis

A gain-of-function mutation of the V2R gene, named nephrogenic syndrome of inappropriate antidiuresis (NSIAD), was first described in 2005 (28–35). Manifestations are opposite those of nephrogenic DI, which is caused by loss of function of the AVP receptor. In the original description of the disease, two unrelated male infants were found to have the clinical picture of SIADH with undetectable plasma AVP levels. In one of the original patients, the arginine on codon 137 was substituted with cysteine (R137C), and his mother was heterozygous for the R137C mutation, suggesting an X-linked inheritance. In the other patient, arginine was substituted with leucine (R137L), with no mutation found in his mother, likely because of a spontaneous mutation. Functional analysis confirmed constitutive activation of this receptor.

More than 200 different mutations on the V2R gene are known to cause nephrogenic diabetes insipidus, so genetic heterogeneity might be expected for NSIAD. However, since the initial description of the disease, R137C has been the mutation found in most subsequently described cases. One report identified the activating missense mutation on R137C in three hemizygous males and four heterozygous females of a large family pedigree (36). All except one female, who was subsequently found to have skewed X inactivation, had either spontaneous hyponatremia or an abnormal water-loading test. The mother of another case of NSIAD caused by R137C has been reported to have persistent hyponatremia (128 mmol/L) (32); measurements of AVP levels found detectable AVP at plasma osmolality levels below the normal osmolar threshold for AVP release, and the mother experienced thirst at a low plasma osmolality. Thus, in this patient, both thirst and renal water handling were abnormal. Thirst has not been studied in other patients with activating V2R mutations.

Mutations in the V2R gene may not explain all cases of NSIAD. In 2001, a three-generation family was found to have an “SIADH-like condition” with undetectable ADH levels. Studies of three affected members of the family (all females) showed normal levels of urine AQP2, a marker of AVP-dependent AQP2 levels. A “gain of function” mutation involving the AVP receptor or AQP channel could have explained these findings, but DNA sequencing for both AVPR2 and AQP2 were normal.

Infants with NSIAD are at high risk for hyponatremia because their diet consists predominantly of liquid with little solute. As awareness of thirst evolves over time, the risk for severe hyponatremia from excessive free water decreases. Because affected individuals can often self-regulate fluid intake, even patients who present in infancy reach adult life with minimal symptomatic episodes. The identification of adult relatives of affected infants with NSIAD suggests that the disease could be present in genetically affected individuals who remain asymptomatic or have never had full evaluation. NSIAD should be suspected in young patients with a clinical diagnosis of idiopathic SIADH, especially if there is a good family history; a good screening test for the condition may be unresponsiveness to V2R antagonists.

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Pharmaceutical-grade urea in a dosage of 2 g/kg per d in four divided doses has been used to treat NSIAD in children, and it has been found to be well tolerated, despite the unpleasant taste as observed by the mother and others (30). The need for urea decreases with the development of a reliable thirst mechanism.

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Clinical Outcomes of Chronic Hyponatremia
Hyponatremia is a common problem in hospitals and in nursing homes. A number of clinical conditions, including heart failure, cirrhosis, pneumonia, HIV infection, chronic obstructive pulmonary disease, myocardial infarction, malignant diseases, and several neurologic conditions, are associated with hyponatremia, and the electrolyte disturbance is associated with a worse prognosis (1).

Mortality
Hyponatremia is known to increase the risk for mortality in patients with acutely decompensated heart failure. A single-center study of 628 patients who presented to the emergency department with acutely
decompensated heart failure found that 24% of patients had serum sodium concentrations ≤135 mmol/L. Patients with hyponatremia were less likely to be male or to have hypertension or coronary artery disease but significantly more likely to have severe symptoms, anemia, and higher amino-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations. In a multivariate Cox proportional hazards analysis, hyponatremia was an independent predictor of 1-year mortality (hazard ratio 1.72; 95% confidence interval [CI] 1.22 to 2.37; \( P = 0.001 \)) as was an NT-proBNP concentration above the median value of 4690 pg/ml (hazard ratio 1.49; 95% CI 1.10 to 2.00; \( P = 0.009 \)). Patients with hyponatremia and patients with a higher NT-proBNP were more likely to develop worsening renal function during their hospitalization; they also had the highest 1-year mortality rates. Hyponatremia was predictive of 1-year mortality only in patients with an elevated NT-proBNP (2).

Wald et al. (3) conducted a 7-year retrospective study of all discharges of adult patients from a 400-bed acute care tertiary university-affiliated teaching hospital in Boston and found that hospital-associated hyponatremia is independently associated with in-hospital mortality, prolongation of length of stay (LOS), and discharge to a facility rather than to home, regardless of whether the electrolyte disturbance was present on admission, was exacerbated after admission, or developed during hospitalization. Similar to what has been reported for patients with heart disease and liver disease, in this unselected hospital population, even serum sodium values that would conventionally be classified as normal or slightly below normal (e.g., 133 to 137 mmol/L) were found to be independently associated with mortality, prolonged LOS, and discharge to a facility. Because of the finding that a serum Na <138 (corrected for the effect of hyperglycemia) is associated with significantly higher mortality, the authors suggested that our current definition of what constitutes normonatremia should be reconsidered. Even in this teaching hospital, postadmission aggravation of hyponatremia was observed in 6% of patients who had hyponatremia on admission, and the serum sodium fell below 138 mmol/L in 38% of normonatremic admissions. In patients with hospital-acquired hyponatremia, a 15-fold increase in the risk for death was observed when the lowest serum sodium fell to ≤127 mmol/L. In comparison, the odds ratios for mortality were more modest in patients with the most severe forms of community-acquired hyponatremia. A sophisticated statistical analytical analysis (restrictive cubic spline) demonstrated a U-shaped relationship between the serum sodium concentration and mortality with a value of 140 mmol/L associated with the lowest risk for mortality and a progressive increase in mortality risk as admission serum sodium level declined (Figure 11); however, because very few patients had an admission serum sodium value <123 mmol/L, the effect of severe hyponatremia (<120 mmol/L) on mortality cannot be accurately estimated from this relationship.

Waikar et al. (4) studied short- and long-term mortality of >95,000 patients who were admitted with and without hyponatremia (serum sodium <135 mmol/L) to two large university teaching hospitals in Boston. Hyponatremia was present on admission in 13% of those hospitalized for at least 2 days. Women with and without hyponatremia accounted for approximately half of all admissions overall, and two thirds of all patients had severe hyponatremia. Patients with hyponatremia on admission were more likely to have congestive heart failure, sepsis, pneumonia, metastatic disease, and volume depletion than patients with normonatremia, and patients who were admitted with hyponatremia had more comorbidity (1.9 versus 1.4; \( P < 0.001 \)) as measured by the Deyo modification of the Charlson index (D-CI), the sum of the weighted
number of comorbid conditions on the basis of 17 diagnostic categories identified from International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis codes. Even mild hyponatremia (serum sodium concentration 130 to 134 mmol/L) carried a significantly increased risk for death in hospital, 1 year after discharge, and 5 years after discharge. Although there was a small difference in the absolute prevalence of hyponatremia (12%) when corrected for hyperglycemia, there was no effect on the association between hyponatremia and mortality. Differences in mortality persisted after multivariable adjustment in all categories of hyponatremia except for serum sodium concentration of <120 mmol/L. Compared with patients with normonatremia, the multivariable-adjusted risk for death after 5 years after admission was increased by 24% in patients with admission serum sodium concentration of 130 to 134 mmol/L ($P < 0.001$), 33% in those with serum sodium concentration of 125 to 129 mmol/L ($P < 0.001$), 29% in those with serum sodium concentration of 120 to 124 mmol/L ($P = 0.003$), and 9% in those with admission serum sodium concentration of <120 mmol/L ($P = 0.52$). Hyponatremia resolved in 3794 (7.2%), persisted in 4524 (8.6%), and was acquired during hospitalization in 1974 (3.8%). Mortality (in hospital, 1 year after discharge, and 5 year after discharge) was highest in those with persistent or acquired hyponatremia, lower in those with hyponatremia that resolved, and lowest in those with normonatremia at both first and last serum sodium measurements. The multivariable-adjusted odds of inhospital mortality associated with hyponatremia differed across clinical subgroups. For example, hyponatremia was not associated with an increased risk for death compared with normonatremia in patients who were admitted with pneumonia, sepsis, liver disease, or medical admissions related to the respiratory system. The risk for death associated with hyponatremia seemed to be particularly strong in patients with cardiovascular disease or cancer and those who underwent orthopedic procedures ($P < 0.001$).

None of these studies can determine whether a causal link exists between hyponatremia and mortality. Severe, acute hyponatremia can lead to life-threatening cerebral edema, but the reasons for increased mortality in less severe hyponatremia are less clear. Hyponatremia can be a marker of severity of illness, and although it may predict mortality, it may not be the cause of death. Important physiologic derange-

ments of severe cardiovascular disease (e.g., low effective circulating volume, decreased GFR, activation of neurohormonal responses) may be responsible for both hyponatremia and an adverse outcome. Alternatively, the association between mild hyponatremia and mortality may reflect as-yet-unidentified adverse effects on organ systems other than the central nervous system. Because the reasons for excess mortality associated with hyponatremia are not well understood, it is premature to conclude that therapeutic interventions (e.g., water restriction, loop diuretics, the newly introduced and extremely expensive vasopressin 2 receptor antagonists) will alter outcomes. Because hyponatremia may not be associated with mortality in sepsis and pneumonia, the benefit of correcting the serum sodium concentration in those populations would be expected to be limited. In contrast, the strong association with mortality in patients with heart disease or cancer and in patients who underwent orthopedic procedures suggests that these groups could be targeted to examine the potential benefit of strategies to normalize serum sodium concentrations.

Hospital Costs

A retrospective cohort study in a large academic teaching hospital in New York City compared patients with moderate to severe hyponatremia (serum sodium level of ≤129 mmol/L at admission, $n = 547$) and patients with mild to moderate hyponatremia (serum sodium level of 130 to 134 mmol/L, $n = 1500$) with 7573 patients who had the same principal admitting diagnoses and a serum sodium level of 135 to 145 mmol/L ($5$). Patients who were admitted with hyponatremia had significantly longer hospital LOS than those who were admitted without hyponatremia (median LOS: moderate to severe hyponatremia 8 days, mild to moderate hyponatremia 8 days, normal 6 days; $P < 0.001$). Patients with more severe hyponatremia were also more likely to be admitted to the intensive care unit during the hospital stay (moderate to severe hyponatremia 32%, mild to moderate hyponatremia 26%, normal 22%; $P < 0.001$). These trends were also reflected in the total costs per admission, with median costs of $16,606 for moderate to severe hyponatremia cases, $14,266 for mild to moderate hyponatremia cases, and $13,066 for normal admissions ($P < 0.001$). The authors speculated that interventions or pharmacotherapies for the prompt treatment of hyponatremia...
could potentially reduce morbidity and LOS, thereby reducing the use of health care resources.

**Falls and Fractures**

Mild chronic hyponatremia is associated with gait and attention deficits and with an increased risk for falls (6–11). Asymptomatic hyponatremia seemed to cause more attention deficits than a serum alcohol level of 0.6 g/L in an age- and gender-matched control group; in a preliminary study, the threshold for gait and attention deficits induced by hyponatremia were 134 and 132 mmol/L, respectively.

A case-control study of 513 ambulatory patients who were aged ≥65 years and presented to a general university hospital with bone fracture after falling found a 13.06% prevalence of hyponatremia (serum sodium <135 mmol/L) as compared with a 3.90% prevalence of hyponatremia among ambulatory age- and gender-matched control subjects who were randomly selected from ambulatory patients without a history of bone fracture (unadjusted odds ratio [OR] 3.47 [95% CI 2.09 to 5.79]; adjusted OR 4.16 [95% CI 2.24 to 7.71]) (10). Hyponatremia was mild and asymptomatic in all patients (mean serum sodium 131 mmol/L) and was either drug induced (36% diuretics, 17% selective serotonin reuptake inhibitors [SSRIs]) or due to idiopathic syndrome of inappropriate antidiuretic hormone secretion (SIADH; 37%). These findings were confirmed in a study of 364 cases of patients aged 65 yr or older presenting to an urban emergency room with fractures of the hip, pelvis or femur; of fracture patients with hyponatremia, 24.2% were taking antidepressants, mostly selective serotonin receptor inhibitors (SSRIs), whereas none were taking these medications in the group without fracture (11). Similarly, a retrospective study of self-reported fractures among 1408 consecutive female patients who had available laboratory data and underwent bone mineral density (BMD) measurement found that hyponatremia (serum sodium concentration <135 mmol/L) was present in 8.7% of patients with a confirmed fracture, whereas the prevalence of hyponatremia was 3.2% among patients without a fracture (P < 0.001) (7). Multivariate logistic regression analysis controlling for age, T score, chronic kidney disease stage, and osteoporotic risk factors and treatments found that a serum sodium concentration <135 mmol/L remained significantly and independently associated with fracture occurrence (P < 0.01).

Thiazide use has been associated with an increased risk for fractures in elderly patients living in nursing homes, a paradox effect considering the beneficial effect of thiazides on mineral balance; however, it is not known whether the fracture risk associated with thiazides can be attributed to thiazide-induced hyponatremia. Similarly, SSRIs in the treatment of depression are associated with falls and fractures with peak fracture risk occurring in the first 2 weeks after initiation of therapy, similar to the time of onset of SSRI-induced hyponatremia; however, it is not yet known whether the fall and fracture risk associated with SSRIs can be attributed to SSRI-induced hyponatremia.

Compounding the risk of falling attributable to hyponatremia, there is also evidence that hyponatremia is associated with osteoporosis (8). Approximately one third of total body sodium resides in the bone, with 40% of bone sodium being exchangeable with the extracellular sodium pool; therefore, long-term sodium depletion could theoretically lead to sodium loss from the bone with consequent bone demineralization. Rats made hyponatremic (serum sodium 110 ± 2 mmol/L) for 3 months have a 30% reduction in BMD, as measured by dual-energy x-ray absorptiometry, as compared with controls. Reductions in both trabecular and cortical bone contents and an increase in the number of osteoclasts per bone area were found, as was a decreased serum concentration of osteocalcin, indicative of increased bone resorption and decreased bone formation. The 30% reduction in BMD found in hyponatremic rats is approximately twice that reported in various well-established rat osteoporosis models over similar periods of time using similar densitometry methods. Data obtained from humans who were aged ≥50 years and had much milder hyponatremia are consistent with the experimental data in severely hyponatremic rodents. The Third National Health and Nutritional Examination Survey (NHANES III) provides information on sodium concentrations and BMD of the hip in a nationally representative sample of US adults. An analysis of data from NHANES III found the adjusted OR for developing osteoporosis to be nearly three times higher among adults with mild hyponatremia (SNa 133.0 ± 0.2 mmol/L) compared with those without hyponatremia (OR 2.85; 95% CI 1.03 to 7.86; P < 0.01). There was also a positive linear association between SNa and femoral neck...
BMD in patients with hyponatremia. Diuretics were used by 11.1 and 6.8% of patients with hyponatremia and normonatremia, respectively. Of these, thiazide diuretics were used by 10.5% of patients with hyponatremia and 4.7% of patients with normonatremia.

A 30% reduction in BMD found in hyponatremic rats and data obtained from humans aged ≥50 years revealed the adjusted OR for developing osteoporosis to be nearly three times higher among adults with mild hyponatremia (SNa 133.0 ± 0.2 mmol/L) compared with those without hyponatremia.

**Rhabdomyolysis**

Self-induced water intoxication presents with brain edema, coma, convulsions, and death as a result of severe hyponatremia. Non-neurologic symptoms such as rhabdomyolysis have been reported in single case reviews. A retrospective review of 22 patients who were treated in a single medical referral center in Japan identified six patients with rhabdomyolysis (Creatine phosphokinase level 12,138 to 319,400) and 16 patients without rhabdomyolysis (12); two patients with rhabdomyolysis developed renal failure (creatinine 2.7 and 6.9 mg/dl), and one patient developed extrapontine myelinolysis. The severity of hyponatremia in the two groups was not different, and there was no association with convulsions, drugs, or alcohol, but the rate of correction (attributable primarily to the excretion of large quantities of dilute urine in the initial few hours after presentation) was significantly more rapid in the group with rhabdomyolysis (2.0 ± 1.3 versus 0.9 ± 0.7 mmol/L per h \(P = 0.017\); 21.3 ± 6.0 versus 10.0 ± 4.6 mmol/L per 24 h \(P = 0.001\)).

**Osmotic Demyelination Syndrome**

An adaptive loss of organic osmolytes permits brain cells to maintain osmotic equality with plasma without a large increase in brain water. Although this adaptation permits survival with extremely low serum sodium concentrations, it also makes the brain vulnerable to injury from rapid correction of hyponatremia. Rapid correction of chronic hyponatremia is analogous to an acute hyperosmolar insult, and because the adaptation to chronic hyponatremia restores brain volume to near normal, rapidly increasing the serum sodium concentration to normal after this adaptation occurs dehydrates the brain just as acute hypernatremia dehydrates the brain in individuals with normonatremia. Indeed, severe hypernatremia can cause osmotic demyelination in patients who were never known to have hyponatremia (13).

Excessive correction of chronic hyponatremia triggers a cascade of injury in the brain beginning with breakdown of the blood-brain barrier and culminating in the programmed death of oligodendrocytes, the cells that make myelin in the central nervous system (14,15).

Studies in experimental animals have conclusively demonstrated that rapid correction of hyponatremia and not hyponatremia itself is the cause of osmotic demyelination (14,15). Consistent with this conclusion, it has been shown that re-lowering the serum sodium concentration after excessive correction prevents demyelinating brain lesions and death in the rat (16). Re-induction of hyponatremia also prevents the opening of the blood-brain barrier that occurs when hyponatremia is rapidly corrected; but although treatment with dexamethasone also prevents opening of the barrier, only re-induction of hyponatremia resulted in a significant decrease in mortality (16). Similar to findings in the rat, in three single case reports, re-lowering of the serum sodium concentration was shown to reverse early findings of osmotic demyelination after overcorrection of hyponatremia (17,18).

Slow recovery of organic osmolytes lost during the adaptation to a low plasma osmolality seems to play a pivotal role in the pathogenesis of osmotic demyelination. Brain regions that are slowest to recover organic osmolytes are the most severely injured after rapid correction of hyponatremia; uremia, which reduces the incidence and severity of demyelinating brain lesions after rapid correction of hyponatremia, is associated with more rapid reuptake of organic osmolytes, particularly myoinositol, and exogenous administration of myoinositol decreases the severity of injury caused by rapid correction (14). Myoinositol protects glial cells from cytotoxicity induced by osmotic shrinkage (19). In cultured astrocytes grown in hypertonic medium, cell survival is reduced and can be partially restored by adding myoinositol, but not other organic osmolytes, to the medium.

Central pontine myelinolysis (CPM), the most classic manifestation of brain injury caused by rapid correction of hyponatremia, was first described in
alcoholics in 1959, before measurements of the serum sodium concentration became routine. Shortly after the description of CPM, a symmetrical demyelinating injury in the center of the pons that spares neurons, similar lesions outside the pons (extrapontine myelinolysis [EPM]) were described. Norenberg (15) recently published a compelling account of how CPM and EPM (also known as osmotic demyelination) came to be associated with excessive treatment of hyponatremia. Often called a “rare” disorder, the number of reported cases calls this characterization into question. After the first reports in the 1980s, several hundred cases in which CPM and EPM complicated the treatment of severe hyponatremia have been reported, and several new cases appear each year: Between January 1, 2008, and August 31, 2010, more than a dozen single case reports, a case series involving adults (20–35), and three case reports involving children (36–38) were published. A 12-year study at a single university medical center in Canada identified 12 patients with CPM and/or EPM documented by magnetic resonance imaging (MRI) or autopsy (23); six of the 12 patients were known to have developed osmotic demyelination after rapid correction of hyponatremia (including two who had diabetes insipidus and developed hyponatremia on desmopressin and experienced a large water diuresis when desmopressin was discontinued), and one case occurred in a patient who had normonatremia and developed hyponatremia (to 176 mmol/L over 3 hours) because of a hemodialysis error. The five patients without a known rapid increase in serum sodium concentration included three who developed CPM/EPM after liver transplantation and two alcoholics for whom data were unavailable. Most patients with hyponatremia presented with the classic biphasic course characterized by nonspecific symptoms including confusion associated with severe hyponatremia at presentation, followed by a relative improvement lasting 2 to 3 days after correction of the electrolyte disturbance, and then a second progressive neurologic deterioration that led to a diagnosis of CPM/EPM after a mean delay of 8 days. The neurologic symptoms that developed after overly rapid correction were varied and included rigidity; cardiorespiratory autonomic dysfunction; seizures (generalized tonic-clonic and partial complex); neuropsychiatric issues (catatonia, emotional lability); altered consciousness; and pyramidal, brainstem, and cerebellar signs. As has been noted in previous reports, neuroimaging was initially normal with lesions appearing with a delay of up to 14 to 21 days and with initial sparing of the pons.

Some of the extrapontine lesions seen after rapid correction of hyponatremia, such as cortical laminar necrosis, are also seen in patients with hypoxic brain damage (35). This has led some investigators to attribute neurologic sequelae in chronic hyponatremia to hypoxia. The experimental models used to support this hypothesis have been criticized on methodologic grounds, and they are difficult to reconcile with the observation that therapeutic re-lowering of the serum sodium concentration prevents brain lesions (18). Furthermore, “hypoxic” brain lesions, such as cortical laminar necrosis, have been reported in patients without a hypoxic insult, having undergone rapid correction of stable chronic hyponatremia (from 105 to 140 mmol/L in 24 hours in one case) (35). Recent case reports of CPM/EPM after rapid treatment of hyponatremia have included data on oxygen saturation on room air (99% on room air in two cases [39,40] and a PO2 of 87 mmHg on room air in a third [40]) that make a diagnosis of hypoxic brain damage untenable.

There have been several reports of CPM/EPM after orthotopic liver transplantation. A review of 1247 patients who received a transplant in Korea identified 11 (0.88%) patients with CPM/EPM (41). Risk factors were compared with 44 control subjects without CPM/EPM, matched by age, gender, and date of operation. Preoperative serum sodium was significantly lower in the CPM/EPM group than in control subjects (126 ± 7 versus 134 ± 7 mmol/L; P < 0.001), and patients who developed the disease had a significantly larger perioperative change in serum sodium concentration (15 ± 6 versus 7 ± 4 mmol/L; P < 0.001). Significantly larger amounts of blood products and crystalloids were given in the CPM/EPM group, and a significant correlation was found between the volume administered and the increase in serum sodium during surgery. Consistent with these observations, three patients with CPM identified after liver transplantation over 3 years in a single center in China each had preoperative hyponatremia (119 to 124 mmol/L), and each underwent correction by >20 mmol/L during surgery (42).

In most patients with severe hyponatremia, neurologic findings suggestive of the osmotic demyelination syndrome emerge after correction by >10 mmol/L per 24 h and/or >18 mmol/L per 48 h. However, there are occasional reports of osmotic demyelination complicat-
ing severe hyponatremia after correction rates below these limits (43). There are several reports of CPM alcohols with mild hyponatremia and occasionally non-nor-manatremia and with liver disease after correction by <10 mmol/L per d (44). In another report, MRI findings consistent with a diagnosis of EPM were identified in a severely ill patient with Addison disease and military tuberculosis associated with a serum sodium of 118 mmol/L that was corrected very gradually (45). However, the title of some case reports is misleading: In a report entitled “Central Pontine Myelolysis Despite Slow Sodium Rise,” an otherwise healthy woman developed MRI-documented CPM and EPM with classic but reversible symptoms after treatment of thiazide-induced hyponatremia (serum sodium 96, serum potassium 2.5 mmol/L) (39). A review of the data showed that the serum sodium increased by 18 mmol/L in <24 hours and 24 mmol/L within 48 hours (39).

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Treatment of Chronic Hyponatremia

Osmotic demyelination syndrome can usually be prevented by avoiding increases in the serum sodium concentration of >10 mmol/L in a single day and/or 18 mmol/L over any 48-hour period; rather than therapeutic goals, these are limits not to be exceeded. If a 4- to 6-mmol/L increase in serum sodium concentration is significant enough to improve the most severe symptoms in patients with acute hyponatremia, a therapeutic goal of 6 mmol/L per d is reasonable in chronic hyponatremia, even when the serum sodium concentration falls to extremely low levels (1). This can be translated to an easily remembered “rule of sixes”: “Correction by 6 mmol/L per d makes sense for safety, so correct by 6 mmol/L for severe sx’s and stop.” In other words, for all patients with chronic hyponatremia, the correction goal is 6 mmol/L during the initial 24 hours, and for those with severe symptoms (seizure, severe delirium, and unresponsiveness), the goal is preloaded in the first 6 hours, postponing subsequent efforts to increase the serum sodium level until the next day. As discussed previously, although the initial rate of correction with this strategy is 1 mEq/L per h (6 mEq/L within 6 hours), the average rate over the first 24 hours is 0.25 mEq/L per h (6 mEq/L per d), well below the traditional limit of 12 mEq/L per d; unfortunately, the daily limit of 12 mEq/L is sometimes expressed as 0.5 mEq/L per h—a formulation that many clinicians find confusing because it can be misinterpreted as meaning that aggressive therapy for severe symptoms should not be given.

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It is a good idea to set correction goals well below rates that are known to result in iatrogenic injury because it is quite easy to “overshoot the mark.” In many patients, the cause of water retention is reversible (e.g., vasopressin release secondary to volume depletion), and when the cause is corrected (e.g., volume repletion), vasopressin levels fall and the ensuing water diuresis increases the serum sodium concentration by as much as 2 mmol/L per h (2). Overcorrection can be prevented or reversed by administering desmopressin to terminate a water diuresis; this strategy has been used successfully in a small series of patients (3). Alternatively, desmopressin can be given before a water diuresis even begins with a concurrent slow infusion of hypertonic saline that is titrated to maintain a correction rate of 6 mmol/L per d (1). Desmopressin is administered every 6 to 8 hours to keep the urine concentrated, eliminating one of the variables that increase the serum sodium concentration. Desmopressin is given less frequently in patients with diabetes insipidus (DI) because the goals are different: In DI, dosing intervals of ≥12 hours allow some escape from water retention to avoid hyponatremia, whereas in patients who have hyponatremia and no longer have a reason to retain water, the goal is to prevent completely the excretion of free water until the serum sodium concentration has been raised with hypertonic saline to a level closer to normal.
Alternatively, to eliminate the need for continuous infusion of 3% saline, desmopressin doses can be periodically withheld each day to allow a brief period of water excretion to raise the serum sodium by the desired 6 mmol/L; however, because the timing of water diuresis when desmopressin is discontinued is unpredictable, this requires much more rigorous hourly monitoring of the patient to avoid unintentional overcorrection. A description of this strategy was recently published in a case report of a patient who survived without neurologic sequelae after presenting with a serum sodium of 96 mmol/L (Figure 12) (1).

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Potassium (K) depletion makes patients with chronically hyponatremia especially vulnerable to overcorrection. The serum sodium concentration is a function of the ratio of exchangeable body sodium plus K divided by total body water. Therefore, administration of K (increasing the numerator of the equation) increases the serum sodium concentration. A recent report described a mildly symptomatic patient (muscle weakness and slurred speech) with a serum sodium of 96 mmol/L and a serum K of 1.6 mmol/L; the patient developed osmotic demyelination after overcorrection that could be attributed primarily to replacement of her large K deficit (4). K replacement was also responsible for a small but potentially dangerous increase in serum sodium concentration above the goal for the aforementioned patient treated with both hypertonic saline and desmopressin (1). K chloride can be given in a hypertonic solution containing 20 mmol of K in 100 ml of water (400 mmol/L); the solution is nearly as concentrated as 3% saline (513 mmol/L); therefore, the rate of 3% saline administration should be slowed when K is being given to avoid unintentional overcorrection.

Renal Replacement Therapy

Patients with acute kidney injury may have concomitant severe hyponatremia. To avoid rapid correction during renal replacement therapy, continuous venovenous hemofiltration can be used with adjustment of the replacement fluid sodium concentration by adding sterile water (5). Stepwise correction of the patient’s serum sodium concentration can be planned using replacement fluid made up to raise the serum sodium concentration successively. The concentration of bicarbonate and K in the final solution will also be reduced, and additional sodium and/or bicarbonate supplementation may be needed.

Vasopressin Antagonists (Vaptans)

Once vasopressin is released into the circulation, its biologic effects are mediated by three receptor subtypes: V1A, V1B, and V2. V1A receptors are located on vascular smooth muscle, platelets, and the liver. By increasing intracellular calcium, activation of the V1A receptor results in vasoconstriction, platelet aggregation, and gluconeogenesis. V1B receptors are located in the anterior pituitary, and their activation results in stimulation of ACTH release. V2 receptors (V2Rs) are located in the principal cells of the renal
collecting duct; when vasopressin binds to the V2Rs, they activate a cAMP-mediated signal transduction pathway that triggers an increased rate of insertion of aquaporin channels in the apical membrane of the renal collecting duct, thereby increasing reabsorption of free water along osmotic gradients, increasing urine osmolality, and producing an antidiuresis. Conversely, when vasopressin secretion is suppressed and the V2R is unoccupied, dilute urine is excreted. Antagonists to the vasopressin V2R, called “vaptans” because of the suffix applied to their generic names, block the binding of vasopressin to renal V2Rs, preventing vasopressin-mediated water reabsorption, decreasing urine osmolality, and increasing urine output. Unlike diuretic agents, which increase the excretion of sodium and water, vaptans enhance free water excretion without increasing the excretion of sodium or K; therefore, the increase in urine output caused by vaptans has been called an “aquaresis” and the vaptans have been called “aquaretic” agents (6).

Elegant experiments performed with V2R agonists and antagonists in awake, unrestrained rats showed that V2R-mediated effects of vasopressin are not only antidiuretic but also antinatriuretic (7). These findings are consistent with observations made in isolated collecting duct or in various mammalian or amphibian cell culture models. In these tissues, application of vasopressin to the basolateral side of the membrane increases amiloride-sensitive sodium transport, an effect mediated by the epithelial sodium channel. In healthy humans and individuals with nephrogenic DI caused by mutations of aquaporin 2, administration of the V2R agonist desmopressin (dDAVP) induces a twofold reduction in the rate of sodium excretion; no change in sodium excretion occurred when dDAVP was given to subjects with mutations of the V2R. Most studies describing the effects of selective nonpeptide V2R antagonists in experimental animals or humans concluded that these drugs behave as pure “aquaretics” with no effect on electrolyte excretion. The natriuretic effect of aquaretics is not readily apparent because compensatory sodium retention occurs after the initial loss. In rats given a V2R antagonist, 24-hour sodium excretion is unchanged, but threefold increases in sodium excretion rate occur in the first 4 to 6 hours. In humans, V2R antagonists have been shown to increase sodium excretion significantly in patients with hyponatremia and with cirrhosis and ascites (an effect that can also be shown in rats with experimental cirrhosis) but not in patients with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Although vaptans increase sodium excretion to some extent, their natriuretic effect remains far smaller than their aquaretic effect; in the rat, the natriuresis produced by furosemide is sevenfold greater than that produced by a V2R antagonist at comparable rates of urine flow.

In the rat, both V2R agonists and antagonists increase K excretion rate. Stimulation of V2R is known to increase K secretion by the collecting duct, and this in vitro effect is mirrored by a dosagedependent increase in transtubular K gradient (TTKG) seen in rats receiving dDAVP. In addition, large increases in urine flow rate increase K excretion by a flow-dependent mechanism; therefore, administration of a V2R antagonist increased urinary excretion without changing the TTKG, an estimate of K secretion.

High dosages of vasopressin have been shown to be natriuretic in rats, dogs, sheep, and humans. In the rat, this dosage-dependent natriuretic effect is largely abolished by the co-administration of a selective V1aR antagonist. Natriuresis associated with vasopressin contributes to hyponatremia in SIADH, and it has been attributed to a physiologic response to volume expansion caused by water retention. In the rat, at least, this V1a-mediated effect is independent of volume expansion. Possible mechanisms include a pressure natriuresis resulting from the vasopressor effects of the hormone, either within the whole circulation or selectively within the kidney vasculature, and stimulation of prostaglandins, which increase sodium excretion by reducing sodium transport in the collecting duct and by increasing medullary blood flow. Vasopressin stimulates prostaglandin production in interstitial medullary cells, which express V1a receptors, and in cortical collecting duct cells, which express V1a receptors on their apical membranes; these apical membranes may respond to vasopressin in the collecting duct lumen, where levels of the hormone are higher than in peripheral blood.

The complex interplay of V2- and V1a-mediated effects on sodium excretion shown in the rat are illustrated in Figure 13 (7). The findings from these experiments have important implications. In patients with hypervolemic hyponatremia as a result of heart failure or cirrhosis, the additional effect of V2 antagonism on sodium excretion may be beneficial and may decrease diuretic use. V2R antagonists may also be beneficial in some forms of salt-sensitive hyperten-
sion; however, more precise information is required regarding V1a and V2 effects in humans to know whether selective rather than mixed antagonists are more appropriate in each of these disorders.

Conivaptan. Intravenous conivaptan is the first vasopressin receptor antagonist to be approved by the US Food and Drug Administration (FDA) for treating euvoletic hyponatremia in hospitalized patients. The drug was initially approved for treating euvoletic hyponatremia caused by SIADH, hypothyroidism, adrenal insufficiency, or pulmonary disorders, and subsequently the FDA approved its use for treating hypervolemic hyponatremia in patients with heart failure. Conivaptan has high affinity for the human vasopressin subtypes V1a and V2. The peak diuretic effect of conivaptan occurs 2 to 4 hours after its infusion, and the aquaretic effect persists for approximately 12 hours. Conivaptan is metabolized by the liver by CYP3A4, and it can interact with other drugs that are metabolized by this enzyme; for this reason, concurrent administration of conivaptan with potent CYP3A4 inhibitors is contraindicated (see later).

Conivaptan’s efficacy for the treatment of hyponatremia has been assessed in three randomized, double-blind, placebo-controlled clinical trials and one open-label, nonrandomized trial; however, only one of the randomized trials studied the intravenous formulation of the drug that was approved for use by the FDA (6,8). Infusion site reactions were the most common reason for discontinuation during clinical trials; a new formulation of the drug that does not include propylene glycol was approved in October 2008 and was expected to decrease the irritation of veins, although no actual studies were done to show that infusion-site reactions were reduced by the formulation.

In addition to these formal clinical trials, a single-center, observational study of 18 patients who were treated with intravenous conivaptan for SIADH provides a “real world” experience with the drug (9). The study found that only 12 (66.7%) patients met the criterion for successful response, defined as an absolute increase in serum sodium 4 mmol/L over baseline. A lower pretreatment serum sodium concentration was associated with significantly larger increases in serum sodium concentration; all six patients with serum sodium concentrations ≤120 mmol/L were corrected by >10 mmol/L per 24 hours, which most investigators now consider excessive.

As noted, conivaptan antagonizes V1a receptors as well as V2 receptors. Because V1a agonists have been effective in treating hepatorenal syndrome, administration of conivaptan to patients with hyponatremia caused by hepatic cirrhosis has not been recommended and is not approved by the FDA. However, a recent study reported a favorable experience in 24 patients who had end-stage liver disease and hyponatremia (serum sodium ≤130 mmol/L) and were treated with conivaptan (10). Systolic BP and serum creatinine did not increase significantly, and variceal hemorrhage or worsening of ascites was not observed. In all patients, correction was ≤6 mmol/L, and in two patients, the increase was 1 mmol/L per 24 h; no neurologic complications were noted in careful follow-up.

An attempt to enroll patients who were treated in neurointensive care units in a controlled trial of conventional therapy versus conventional therapy plus conivaptan was terminated because of difficulty recruiting patients after only six patients had entered the trial (11). However, a single-center retrospective study reported on 22 patients who were treated for hypona-
tremia in a neurointensive care unit with conventional dosing of conivaptan (12). Half of the patients had hyponatremia after failure of conventional therapies. The serum sodium concentration increased by ≥6 mmol/L in 19 (86%) of 22 patients, with an average time to goal of 13.1 hours; no patient was rapidly corrected. However, in a single-patient case report, a 24-year-old woman with hyponatremia (121 mmol/L) associated with a large pituitary macroadenoma experienced an excessively rapid correction of serum sodium after receiving approved dosages of intravenous conivaptan. After approximately 25 mg of the drug, her sodium increased by 16 mmol/L over 8.5 hours; fortunately, the patient experienced no adverse effects.

The approved dosing for conivaptan is a 20-mg bolus followed by a 20-mg/d continuous infusion over 1 to 4 days, a regimen that may increase the risk for phlebitis and that necessitates administration in large veins and changing the infusion site every 24 hours (6,12). Administration of a conivaptan bolus to healthy adults without a subsequent infusion increased urine output and decreased urine osmolality, an effect that peaked in 2 hours and persisted for 6 hours. An uncontrolled study of bolus dosing of conivaptan with no subsequent infusion in 19 patients who had acute euvoletic hyponatremia and were treated in a neurointensive care unit showed this to be an effective dosing strategy; the serum sodium increased by at least 4 mmol/L within 12 hours in 59% of patients (13). The drug consistently led to increased urine output and a significant drop in urine specific gravity, and no cases of phlebitis were observed despite administration of conivaptan through peripheral intravenous lines. In a single case report, a single 20-mg bolus of conivaptan (without a sustaining infusion) was given to a patient with traumatic brain injury complicated by increased intracranial pressure when his serum sodium concentration fell to 128 mmol/L (14); an aquarexis developed 3 to 5 hours after the dose, with urine output peaking at 1 L/h, and by 8 hours, the serum sodium had risen to 146 mmol/L (an increase of 18 mmol/L within 8 hours). Intracranial pressure fell from 11 to 15 mmHg before conivaptan to 2 mmHg after 4 hours and remained reduced after 8 hours.

**Tolvaptan.** Tolvaptan is the first oral nonpeptide selective vasopressin V2R antagonist approved for use in the United States by the FDA. Tolvaptan has an affinity for the V2R that is 29 times greater than that for the V1A receptor, and it has no appreciable affinity for the V1B receptor. The Study of Ascending Levels of Tolvaptan in Hyponatremia (SALT-1 and SALT-2) showed that tolvaptan increases the serum sodium concentration over the short term (≤30 days) in patients with euvolemic and hypervolemic hyponatremia, and a multicenter, open-label extension of these trials, called SALTWATER, documented the long-term effectiveness and safety of tolvaptan in 111 patients who had hyponatremia and were treated for a mean follow-up of 701 days (15). Responses were comparable between patients with euvoletic and those with heart failure but more modest in patients with cirrhosis.

A recent review of the literature identified nine published trials that investigated the use of the vasopressin V2R antagonist tolvaptan as of February 2010 (16), and meta-analysis publications through 2009 (8) analyzed outcomes. When used to treat hyponatremia, tolvaptan was associated with significantly greater increase in serum sodium concentrations compared with placebo on treatment days 1 (3.62 ± 2.68 versus 0.25 ± 2.08 mmol/L; P < 0.001) and 30 (6.22 ± 4.10 versus 1.66 ± 3.59 mmol/L; P < 0.001). When used to treat patients with heart failure, tolvaptan at dosages of 30, 60, and 90 mg/d was associated with mean weight changes of −1.80, −2.10, and −2.05 kg, respectively, versus −0.60 kg with placebo (P = 0.002, P = 0.002, and P = 0.009), but it does not alter disease progression or mortality. The most commonly reported adverse events associated with tolvaptan in clinical trials were dry mouth (4.2 to 23.0%), thirst (7.7 to 40.3%), and polyuria (0.6 to 31.7%), all consistent with the mechanism of action of the drug. The academic pharmacists who authored this review also provide an extensive discussion of the pharmacology of tolvaptan. Tolvaptan is metabolized exclusively in the liver with an estimated half-life of 12 hours. Aquaretic and sodium-increasing effects of the drug have been reported to begin within 2 to 4 hours (as compared with the diuretic effect of conventional loop diuretics, which act within 30 to 60 minutes), and approximately 60% of the effect occurs within the first 12 hours. Because tolvaptan is metabolized primarily by the CYP3A isoenzyme, numerous drug–drug interactions are possible. Concurrent administration of ketoconazole, a strong inhibitor of CYP3A, increases tolvaptan exposure by 82%. Higher dosages of ketoconazole and other strong inhibitors of CYP3A (e.g., itraconazole, clarithromycin, saquinavir, ritonavir, ne-
fazodone) administered at maximum dosages would be expected to result in even greater increases in tolvaptan exposure. Therefore, although no adverse effects have been reported from these interactions, concurrent administration with strong inhibitors of CYP3A is best avoided. There are no data on the effects of moderate inhibitors of CYP3A (e.g., verapamil, diltiazem, fluconazole, erythromycin), but on the basis of known metabolism and pharmacokinetics, a considerable increase in tolvaptan exposure would be expected. Conversely, rifampin, which induces the enzyme, decreases tolvaptan levels by more than sevenfold and would be expected to diminish the effect of tolvaptan. Similar interactions would be expected with other CYP3A inducers (e.g., rifabutin, barbiturates, phenytoin, carbamazepine, St. John’s wort).

Tolvaptan was shown to be effective in correcting hyponatremia in a 30-day placebo-controlled trial of 19 patients with schizophrenia and stable asymptomatic idiopathic hyponatremia (mean serum sodium 130.3 mmol/L) (17); seven patients received tolvaptan, and 12 received placebo. All patients had evidence of impaired water excretion with persistent hyponatremia despite water restriction or laboratory evidence of SIADH, with urine osmolality >100 mOsm/kg despite a serum sodium <130 mmol/L. During the initial 4 days of therapy, patients who were given the study drug received increasing dosages of tolvaptan escalating from 15 to 60 mg/d as needed to correct hyponatremia slowly. Fluids were unrestricted unless morning weights were 7.5% higher than their regular dry weight (and this occurred in only one placebo patient and one control subject). Beginning at approximately 8 hours and continuing until the drug was stopped, mean serum sodium concentrations during treatment with tolvaptan were significantly higher than placebo. One patient underwent a 12-mmol/L increase in serum sodium concentration (from 127 to 139 mmol/L) in the first day of therapy associated with hypotensive symptoms, ataxia, and slurred speech but ultimately recovered; no data on urine osmolality were reported for any of the patients. The results of this small study are similar to other studies of tolvaptan and other vasopressin antagonists in patients with SIADH or hyponatremia caused by heart failure or hepatic cirrhosis. Unfortunately, the study leaves unanswered the important question as to whether vasopressin antagonists would be useful in preventing episodes of symptomatic hyponatremia in patients with schizophrenia and polydipsia and with self-induced water intoxication. Epidemiologic studies show that 10 to 20% of patients with schizophrenia have polydipsia (water intake >3 L/d), and a small percentage of this population with polydipsia develop acute water intoxication. There is considerable evidence that most patients with schizophrenia and polydipsia develop hyponatremia during periods when their water intake exceeds normally functioning water excretion. Even with maximally dilute urine (approximately 50 mOsm/L), maximum water output cannot exceed approximately 1 L/h while excreting a normal dietary solute load (approximately 900 mOsm/d).

References
Hypernatremia

**Physiology**

Maintenance of a normal serum sodium concentration depends on the ability to balance water intake and water excretion. Thirst is the primary defense against hypernatremia because water intake should normally compensate for water losses if water is available; a very readable and comprehensive review of the subject was recently published (1).

The ability to concentrate urine is essential when water is scarce. The renal medulla produces a concentrated urine by generating an osmotic gradient extending from the corticomedullary boundary to the tip of the inner medulla. In the presence of the antidiuretic hormone arginine vasopressin (AVP), water is reabsorbed across the collecting ducts so that the luminal fluid achieves osmotic equilibrium with the surrounding interstitium; the reabsorbed water is returned to the circulation in the ascending vasa recta.

The gradient is classically attributed to countercurrent multiplication of small transepithelial concentration differences, the so-called “single effect.” Our understanding of the complex interactions among the nephron segments of the renal medulla and its vasculature that generate and maintain the concentration gradient is still incomplete and was the subject of recent reviews (2–5). In the outer medulla, the gradient can be attributed to active sodium chloride reabsorption in the thick ascending limb. Because the thin ascending limb is incapable of active transport, passive mechanisms for the single effect were proposed for the inner medulla in 1972, based on what was understood about differences in water, urea, and sodium permeabilities of the thin descending (water permeable but impermeable to sodium and urea) and thin ascending limbs (impermeable to water but highly permeable to sodium, less so to urea). However, mathematical models using original assumptions regarding permeability differences failed to account for the gradient. Other models based on hydrostatic pressure generated by peristaltic contractions of the pelvic wall have been proposed. More recently, new findings have emerged about the complex functional architecture of the renal medulla and the diverse permeability characteristics of the loop of Henle: Tubules are organized around tightly packed vascular bundles, and differences in their anatomic arrangements in the outer and inner medulla may have functional significance (Figures 14 and 15); approximately 85% of descending thin limbs lack aquaporin 1 (AQP1) and are therefore water impermeable, whereas AQP1 is present in those nephrons with longer loops of Henle; loops of Henle in the inner medulla lack urea transporters and are therefore urea impermeable. These new findings have prompted new computer simulations that are consistent with a passive model.

Urea plays an important role in the urine-concentrating mechanism because protein deprivation impairs and urea administration restores urine-concentrating ability. AVP phosphorylates the urea transporter UT-A1 via a cAMP-mediated process that, together with an AVP-independent effect of hyperosmolality, results in insertion of UT-A1 in the luminal membrane of the papillary collecting duct, increasing its permeability to urea. During an antidiuresis, water is osmotically reabsorbed from the urea-impermeable parts of the outer medullary collecting ducts through AQP2 water channels inserted by AVP. With the extraction of water, urea concentration increases in the collecting duct lumen, and urea is absorbed once it reaches the papillary tip, which is urea permeable when AVP is acting; this absorption achieves high concentrations in the medullary interstitium and contributes to the medullary concentration gradient. Gene knockout mice have been created for the terminal collecting duct urea transporter UT-A1, whose activity on the luminal membrane is acutely regulated by AVP; for UT-A3, located on the basolateral membrane of the terminal collecting duct; for UT-A2, located on thin descending limbs of the loop of Henle; and for the descending vasa recta isoform, UT-B (3). Studies of these knockouts have enhanced our understanding of the role of urea transport in water conservation. Mice lacking both terminal collecting duct urea transporters UT-A1 and UT-A3 have a normal ability to conserve water when fed a low-protein diet; on a high-protein diet, which generates more urea, the inability of the A1/A3 knockout to reabsorb urea results in polyuria because of a urea diuresis. However, the A1/A3 knockout is
able to generate a corticomedullary sodium chloride concentration gradient that is indistinguishable from that of wild-type mice. Although this seems to argue against the passive model for sodium reabsorption in the thin ascending limb, which relies on accumulation of the urea in the interstitium of the inner medulla (3), recent mathematical modeling of these data concluded that the findings in the A1/A3 knockout are consistent with predictions of the passive mechanism (6). UT-A2 knockout mice, in which urea secretion into the thin descending limb is impaired, do not have a concentrating defect, but UT-B mice, which lack a urea transporter on vasa recta, have a high plasma urea concentration and a “urea-selective” urine-concentrating defect with a lower inner medullary urea concentration. Humans with genetic loss of the UT-B transporter (present on vasa recta) are unable to concentrate their urine above 800 mOsm/kg.

Halperin et al. (4) proposed a novel interpretation of the concentrating mechanism, based on the premise that its function is not only to conserve water but also to avoid an excessively concentrated urine that would result in stone formation; we only briefly summarize this detailed quantitative analysis. The authors suggested that the amount of dilution of the medullary interstitium caused by AVP-stimulated re-absorption of water in the medullary collecting duct controls the amount of sodium chloride absorbed in the thick ascending limb (which then restores the sodium chloride concentration of the interstitium) so that it transports the “right” amount of salt into the interstitium, too much of which would result in an excessively concentrated urine. The proposed regulator of this process is the calcium receptor on the basolateral membrane of the ascending limb, which, when occupied, inhibits ROMK function and decreases sodium chloride reabsorption. The entry of water from the collecting duct into the interstitium lowers the calcium concentration in the interstitial fluid, releasing the ROMK from inhibition from an occupied calcium receptor. In the inner medulla, dilution of the interstitial sodium chloride concentration by reabsorption of an iso-osmolar urea solution in response to AVP (urea acting as an ineffective osmole when the papillary urea transporters allow it to diffuse out of the lumen with water) creates the driving force for passive salt reabsorption without water from the water-impermeable thin ascending limb; with the addition of sodium and chloride derived from the thin ascending limb, the sodium concentration of the medullary interstitium returns nearly to the concentration that preceded its dilution with urea and water from the collecting duct.
Whereas countercurrent multiplication creates the medullary concentration gradient and countercur- rent exchange in the vasa recta sustains it, AVP is ultimately responsible for the excretion of a concentrated urine. In response to very minor dehydration, enough to increase the plasma osmolality by as little as 2 mOsm/kg, AVP is released from the posterior pituitary. AVP binds to vasopressin 2 receptors (V2Rs) in the basolateral membrane of collecting duct principal cells, stimulating production of cAMP, which activates protein kinase A and phosphorylates AQP2, resulting in the exocytic insertion of AQP2 water channels stored in intracellular vesicles into the luminal membrane of the collecting duct. In response to AVP, water is reabsorbed across the collecting duct and achieves osmotic equilibrium with the surrounding hyperosmotic medullary interstitium.

Recently, AVP-independent mechanisms controlling water homeostasis have been identified. The biologic effects of secretin and oxytocin in this process have recently been reviewed (7). Oxytocin, which plays an important role in reproduction, and AVP are closely related peptide hormones; both are secreted from the posterior pituitary, and seven of their nine amino acids are identical. Oxytocin exerts its antidiuretic effect by binding to the AVP V2R but with lower affinity. Its antidiuretic effect occurs primarily at supraphysiologic concentrations that can be achieved when oxytocin is given at high dosages to induce labor. Secretin is a gastrointestinal hormone that stimulates water and electrolyte secretion in the intestine, liver, and pancreas. Secretin receptors and secretin-sensitive adenylcyclase have been identified in renal epithelia. Secretin increases intracellular cAMP levels via binding to SCTR on the basolateral membrane which is coupled to the adenylcyclase VI through the G-protein GS. Similar to the action of AVP, increased cAMP induced by secretin leads to the exocytic insertion of AQP2-bearing vesicles into the apical plasma membrane and, through unknown transcription factors, increases the protein and transcript levels of AQP2. Several lines of evidence support a physiologic role for secretin in water homeostasis: Plasma secretin levels increase in water-deprived mice, secretin has an antidiuretic effect in the AVP-deficient Brattleboro rat, and mice genetically deficient in the secretin receptor have a defect in water conservation. The authors speculated that dysfunction of secretin and its receptor are potential causes of nephrogenic diabetes insipidus (DI) in humans and that secretin may be a candidate for treating X-linked nephrogenic DI. Studies in cultured cell models have identified a host of additional factors that influence the abundance of AQP2 in the renal collecting duct, including insulin, calcium, pro-inflammatory factors, and aldosterone (8).

**Essential Hypernatremia**

Appropriate responses to an increase in serum sodium concentration are greater water intake driven by thirst and reduced urinary water output caused by the secretion of AVP. “Essential hypernatremia” is characterized by upward resetting of the osmotic set point for both thirst and AVP release, resulting in persistent euvolemic hypernatremia. In most cases, structural abnormalities as a result of trauma, tumor, or
inflammation are detected in the hypothalamic-pituitary area. However, several cases of idiopathic essential hypernatremia have been reported, all of them in patients who were younger than 13 years.

Studies in mice have demonstrated that the Na$_x$ channel, expressed in the posterior pituitary and three circumventricular organs in the brain (the subfornical organ [SFO], the organum vasculosum of the lamina terminalis [OVLT], and the median eminence) is the Na-level sensor of body fluids in the brain. Na$_x$-knockout mice do not stop ingesting salt when dehydrated, whereas wild-type mice avoid salt; unlike wild-type mice, salt-aversive behavior does not occur in knockout mice.

The investigators who first reported these findings recently identified a patient who had essential hypernatremia and developed autoantibodies to Na$_x$ (9). The patient, a 6.5-year-old Asian girl, had a ganglioneuroma adjacent to the adrenal gland composed primarily of Na$_x$-positive Schwann-like cells, and the neoplasm most likely evoked an antitumor immune response (a paraneoplastic disease). She presented with serum sodium levels as high as 199 mmol/L with a normal BP and pulse and little change in consciousness. Serum AVP levels when her serum sodium was extremely high were detectable (2.1 pg/ml) but approximately half the levels that would be expected in a patient with even mild dehydration. Resection of the tumor did not cure the hypernatremia, and she continued to exhibit abnormal osmoregulation 4 years after surgery. Plasma AVP levels remained nearly constant with plasma osmolalities ranging from 280 to 390 mOsm/kg. Administration of desmopressin combined with fluid deprivation resulted in a urine osmolality of 1009 mOsm/kg, indicating that the patient could concentrate her urine normally, but she had no complaint of thirst during the fluid deprivation test. She exhibited hyperphagia and hyperhidrosis (increased sweating), which contributed to water loss. Four years after surgical removal of the Na$_x$-positive tumor, the patient’s serum continued to contain autoantibodies to Na$_x$.

Passive transfer of the patient’s IgG to wild-type mice reduced their water intake and inhibited AVP release as a result of complement-mediated cell death in the circumventricular organs where Na$_x$ is expressed. The patient’s IgG fraction depleted of autoantibodies to Na$_x$ did not induce symptoms. The mice that were administered an injection of the patient’s IgG differed from Na$_x$-knockout mice in that the knockout mice had normal AVP levels. Na$_x$ is expressed in cells in the SFO and OVLT, which have projections to the supraoptic and paraventricular nuclei, which are responsible for the regulation of AVP secretion. Osmoreceptors, including TRPV1 and TRPV4, are thought to be involved in the regulation of the activity of these neurons. After injection of mice with the patient’s antibodies, evidence of cell degeneration in the SFO, OVLT, and posterior pituitary were found.

**Neurogenic DI**

**Familial Neurogenic DI.** Familial neurohypophyseal DI is an autosomal dominant disorder caused by mutations in the gene that encodes neurophysin II, the AVP carrier protein. Affected patients have a normal ability to conserve water at birth, and progressive polyuria develops later in childhood, usually within the first 6 years of life, with progressively worsening polyuria and compensatory polydipsia. Because these patients have progressive loss of AVP, they may initially respond normally to water-deprivation testing and have normal pituitary findings on brain magnetic resonance imaging (MRI). These normal findings have sometimes led to an erroneous diagnosis of psychogenic polydipsia; genetic testing may be helpful in making the correct diagnosis and avoids the need for frequent surveillance of family members (10). Studies in knock-in mice expressing a mutant neurophysin II gene that causes familial DI in humans showed that polyuria progresses without loss of AVP neurons (11–13). Inclusion bodies were found in the AVP neurons in the supraoptic nucleus, and their size and number gradually increased in parallel with the increases in urine volume. Electron microscopy showed that aggregates formed in the endoplasmatic reticulum of AVP neurons; these aggregates, rather than cell death, are associated with progressive polyuria. Interestingly, administration of desmopressin to knock-in mice with the human disease phenotype decreased AVP mRNA expression and diminished the formation of inclusion bodies in the AVP neurons (14). Animals treated with desmopressin remained significantly less polyuric than controls for 14 days even after desmopressin administration ended. Increasing expression of AVP with the administration of hypertonic saline enhanced the formation of inclusion bodies in AVP cells. These data show that activation of AVP neurons accelerates the
formation of aggregates and exacerbates the progression of polyuria.

**Lymphocytic Hypophysitis.** Lymphocytic hypophysitis is an uncommon autoimmune disease characterized by inflammatory enlargement of the pituitary gland with eventual destruction of pituitary tissue and replacement by fibrosis (15). The disease occurs more commonly in women and often presents late in pregnancy. Visual field impairment as a result of extracellular pituitary enlargement may develop, and patients present with varying degrees of dysfunction of the anterior (lymphocytic adenohypophysitis) and posterior pituitary (lymphocytic infundibuloneurohypophysitis).

**IgG4 Disease.** IgG4-related disease, also known as IgG4-positive multiorgan lymphoproliferative syndrome, is characterized by high serum levels of IgG4 and dense infiltration of IgG4 plasma cells into multiple organs and tissues, causing pancreatitis; Sjögren syndrome; interstitial lung disease; and involvement of the liver, bile duct, gall bladder, kidney, and retroperitoneum. A few cases of IgG4-related hypophysitis with neurogenic DI have been reported (16).

**Neurosurgical DI.** DI is a common complication after resections of pituitary adenoma and after traumatic brain injury (17,18). In a study of 57 patients who underwent resection of a pituitary adenoma at a German academic center, 38.5% developed isolated DI and 15.7% developed DI followed by hyponatremia. The onset was typically on the second day of surgery, and in 8.7% of patients, desmopressin was required for more than 3 months.

**Congenital Nephrogenic DI**

Defects in the V2R or AQP2 lead to nephrogenic DI (NDI), a disorder in which patients are unable to concentrate their urine normally, resulting in polyuria, dehydration, and hyponatremia. The V2R gene, AVPR2, is located on the X chromosome, and AVPR2-linked NDI follows an X-linked recessive inheritance pattern. The AQP2 gene is located on chromosome 12. In most cases, AQP2-linked NDI follows an autosomal recessive inheritance pattern.

Approximately 90% of congenital NDI cases are caused by AVPR2 mutations encoding the V2R; because this gene is located on the X chromosome, the disease is generally a male disease with X-linked recessive inheritance. Female carriers of AVPR2 mutations are usually asymptomatic, but some females have symptoms even though they are genetically characterized as carriers of the mutation. During X-chromosome inactivation, a natural process that occurs in every female during embryonic development, one of the two X chromosomes is inactivated. The process is random, but in individual cells or tissues, a disproportionate number of chromosomes containing the unaffected gene can be inactivated. This can lead to mild symptoms of the disease. In one reported family, the mother of a boy and a girl with symptomatic NDI was asymptomatic with a random pattern of X-chromosome inactivation; her affected daughter expressed a skewed inactivation pattern of 7:93 in favor of the variant X chromosome (19). Patients with partial disease are able to reach a urine osmolality >300 mOsm/kg and <750 mOsm/kg after fluid deprivation, and they may respond to high dosages of AVP or desmopressin (dDAVP). Combinations of indomethacin and thiazide diuretics, however, are the most effective therapy.

The V2R, expressed in vascular endothelial cells as well as in kidney principal collecting duct epithelial cells, regulates secretion of the von Willebrand factor (vWF), the carrier protein for coagulation factor VIII (FVIII). Stimulation of the V2R with AVP leads to exocytosis of the vWF storage organelle Weibel–Palade bodies (WPb). In patients with NDI, the release of WPb in response to the synthetic AVP analog dDAVP increases plasma levels of vWF, FVIII, and tissue-type plasminogen activator (t-PA; co-stored with vWF in WPb), indicating that the V2R is functioning normally and that the concentrating defect is caused by a defect in the AQP2 gene. In patients with AVPR2-linked NDI, there is no response to dDAVP.

Carriers of the AQP2 gene mutation have an increased risk for thromboembolism (20). Elevated plasma levels of FVIII are a risk factor of venous thrombosis, and levels of FVIII depend on levels of its carrier protein, vWF. Hypothetically, NDI-linked AQP2 mutations would be expected to cause upregulation of AVP release and V2R expression, resulting in increased vWF secretion from the endothelium. Consistent with this hypothesis, a study of 14 NDI carriers (nine with an AVPR2 mutation and five with an AQP2 mutation) found that in comparison with unaffected family members, AVP levels were increased only in AQP2 carriers (21). This suggests that AVP release is indeed upregulated in carriers of AQP2-linked NDI to compensate effectively for increased fluid loss. The highest levels
of vWF propeptide, a measure of the vWF secretion rate and the highest levels of vWF antigen and factor FVIII activity, were also observed in carriers of AQP2 mutations (21).

**Secondary NDI.** Secondary NDI may also occur as a complication of other inherited tubulopathies, such as cystinosis, nephronophthisis, Bartter syndrome and apparent mineralocorticoid excess, and distal tubular renal tubular acidosis (22). Children with these disorders may present with recurrent episodes of hypernatremia with hypokalemic urine unresponsive to dDAVP, leading to a misdiagnosis of congenital NDI, delaying recognition of the underlying disorder. In cystinosis, trapping of cystine in lysosomes primarily affects the proximal tubule, with resulting Fanconi syndrome, but it can theoretically impair function of any cell; the incidence of concentrating defects in this disease has not been studied systematically, but one patient with hypernatremia and hypotonic urine unresponsive to dDAVP, an apparent concentrating defect in a renal concentrating ability that was associated with decreased urinary AQP2 and cAMP were correlated with the duration of lithium therapy; none of the patients harbored mutations in genes coding for the V2R or AQP2.

Nephrotoxic effects of lithium may be detected 8 weeks after the start of treatment. Patients who are on lithium therapy for >10 years may develop chronic kidney disease or hypercalcemia, prompting discontinuation of the drug. NDI symptoms may disappear in as little as 3 weeks after lithium is stopped; however, urine-concentrating defects usually persist for years after ending treatment. Acute administration of lithium inhibits the formation of cAMP, thereby preventing activation of phosphokinase A (PKA) (26). Phosphorylation of AQP2 and UT-A1 by PKA is required for translocation and insertion of these key transporters into the apical plasma membrane of the inner medullary collecting duct. This initial dysregulation of AVP-regulated water reabsorption contributes to the urine-concentrating defect observed in lithium-treated rats (26). Long-term lithium administration reduces the amount of AQP2 and UT-A1 in rat inner medulla. Although the urea transporters recovered to basal levels 14 days after discontinuation of lithium administration, AQP2 expression did not (27).

Lithium is a potent inhibitor of glycolgen synthase kinase 3β (GSK3β), a serine/threonine protein kinase. Knockout mice with a deletion GSK3β have impaired urine-concentrating ability in response to water deprivation or treatment with an AVP analog associated with reduced levels of mRNA, protein, and membrane localization of the AVP-responsive water...
channel AQP2. The knockout also expressed lower levels of pS256-AQP2, a phosphorylated form of the water channel crucial for membrane trafficking (28). Levels of cAMP, a major regulator of AQP2 expression and trafficking, were also lower in the knockout mice. Both GSK3β gene deletion and pharmacologic inhibition of GSK3β reduced adenylyl cyclase activity. Thus, GSK3β inactivation by lithium is a plausible mechanism for its inhibitory effect on AVP action in the renal collecting duct.

Amiloride inhibits the uptake of lithium in the collecting duct by binding to the epithelial sodium channel and was used clinically to ameliorate polyuria in two open-label studies. Eleven patients who were on long-term lithium therapy (patients aged 8 to 34) were enrolled in a randomized, placebo-controlled, crossover trial investigating the actions of amiloride (10 mg/d for 6 weeks) on dDAVP-stimulated urine-concentrating ability and AQP2 excretion (25). After 6 weeks of amiloride but not after placebo, urine osmolality increased to 164.5 ± 8.0% of baseline after the administration of dDAVP (P ≤ 0.05) with an associated increase in urinary AQP2; because the increase over baseline during the placebo portion of the trial was approximately 134%, the effect of amiloride on absolute urine osmolality seems to be modest.

NDI is a common complication of amphotericin B, and use of the less toxic liposomal preparation does not prevent NDI (29). Hypokalemia associated with the drug may be an exacerbating factor, but renal concentrating defects have been demonstrated in patients who were treated with amphotericin and whose plasma potassium concentrations were normal. In vitro, amphotericin B partially inhibits AVP-stimulated water permeability and urea transport in the rat inner medullary collecting duct, and it decreases the abundance of AQP2 water channels because of inhibition of adenylcyclase and/or G proteins. NDI is a widely known complication of another antibiotic, demeclocycline, and this frequent adverse effect has been exploited in the treatment of syndrome of inappropriate antidiuretic hormone secretion. The drug inhibits AVP-induced water flow in the toad bladder, but the mechanism of interference with the AVP-AQP2 cascade is unknown.

**Consequences of Hypernatremia Mortality.** In general medical-surgical units that treat non–critically ill patients, the prevalence of hypernatremia is approximately 1%; among critically ill patients who are treated in intensive care units (ICUs), the incidence ranges between 10 and 26%, and, in most cases, hypernatremia develops during the ICU stay. Several studies suggested an association between hypernatremia and hospital mortality. However, most of these studies were retrospective, single-center studies with small numbers of patients and with inadequate adjustment for confounders or occurrence of adverse events during the ICU stay. A retrospective, observational study on a prospectively collected multicenter database fed by 12 French ICUs was conducted to determine the effect of mild (>145 but <150 mmol/L) and severe (>150 mmol/L) hypernatremia on mortality after adjustment for confounders (31). The inves-
tigators compared 6895 patients who did not have ICU-acquired hypernatremia (hospital mortality 15.2%) with 901 patients who had mild ICU-acquired hypernatremia (hospital mortality 29.4%) and 344 patients who had moderate to severe ICU-acquired hypernatremia (hospital mortality 46.2%). Most (69.8%) of the patients were admitted to the ICU for a medical condition, the most common of which were acute respiratory failure, coma, and septic shock. The overall prevalence of hypernatremia was 15.3%. Factors independently associated with ICU-acquired hypernatremia were male gender; greater disease severity on ICU admission; and septic shock, acute respiratory failure, or coma at ICU admission. Other factors associated with hypernatremia were the need for a bladder catheter, central venous catheter, or vasoactive agents and the use of steroids or antibiotics. No data were available to evaluate fluid balance or use of diuretics; in addition, the investigators were unable to correct the serum sodium for the effect of hyperglycemia, and hyperglycemia was not included as one of the confounding factors. Both mild and severe hypernatremia remained highly significant independent risk factors for mortality after stratification by center and adjustment for time-dependent and non–time-dependent confounders. However, the study could not determine why ICU-acquired hypernatremia was associated with increased risk for death, and it remains uncertain from this and other studies whether the association reflects a direct effect of hypernatremia or a marker for suboptimal quality of care.

Although ICU-acquired sodium disturbances are common in critically ill patients, few studies have examined sodium disturbances in patients after cardiac surgery. A single-center study from a university hospital in Austria examined the incidence of hypernatremia in patients who were treated in a cardiothoracic surgery ICU, including 2314 patients who underwent coronary artery bypass grafting, open heart surgery, aortic surgery, heart or lung transplant, or thromboendarterectomy of the pulmonary arteries (32). During their stay in the ICU, 221 (10%) patients developed hypernatremia (serum sodium >145 mmol/L), and patients with ICU-acquired hypernatremia had higher ICU mortality (19 versus 8%; P < 0.01) and a longer ICU stay (17 versus 3 days; P < 0.01) compared with patients without ICU-acquired hypernatremia. ICU-acquired hypernatremia was associated with an increased probability of mortality after adjustment for the SAPS II score, length of surgery, surgery type, and maximum lactate level immediately after surgery. However, when adjusted for other confounders, the investigators could not demonstrate an increased risk for mortality dependent on the severity of ICU-acquired hypernatremia. However, the authors were able to exclude factors that have been proposed as being responsible for the excess mortality with ICU-acquired hypernatremia, showing that even after adjustment for acute renal failure, administration of furosemide, plasma lactate levels, and acid-base status, hypernatremia remained an independent predictor of mortality. A similar single-center study from a regional cardiovascular ICU in Canada identified 6727 patients who underwent cardiac surgery (74% for elective coronary artery bypass grafting) and whose serum sodium levels were normal on entry, excluding patients with preexisting dialysis dependence and patients who received renal replacement therapy on the first day in the cardiovascular ICU (33). Hypernatremia (>145 mmol/L) developed in 4% of patients, more commonly among patients who had higher APACHE II scores, were on mechanical ventilation, had greater length of hospital stay before ICU admission, had greater length of stay in the ICU, and had the presence of hyperglycemia or abnormal serum potassium. Compared with patients with normal serum sodium levels, hospital mortality was increased in patients with ICU-acquired hypernatremia (1.6 versus 14.0%; P < 0.001) and similar to that of patients with ICU-acquired hyponatremia (10%). In contrast to the risk for hyponatremia, which was greatest in the first few days of ICU stay, the risk for developing ICU-acquired hypernatremia steadily increased over time. Twenty-six (10.7%) patients with ICU-acquired hypernatremia experienced a change in serum sodium ≥12 mmol/L per d; compared with patients with lower rates of change, these patients had higher ICU (28.2 versus 1.3%; P < 0.001) and hospital mortality (31.8 versus 2.7%; P < 0.001). The investigators were unable to determine whether ICU-acquired hypernatremia was a marker of illness severity, and one cannot infer from the results of the study that correction of hypernatremia would improve outcomes.

In patients with severe burns, microvascular integrity is lost and a plasma-like fluid leaks into the interstitial place. For ensuring oxygen delivery, fluid resuscitation is necessary until cellular integrity is restored. Eventually, fluid volume needs to be normal-
ized, but hypernatremia should be avoided because there is evidence that it may induce apoptosis and deepen the depth of the burn wound (34). A single-center study of 40 patients with severe burns (a totally burned surface area >10%) compared 15 patients who had hypernatremia (>145 mmol/L) with 25 patients who did not have hypernatremia (34). All patients were treated with albumin in Ringer’s lactate, and no patient was treated with hypertonic fluids. However, there was a significant association between the use of mechanical hyperventilation and the development of hypernatremia. Hypernatremia occurred 5.0 ± 1.4 days after admission to the burn unit and persisted for 4.6 ± 2.7 days. Although there were no differences in age, gender, or severity of the burns, all of the patients with normonatremia survived and three (20%) of the patients with hypernatremic died (P = 0.045).

**Brain Injury from Hypernatremia**

As discussed in the section on hyponatremia, severe hypernatremia can cause central pontine and extrapontine myelinolysis similar to the lesions that have been described after rapid correction of hyponatremia, except in certain cases with a predilection for the limbic system. A 58-year-old woman who developed extreme hypernatremia (serum sodium 200 mmol/L), status epilepticus, and coma after a laparoscopic excision of a hydatid cyst was reported. A 30% saline solution is used to eradicate these cysts, and when the procedure was complicated by intraperitoneal rupture of the cyst, the peritoneal cavity was lavaged with the 30% saline solution. Emergency hemodialysis was started immediately to correct hypernatremia, but MRI of the brain in the ensuing 2 weeks demonstrated cerebral lesions along the limbic system network, in a similar distribution that has been seen after administration of glutamate (an excitotoxic organic osmolyte). In a perplexing report from India, 11 postpartum young women presented after delivery (during the second and third weeks in two and during the sixth week in one) with fever and neurologic symptoms associated with very severe hypernatremia (>190 mmol/L in six of the patients) and azotemia (35). MRI of the brain before treatment of hypernatremia showed hyperintensity in the corpus callosum in all patients and various combinations of hyperintensities, consistent with demyelination, in the internal capsule, corona radiata, cerebellar peduncles, and hippocampus. Seven of the patients eventually improved neurologically, and four died. Although it is plausible that the brain lesions were caused by hypernatremia, there was really no satisfactory explanation for the extreme electrolyte abnormalities in these young women. The authors mentioned that it is customary in some parts of Southern India to restrict water and fluid intake during the puerperal state and speculated that this practice may have compounded fluid losses from fever and the heat of the summer; none of the patients had a history of polyuria, and those who recovered neurologic function had no apparent abnormalities of water balance.

**Treatment of Hypernatremia**

Hypernatremia is common in patients who are cared for in ICUs because critical illness is often associated with impaired fluid regulation and with impaired water intake caused by impaired consciousness and inability to drink. The physician must compensate for the patient’s inability to replace free water losses by prescribing appropriate fluid therapy. For determination of the causes of hypernatremia treated in a university hospital ICU in Austria, data were rigorously analyzed for 69 patients (6% of the patients admitted to the ICU during the study period) whose serum sodium levels rose to >149 mmol/L (maximum 150 to 164 mmol/L) after entering the ICU with a serum sodium of <146 mmol/L (36). Of the 69 patients, 24 were excluded because of incomplete data. Positive sodium and potassium balance were found in 38% of patients, and 44% had a negative fluid balance; the remaining patients had a combination of positive cation balance and negative fluid balance. Polyuria from diuretics (50%), osmotic diuresis from glucose or urea (30%), and DI (4%) were present in 38% of patients; excess extrarenal fluid losses from fever and/or diarrhea were found in 63%. In addition to the use of bicarbonate (13% of cases), the addition of potassium chloride to isotonic saline created a hyper-tonic solution, leading to a positive sodium/potassium balance in 27% of patients. During the development of hypernatremia, the serum sodium concentration increased by 5.3 ± 3.3 mmol/L per d, and almost all patients required approximately 2 days to develop hypernatremia. Therefore, with frequent monitoring of serum electrolytes (every 8 hours), it should have been possible to recognize the trend toward hypernatremia and correct it with prescription of hypotonic fluids.
The investigators believed that prescribers avoided hypertonic fluids because of the fear of causing hypernatremia in patients with conditions expected to result in nonosmotic release of AVP.

The same group analyzed balance data in their ICU population comparing the ability of three published formulas (Adrogue-Madias, Barsoum-Levine, and Kurtz-Nguyen) to predict measured changes in serum sodium using daily measurements of sodium/potassium and fluid/electrolyte balances (37). Although all of the formulas correlated significantly (P < 0.05), differences between predicted and measured values as high as 15 mmol/L were observed, and were too large for these formulas to be useful in clinical practice.

Rapid correction of hypernatremia in children is known to cause cerebral edema, leading to seizures. Although it is generally accepted that a slow reduction of the serum sodium concentration by <10 mmol/L per d or 0.5 mmol/L per h is desirable, there is little documented evidence as to what constitutes a safe rate of rehydration. A single-center study in a tertiary children’s hospital in China compared rehydration regimens in 49 patients (aged 11.9 ± 8.4 months) who developed cerebral edema during treatment for hypernatremia with 48 patients (aged 14.2 ± 10.9 months) whose recovery was uneventful (38). The mean serum sodium of the 96 patients on presentation was 164.5 mmol/L (range 151.0 to 184.0 mmol/L), and associated symptoms included irritability in 72, irritability alternating with lethargy in 18, and lethargy alone in seven; all patients were febrile and had oliguria with either thirst or dry mucous membranes, and only 11 patients had hypotension with poor pulses. Cerebral edema occurred within the first 24 hours in all cases (range 4 to 23 hours). All patients were rehydrated with hypertonic fluids ranging from 0.20 to 0.67% saline in dextrose after an initial fluid bolus of isotonic saline in half of the patients. Risk factors for cerebral edema were an initial fluid bolus (29/49 versus 15/48; P = 0.006), severity of hypernatremia (167.7 ± 7.8 versus 161.3 ± 7.9 mmol/L; P < 0.001), and the overall rehydration rate (8.2 ± 1.1 versus 6.4 ± 0.6 ml/kg per h; P < 0.001). On logistic regression, the odds ratio for developing cerebral edema was unaffected by the tonicity of the solution used for rehydration, but it was significantly higher in patients with a higher initial serum sodium concentration and for bolus therapy to expand the plasma volume; a rapid rate of rehydration was the most significant contributor to cerebral edema. The rate of reduction of serum sodium in the cerebral edema group was 1.0 ± 0.3 mmol/L per h and in the group without cerebral edema was 0.5 ± 0.1 mmol/L per h (P < 0.001). The authors proposed that the overall rate of rehydration in the first 24 hours of therapy for hypernatremia not exceed 6.8 ml/kg per h, with preference for a slow and uniform rate. Initial normal saline fluid boluses should be restricted to patients with signs of circulatory collapse or shock. The greater the severity of hypernatremia, the slower the rate of rehydration and the higher the sodium concentration of the rehydration fluid should be, with a goal of correction of not more than 0.5 mmol/L per h (38).

Pediatric or adult patients with acute kidney injury may have concomitant severe hypernatremia. For avoiding rapid correction during renal replacement therapy, continuous venovenous hemofiltration has been used with adjustment of the replacement fluid sodium concentration using 30% saline additives (39). Each 5 ml of 30% saline added to a 5-L bag of replacement fluid containing a sodium concentration of 140 mmol/L raises the fluid sodium concentration by 5 mmol/L. Thus, for example, for a patient with a serum sodium concentration of 165 mmol/L, addition of 20 ml of 30% saline to the replacement solution will produce a solution with a sodium concentration of 160 mmol/L. In the United States, 23% saline is available rather than the 30% solution used in this study; 6 ml of 23% saline is equivalent to 5 ml of 30% saline, and, if added to a 5-L bag of replacement solution, it will raise the fluid sodium concentration by 5 mmol/L. Stepwise correction of the patient’s serum sodium concentration can be planned using replacement fluid made up to lower the serum sodium concentration successively. If the serum sodium decreases by >2 mmol/L in 6 hours, either the rate of filtration should be decreased or the fluid replacement bag should be changed to bags with a higher sodium concentration. Because the volumes of 30% saline additives are small, they will not substantially alter the concentration of other electrolytes in the replacement solution.

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176


Edema and Diuretics

Cirrhosis and Ascites

The formation of ascites depends on the balance between increased local filtration of fluid in the hepatic sinusoids and intestinal capillaries and augmented lymph drainage (1); accumulation of ascites also requires sodium and water retention. Although it would be logical to attribute renal sodium retention in cirrhosis to an adaptive response to underfilling of the circulation caused by fluid transudation into the abdominal cavity, measurements of plasma volume do not support this explanation. An alternative theory, the vasodilation hypothesis, holds that systemic and splanchnic vasodilation associated with increased circulating nitric oxide lowers arterial pressure despite an expanded plasma volume (i.e., the capacitance of the circulation is increased), triggering the usual neurohumoral responses to arterial underfilling (renin-angiotensin-aldosterone, the sympathetic nervous system, and nonosmotic release of vasopressin), which then promote renal sodium and water retention. However, a recent review that detailed study of the evolution of systemic hemodynamics and sodium balance in an experimental model of cirrhosis in the dog found that volume expansion preceded systemic vasodilation and that natriuresis develops in patients with cirrhosis after placement of a porto-systemic vascular shunt despite increased peripheral vasodilation; these observations suggest that systemic vasodilation is not the primary event in the pathogenesis of salt retention but rather a homeostatic response to extracellular fluid volume expansion (2). The review proposed that renal salt retention is a primary event caused by pathologic activation of a hepatic vascular sensor involved in volume control. The presence of an afferent sensor in the hepatic circulation is supported by several observations: (1) The liver has sensors that regulate renal function (e.g., electrical stimulation of perivascular portal nerves increases glomerular filtration and renal sympathetic nervous system; hepatic denervation diminishes natriuresis; renal nerve activity increases after an oral salt load or portal vein infusion of hypertonic saline); (2) hepatic vein thrombosis or occlusion stimulates renal salt and water retention that is normalized by side-to-side portocaval shunts (which lower both hepatic vein and portal vein pressure and maintain mixing of portal venous and hepatic arterial blood supplying

![Figure 16](image-url)
the liver) but not by end-to-side shunts (which lower only portal vein pressures and prevent mixing of portal and hepatic arterial blood) (Figure 16); and (3) the hepatic artery has significant autoregulatory capacity, suggesting the presence of an afferent sensor analogous to other circulations with this capacity—the kidney’s baroreceptor and the brain’s carotid sinus receptor.

The American Association for the Study of Liver Diseases (AASLD) has published evidence-based guidelines for the management of ascites caused by cirrhosis (3). Since 1994, the guidelines have advocated combinations of furosemide and spironolactone for the management of ascites. However, until recently, this recommendation was not backed by evidence from controlled trials (4). Angeli et al. (5) recently found that beginning with combined treatment was preferable because it achieved more rapid resolution of ascites (15 versus 21 days) with a lower incidence of hyperkalemia than a strategy of beginning with spironolactone alone and adding furosemide if diuretic resistance were encountered. Previous studies showing better results with monotherapy enrolled a high percentage of patients with new-onset ascites, whereas most of the patients in the more recent study had recurrent ascites.

A group in Italy reported favorable outcomes in treating patients who had diuretic-resistant heart failure with extremely high dosages of intravenous furosemide (250 to 1000 mg twice daily) combined with hypertonic saline (150 ml of 1.4 to 4.6% saline, depending on the serum sodium concentration) and more liberal dietary sodium intake. The investigators reported a pilot study of the effectiveness of this novel approach for patients with hepatic cirrhosis and ascites resistant to >160 mg of furosemide and 400 mg spironolactone daily. High-dosage furosemide and hypertonic saline (60 patients) was compared with a standard diuretic schedule and two to three daily paracenteses (24 patients) (6). The hypertonic saline/furosemide regimen was well tolerated and resulted in higher urine output, high plasma sodium concentrations, lower body weight, less leg edema, and less pleural fluid than patients who were treated with paracenteses and lower dosages of diuretic. Several possible explanations have been offered for why this counterintuitive approach to edema might work (7). Studies in isolated perfused hearts showed that hypertonicity may have a direct effect on myocardial performance, possibly by increasing intracellular calcium and possibly by reducing cardiomyocyte edema. Other proposed mechanisms include markedly reduced renal vascular resistance and reduced levels of inflammatory cytokines associated with hypertonic saline.

Transjugular intrahepatic portosystemic shunt (TIPS) has been proposed as an alternative to paracentesis in patients who have ascites and do not respond to diuretics, and a comprehensive review of the procedure has been published (8). TIPS reduces the filtration pressure favoring ascites formation and increases urinary sodium excretion and urine volume and reduces serum creatinine concentration; these findings are associated with decreased plasma renin, aldosterone, and norepinephrine and are consistent with improvement in arterial underfilling. Meta-analyses of five randomized trials suggested an improved survival after TIPS in comparison with that in patients who required repeated and frequent paracenteses, but the number of patients studied only totals 305. Several uncontrolled studies recommended TIPS for the treatment of hepatic hydrothorax.

The vasopressin receptor antagonist tolvaptan has been shown to increase urine output and decrease body weight in patients with heart failure and to raise the serum sodium concentration in patients with hyponatremia. In an open-label dose-ranging study, without a placebo control, the vasopressin antagonist tolvaptan was used as add-on therapy to 17 patients with normonatremia and decompensated liver cirrhosis and with ascites and edema resistant to furosemide at a dosage of ≥40 mg/d (9). Patients were allowed to increase their intake of water if they became thirsty. Tolvaptan was initiated at 15 mg/d. If ascites and edema persisted after 3 days, then the dosage was titrated to 30 mg/d for 3 days and then to 60 mg for another 3 days. At a dosage of 15 mg, tolvaptan improved clinical signs of ascites in edema as measured by abdominal circumference, body weight, and lower limb pitting in 65% of patients; similar results were shown in 80% of patients at a dosage of 30 mg and 91% of patients at a dosage of 60 mg. After 9 days of therapy, with escalating dosages of tolvaptan every 3 days, the overall decrease in body weight averaged 3.4 ± 2.1 kg. Administration of tolvaptan significantly increased urine volume from baseline (1445 ml/d) to 3240 ml/d on 15 mg, 3943 ml on 30 mg, and 4537 ml on 60 mg; compared with baseline, the drug decreased urine osmolality (by approximately 50%), increased
serum sodium (by approximately 3 mmol/L), and increased plasma vasopressin levels (by approximately 2 to 3 pg/ml).

A similar randomized, placebo-controlled trial of 148 patients with cirrhosis and ascites without hyponatremia (all serum sodium values >130 mmol/L, mean serum sodium 136 to 137 at baseline) explored the effectiveness of the investigational vasopressin 2 receptor antagonist satavaptan in combination with fixed dosages of spironolactone (100 mg/d) and furosemide 20 to 25 mg/d (10). Administration of satavaptan for 14 days was associated with a significant reduction in weight at all dosages (5.0, 12.5, and 25.0 mg/d) averaging 2.08 to 2.46 kg compared with 0.36 kg on placebo. The drug increased urine volume to as high as 5 L/d in some patients and, as would be expected, decreased urine osmolality, although there was no measured increase in sodium excretion. Fluid intake was not restricted, so the mean serum sodium concentration increased by only 0.8 to 2.5 mmol/L, in a dosage-dependent manner. Four of 38 patients who were treated with the highest dosage experienced an increase in serum sodium of >8 mmol/L per d (as high as 14 mmol/L) without associated neurologic complications, and 28% of patients noted increased thirst at the highest dosage. Renal function was not adversely affected.

**Heart Failure**

Although high dosages of spironolactone (up to 400 mg/d) are widely accepted for the treatment of fluid retention in hepatic cirrhosis, in congestive heart failure, spironolactone has been administered in dosages that do not significantly increase sodium excretion (approximately 25 mg/d) with the goal of preventing cardiac and vascular fibrosis, rather than conquering diuretic resistance. In patients who have advanced heart failure and are resistant to loop diuretics, diuretic dosages of spironolactone have been avoided because concurrent treatment with angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, and β blockers increase the risk for hyperkalemia. In small trials of diuretic-resistant patients with heart failure, high dosages of spironolactone (100 to 200 mg/d) significantly increased sodium excretion without hyperkalemia. Recent editorial reviews argued that combinations of natriuretic dosages of mineralocorticoid antagonists need not have a prohibitive incidence of hyperkalemia when these are combined with high dosages of loop diuretics and that this strategy warrants a carefully designed randomized trial (11,12).

Plasma levels of B-type natriuretic peptides (BNPs) have been widely used to guide treatment of patients with chronic heart failure. However, the benefits of this approach have been uncertain. A meta-analysis of eight randomized, controlled trials with a total of 1726 patients found a significantly lower risk for all-cause mortality (relative risk 0.76; 95% confidence interval 0.63 to 0.91; \(P = 0.003\)) in the BNP-guided therapy group compared with the control group but not in patients who were aged ≥75 years (13). A higher percentage of patients achieved target dosages of angiotensin-converting enzyme inhibitors and β blockers during the course of these trials in the BNP group than in control subjects (21 to 22% in the BNP group versus 11.7 and 12.5% in control subjects, respectively).

Use of loop diuretics in the treatment of heart failure has been implicated in the pathogenesis of worsening renal function, and they may worsen secondary hyperaldosteronism. Concern about the safety of loop diuretics has spawned clinical trials to identify alternative therapies for reducing congestion in acute decompensated heart failure (ultrafiltration, natriuretic peptides, vasopressin receptor antagonists, and adenosine type 1 receptor antagonists). Loop diuretics have been viewed as a “necessary evil” that may actually be doing harm. Recent observations suggested that concern about diuretic-induced azotemia may be misplaced. A retrospective analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial database found that despite receiving higher dosages of loop diuretics and a greater risk for worsening renal function, patients with the greatest degree of hemocoagulation (as evidenced by an increase in serum levels of albumin and total protein and/or increase in hematocrit in response to treatment during hospitalization) had markedly reduced posthospitalization mortality when compared with patients who did not show evidence of hemocoagulation (14).

A desire to achieve adequate decongestion of heart failure while avoiding the potentially adverse affects of diuretic therapy has led to interest in the use of ultrafiltration rather than diuretics to treat heart failure in patients with preserved renal function. In an unblinded trial funded by the manufacturer of an ultrafiltration device, patients were randomly assigned.
to ultrafiltration (n = 100) or to standard intravenous diuretic therapy; patients in the diuretic arm received either bolus injection (n = 68) or continuous infusion (n = 32) at the discretion of the treating physician (15). At 90 days, the ultrafiltration group had significantly fewer rehospitalizations and unscheduled visits (0.65 ± 1.36) than the bolus (1.31 ± 1.87; P = 0.05) or continuous infusion (2.29 ± 3.23; P = 0.016) diuretic group. However, although the net fluid loss achieved by ultrafiltration (4.6 ± 2.6 L) was not statistically different from that in patients who were given bolus diuretics (2.9 ± 3.5 L) or continuous diuretics (3.6 ± 3.5 L), the trend favored ultrafiltration. Furthermore, weight loss at 48 hours in the ultrafiltration group (5.0 ± 3.1 kg) was significantly higher than in the bolus diuretic group (3.1 ± 2.6 kg) or continuous infusion diuretic group (2.9 ± 3.23 kg). Therefore, it remains unclear whether the amount of fluid removed or the composition of fluid removed affects outcomes. There was no difference in mortality or serum creatinine between diuretic and ultrafiltration therapy. A larger blinded trial designed to achieve equal fluid removal is needed before this invasive and expensive therapy can be recommended.

Nephrotic Syndrome

The pathogenesis of edema formation in the nephrotic syndrome remains undefined. Loss of oncotic pressure because of proteinuria and hypoalbuminemia is an inadequate explanation for edema because many patients have evidence of volume expansion with suppression of components of the renin-angiotensin-aldosterone system during times of avid sodium retention, because natriuretic responses to steroids often precede recovery of hypoalbuminemia, and because sodium retention occurs only on the affected side of a unilateral nephrotic rat model. The “overfill hypothesis” suggests that volume overload in at least some case of the nephrotic syndrome is generated by a primary defect in renal sodium handling.

Regulated by aldosterone and vasopressin, the epithelial sodium channel (ENaC) plays a key role in the pathogenesis of edema formation in heart failure, hepatic cirrhosis, and the nephrotic syndrome. However, adrenalectomized animals and the vasopressin-deficient Brattleboro rat can develop nephrosis, and not all patients with the nephrotic syndrome have elevated levels of aldosterone and vasopressin. Recent evidence suggested that a leaky glomerular filtration barrier allows filtration of proteases or precursors of proteases with the ability to activate ENaC (16). Plasmin, which has the ability to activate ENaC by cleaving its γ-subunit, seems to be the predominant aprotinin-sensitive serine protease identified in nephrotic urine from rats and humans. Plasminogen filtered by the damaged glomerulus is cleaved to its active form, plasmin, by urokinase and other proteases in the urine (17).

The overfill hypothesis does not always fit patient characteristics in clinical practice, particularly children with idiopathic nephrotic syndrome. Pediatricians are reluctant to treat patients with diuretics without concurrent infusion of albumin because of concerns about hypovolemia and increased risk for thromboembolic complications. A recent report analyzed 10 consecutive children with idiopathic nephrotic syndrome and found that a fractional excretion of sodium (FENa) <0.2% was predictive of high renin, aldosterone, and vasopressin levels and a high blood urea nitrogen–creatinine ratio supporting a diagnosis of volume contraction; a higher FENa seemed to reflect volume expansion. The investigators applied this standard to a second set of 20 children with nephrosis and classified nine as volume contracted and 11 as volume expanded (18). The volume expanded group (FENa ≥0.2%) was treated without albumin (intravenous furosemide 1 mg/kg to a maximum of 40 mg twice daily) and oral spironolactone (2.5 mg/kg per d to a maximum 100 mg twice daily). Volume-contracted patients (defined by a FENa <0.2%) were treated with 25% albumin at 0.5 g/kg twice daily over 2 to 3 hours, followed by intravenous furosemide at 1 mg/kg per dose (maximum 40 mg) at the end of albumin infusion for severe edema. All patients received steroids and dietary sodium and fluid restriction. Treatment with diuretics without concurrent albumin infusion was well tolerated, and there was no difference in hospital stay or weight loss between the volume-contracted and volume-expanded groups after treatment. The authors suggested that FENa can successfully identify patients who are safe to treat with diuretics without albumin.

References
Nephrology Self-Assessment Program

Examination Questions

Instructions to obtain 8 AMA PRA Category 1 Credits™

Date of Original Release: March 2011

Examination Available Online: on or before Monday, March 7, 2011
Audio Files Available: On or before Tuesday, March 15, 2011. A notice will be posted on the ASN website when the audio files become available.

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UpToDate Links Active: March and April 2011
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Target Audience: Nephrology Board and recertification candidates, practicing nephrologists, and internists.

Method of Participation:
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MOC points will be applied to only those ABIM candidates who have enrolled in the program. It is your responsibility to complete the ABIM MOC enrollment process.
1. A 50-year-old woman with a history of hypertension and coronary artery disease is treated for esophageal squamous carcinoma with 4 days of 5-fluorouracil followed by a single dose of cisplatin. Five days later, she complains of dizziness. Supine heart rate (HR) is 120 bpm, and systolic BP is 100 mmHg. She refuses to have her orthostatic vital signs recorded because of severe light headedness. Laboratory values are as follows: Serum Na 122 mmol/L, serum osmolality 264 mOsm/kg, blood urea nitrogen (BUN) 42 mg/dl, creatinine 1.0 mg/dl, glucose 90 mg/dl, serum cortisol 26.6 µg/L, urine Na 160 mmol/L, and urine osmolality 504 mOsm/kg. The patient is given 4 L of isotonic saline intravenously.

Which ONE of the following is the expected response to this treatment?

A. It will correct the orthostatic symptoms but not affect the hyponatremia.
B. It will correct the orthostatic symptoms but exacerbate the hyponatremia.
C. It will not correct the orthostatic symptoms or the hyponatremia.
D. It will not correct the orthostatic symptoms, but it will correct the hyponatremia.
E. It will correct the orthostatic symptoms and the hyponatremia.

2. A 24-year-old with insulin-dependent diabetes and a history of cocaine and alcohol abuse, a dilated cardiomyopathy (Ejection Fraction 20%), and ESRD treated with hemodialysis is admitted on a Sunday night with complaints of shortness of breath, abdominal pain, and vomiting after skipping a dialysis treatment and stopping her insulin. She is obtunded, does not respond to questions, and exhibits Kussmaul’s respirations. BP is 200/100 mmHg, HR is 100, respirations are 30, and temperature is 36°C. Oxygen saturation on 4 L/min nasal prong O2 is 90%. Jugular veins are distended to the car- lobes, there are bilateral crackles at the lung bases and a prominent S3 gallop, the liver is distended and tender, the abdomen is slightly distended with hypoactive bowel sounds, and there is I+ pretibial edema. There is a blizzard and there is going to be a substantial delay in assembling the dialysis team. Laboratory data are as follows: Serum Na 108 mmol/L, serum K 7.2 mmol/L, serum Cl 75 mmol/L, serum HCO3 6 mmol/L, BUN 112 mg/dl, creatinine 17 mg/dl, Ca 7 mg/dl, PO4 9 mg/dl, glucose 1800 mg/dl, and plasma osmolality 386 mOsm/kg. Blood pH is 7.10, and Pco2 is 20 mmHg. Electrocardiogram showed peaked T waves with QRS 0.10.

In addition to insulin, which ONE of the following is the BEST initial therapy?

A. 50 ml of 1 M NaHCO3 over 15 minutes, times three; 1 ampule of calcium gluconate; and 30 g of sodium polystyrene sulfonate
B. 1 L of 0.9% saline over 1 hour, 1 ampule of calcium gluconate, and 30 g of sodium polystyrene sulfonate
C. No intravenous fluids, 1 ampule of calcium gluconate, and 30 g of sodium polystyrene sulfonate
D. 1 L of 0.45% over 4 hours
E. No additional therapy other than insulin

3. A 30-year-old man, despondent over a recently diagnosed brain tumor, goes on a drinking binge and consumes several quarts of beer in a short period. He is complaining of a headache and vomiting and is mildly confused. On physical examination, weight is 100 kg, BP is 120/80 mmHg, HR is 100. There is no jugular venous distention, pupils are equal and reactive, ocular fundi are normal, chest is clear, heart has no gallop, there is no edema, and there are no
focal neurologic findings. Laboratory data are as follows: Serum Na 122 mmol/L, serum K 3.2 mmol/L, serum Cl 88 mmol/L, serum HCO₃ 29 mmol/L, BUN 4 mg/dl, creatinine 0.6 mg/dl, glucose 90 mg/dl, osmolality 270 mOsm/kg, aspartate aminotransferase 220, alanine aminotransferase 80, bilirubin 2.2, alkaline phosphatase 120, urine Na 150 mmol/L, and urine osmolality 420 mOsm/kg.

**Which ONE of the following is the BEST initial therapy?**

A. 100 ml of 3% saline over 15 minutes, times three
B. 3% saline at 20 ml/h for 24 hours
C. Fluid restriction
D. Isotonic saline 1 L over 1 hour
E. Conivaptan 20-mg bolus

4. A 63-year-old woman with a history of hypertension treated with losartan/hydrochlorothiazide, 50.0/12.5 mg/d, presents with 5 days of cough, diarrhea, anorexia, and progressive weakness. She denies use of laxatives or herbal supplements.

On physical examination, she is lethargic but awake and oriented with slurred speech. Weight is 60 kg, BP is 138/70 mmHg supine and 120/90 mmHg standing, HR is 88/min supine and 129/min standing, and temperature is 37°C. Oxygen saturation is 99% on room air. Jugular veins are just visible at 30°, lungs are clear, heart has no murmur or gallop, and there is no edema. Neurologic exam shows 3/5 proximal muscle weakness with decreased deep tendon reflexes.

Laboratory values are as follows: Serum Na 100 mmol/L, serum K 1.7 mmol/L, serum Cl <60 mmol/L, serum HCO₃ 37 mmol/L, BUN 10 mg/dl, creatinine 0.6 mg/dl, glucose 125 mg/dl, urine Na 22 mmol/L, urine K 50 mmol/L, and urine osmolality 550 mOsm/kg.

She is treated with 2 L of 0.9% saline and potassium replacement. On the second hospital day, her serum sodium concentration is 118 mmol/L, her serum potassium is 3.0 mmol/L, muscle weakness has improved, and she has no complaints. On the third hospital day, her serum sodium is 123 mmol/L and her serum potassium is 3.3 mmol/L, but she is no longer responding to questions. Physical examination reveals an oxygen saturation of 90%, increased muscle tone in the lower extremities, and bilateral Babinski reflexes. Magnetic resonance imaging of the brain is normal.

**In addition to improving oxygenation, which ONE of the following is the BEST treatment for these findings?**

A. KCl to increase the serum potassium to >4 mmol/L
B. 3% saline to increase the serum sodium to 128 mmol/L
C. KCl to increase the serum potassium to >4 mmol/L and 3% saline to increase the serum sodium to 128 mmol/L
D. 1 g of solumedrol and 3% saline to increase the serum sodium to 128 mmol/L
E. Desmopressin and 5% dextrose in water to lower her serum sodium to 118 mmol/L

5. A 30-year-old who has schizophrenia and has been treated with lithium in the past develops trigeminal neuralgia and is started on carbamazepine. Two days later, she presents with a major motor seizure. On admission, she is comatose with a BP of 200/100 mmHg. Weight is 50 kg. Neurologic examination reveals bilateral Babinski reflexes but no other localizing findings. Laboratory values are as follows: Serum Na 116 mmol/L, serum K 3.4 mmol/L, serum Cl 80 mmol/L, serum HCO₃ 10 mmol/L, BUN 5 mg/dl, creatinine 0.5 mg/dl, glucose 90 mg/dl, urine osmolality 340 mOsm/kg, urine Na 110 mmol/L, and urine K 20 mmol/L.

Computed tomography scan of the head shows diffuse cerebral edema. In the emergency department (ED), she is given 1 L of 0.9% saline and then 300 ml of 3% NaCl over 3 hours. Her serum sodium concentration increases to 122 mmol/L, but over the next 6 hours she puts out 5 L of urine. Repeat urine chemistries obtained during her diuresis show osmolality 360 mOsm/kg, Na 120 mmol/L, and K 10 mmol/L. After desmopressin, urine osmolality increases to 486 mOsm/kg.

**Which ONE of the following is the BEST explanation for her large urine output?**
A. A physiologic water diuresis caused by her hyponatremia
B. Cerebral salt wasting
C. Diabetes insipidus (DI) as a result of brain death
D. Nephrogenic diabetes as a result of previous use of lithium
E. A physiologic solute diuresis caused by volume expansion

6. A 5-year-old boy develops severe thirst, drinking up to twenty 8-oz glasses of water daily, and excessive urination, going to the bathroom every hour and wetting the bed at night. His father, paternal grandfather, and paternal aunt have DI that responds to desmopressin. After a 7-hour dehydration test, the patient’s plasma osmolality is 285 mOsm/kg and urine osmolality is 477 mOsm/kg.

On the basis of these findings, which ONE of the following is the BEST course of action?
A. Tell the parents that the dehydration test is diagnostic of psychogenic polydipsia and recommend a psychiatric evaluation.
B. Recommend magnetic resonance imaging and if it shows that a pituitary bright spot is present, excluding neurogenic DI, then refer the child for a psychiatric evaluation.
C. Tell the parents that the child may have familial DI but that it would be best to postpone therapy because early treatment with desmopressin has been shown to accelerate the loss of vasopressin-secreting neurons in animal models.
D. Begin therapy with desmopressin because the dehydration test is diagnostic of DI.
E. Recommend a DNA sequence analysis of the AVP gene and treat with desmopressin if it confirms the presence of a mutation in the gene encoding neurophysin II.

7. A 75-year-old man with a history of chronic lymphocytic leukemia and stage 3 renal disease treated with an angiotensin-converting enzyme inhibitor is seen in his doctor’s office complaining of fatigue. Outpatient laboratory data show a hematocrit of 26, white blood cell count of 250,000, predominantly mature lymphocytes, potassium 7.2 mmol/L with no other electrolyte abnormalities, and creatinine 2.0 mg/dl. The patient is sent to the ED for further treatment. The electrocardiogram on arrival in the ED shows no abnormalities.

Which ONE of the following should be carried out next?
A. Filter the blood sample in the laboratory to separate the lymphocytes from the plasma.
B. Compare the plasma potassium with the serum potassium.
C. Start emergency treatment for hyperkalemia.
D. Send the specimen to the laboratory through the tube system for a crisis measurement of whole-blood potassium.
E. Repeat the test using a blood sample hand carried to the laboratory and allowed to clot.

8. A mother brings in her 10-year-old daughter for evaluation of polydipsia and polyuria. Her father (the girl’s maternal grandfather) and two nephews have been diagnosed as having DI that does not respond to desmopressin. The girl’s mother and father are completely healthy and have no problems with polyuria or polydipsia. The girl’s urine tests negative for glucose, and a random specific gravity of her urine is 1.010.

Which ONE of the following is the BEST interpretation of these findings?
A. DI in other family members is likely a recessively inherited form of nephrogenic DI (NDI).
B. DI in other family members is likely an X-linked form of NDI.
C. DI in other family members is likely an autosomal dominant form of NDI.
D. DI in other family members is likely an X-linked form of NDI, but the girl cannot be affected because her mother is normal.
E. The girl may be a compound heterozygote for X-linked NDI and the recessively inherited form of NDI.
9. A 6-month-old infant is admitted in a lethargic condition after several days of severe diarrhea. BP is 90/50 mmHg, and HR is 110 bpm. Mucous membranes are dry, and skin turgor is poor. The abdomen is soft with hyperactive bowel sounds. Laboratory data show a serum sodium of 174 mmol/L.

Which ONE of the following treatments should be used in an attempt to avoid neurologic complications?
A. An initial bolus of isotonic saline and correction to a serum sodium of 150 mmol/L in the first 12 hours
B. An initial bolus of isotonic saline followed by gradual correction to a serum sodium of 162 mmol/L in the next 24 hours
C. No initial bolus of isotonic saline and gradual correction to a serum sodium of 150 mmol/L in the first 24 hours
D. No initial bolus of isotonic saline and gradual correction to a serum sodium of 162 mmol/L in the next 24 hours

10. A 50-year-old woman visiting from Sri Lanka is brought in by her daughter with severe nausea, vomiting, and abdominal pain. The daughter found a suicide note and a partially eaten package containing what she believes to be Oleander seeds, a poison commonly used in suicide attempts in Southern Asia. BP is 100/50 mmHg, and HR is 40 bpm. Electrocardiogram shows complete atrioventricular block with a QRS of 0.10; serum potassium is 7 mmol/L, and serum creatinine is 0.6 mg/dl.

Which ONE of the following is the BEST therapeutic approach to this problem?
A. Emergency hemodialysis
B. Calcium gluconate, insulin, and kayexalate
C. Calcium gluconate, insulin, and furosemide
D. Insulin and digoxin-specific Fab antibody
E. Insulin, saline, and fludrocortisone

11. A 50-year-old man sustains multiple injuries from a motor vehicle accident. He develops acute renal failure from rhabdomyolysis and hypernatremia from infusion of 3% saline used to treat increased intracranial pressure. Five days after admission, his intracranial pressure is normal but azotemia has progressed.

Current laboratory data reveal the following:
- Serum Na 165 mmol/L
- Serum K 5.9 mmol/L
- Serum Cl 129 mmol/L
- Serum HCO3 18 mmol/L
- BUN 95 mg/dl
- Creatinine 7 mg/dl
- Glucose 140 mg/dl.

Which ONE of the following is the BEST strategy?
A. Conventional hemodialysis
B. Conventional hemodialysis supplemented with 50 ml of 3% saline every hour during dialysis
C. Venovenous hemofiltration with standard replacement fluid
D. Venovenous hemofiltration with standard replacement fluid supplemented with 50 ml of 3% saline after 6 hours
E. Venovenous hemofiltration with 25 ml of
30% saline or 30 ml of 23% saline added to each 5-L bag of replacement solution

13. An African American man with stage 3 chronic kidney disease (CKD) and recalcitrant hypertension (BP 160/95 mmHg) despite treatment with an angiotensin-converting enzyme inhibitor and a diuretic sees his internist, who recommends additional treatment with spironolactone. His serum potassium is 4.4 mmol/L, and estimated GFR (eGFR) is 47 ml/min.

Which ONE of the following is the MOST likely clinical outcome?
A. BP 125/80 mmHg, K 4.7 mmol/L, eGFR 25 ml/min
B. BP 165/100 mmHg, K 4.7 mmol/L, eGFR 45 ml/min
C. BP 125/80 mmHg, K 4.7 mmol/L, eGFR 45 ml/min
D. BP 125/80 mmHg, K 6.5 mmol/L, eGFR 45 ml/min

14. A 36-year-old woman develops amenorrhea, followed a few months later by progressive anorexia, abdominal pains, and postural dizziness. Physical examination reveals increased skin pigmentation and BP of 100/50 mmHg supine and 80/40 standing.
Laboratory data reveal the following: Serum Na 110 mmol/L, serum K 5.9 mmol/L, serum Cl 75 mmol/L, serum HCO3 19 mmol/L, BUN 39 mg/dl, creatinine 1.8 mg/dl, blood glucose 90 mg/dl, urine osmolality 650 mOsm/kg, urine sodium 60 mmol/L, and urine potassium 24 mmol/L.
She is treated with hydrocortisone and 2 L of isotonic saline. Eight hours later, her urine output increases to 1 L/h.

Which ONE of the following treatments should be instituted at this time?
A. Match urine output with 0.9% NaCl
B. Give fludrocortisone 0.1 mg orally
C. Start 5% dextrose in water at 250 ml/h
D. Increase the dosage of hydrocortisone
E. Give desmopressin

15. A 20-year-old woman has had NDI diagnosed in childhood. She has a history of deep venous thromboembolic and pulmonary embolus. One of her four sisters but no other family members has the disease.
Which ONE of the following is the MOST likely explanation for her increased episodes of venous thrombosis?
A. The patient has an activating mutation of the vasopressin 2 receptor (V2R), which results in increased release of von Willebrand factor from endothelial cells.
B. The patient has an inactivating mutation of the V2R, which results in failure to inhibit release of von Willebrand factor from endothelial cells.
C. The patient has a mutation of aquaporin 2, resulting in its failure to traffic to the endothelial cell membrane, where it normally inhibits release of von Willebrand factor.
D. The patient has a normal V2R and persistently elevated levels of vasopressin, which results in increased release of von Willebrand factor.

16. A 20-year-old woman with paroxysmal nocturnal hemoglobinuria develops severe diuretic-resistant ascites caused by hepatic vein thrombosis. A portosystemic shunt is proposed.
Which ONE of the following would be MOST successful in increasing sodium excretion in the urine?
A. A side-to-side anastomosis.
B. An end-to-side anastomosis.
C. The two shunts would be equally effective.
D. Neither form of shunt would improve sodium excretion.

17. A 50-year-old man with hepatic cirrhosis develops progressive edema and ascites on spironolactone 100 mg/d. The serum potassium is 4.5 mmol/L, and the serum creatinine is 0.6 mg/dl.
A spot urine sample shows a urine Na concentration of 40 mmol/L and a urine creatinine concentration of 100 mg/dl.

Which ONE of the following is the BEST approach?
A. Continue the current dosage of spironolac-
tone and request a dietary consultation to instruct the patient in a low-sodium diet.
B. Increase the dosage of spironolactone to 200 mg/d
C. Order a large-volume paracentesis
D. Start furosemide 40 mg twice daily and continue spironolactone
E. Start furosemide 40 mg twice daily and discontinue spironolactone

18. Milk-alkali syndrome was first described in the early 1900s, when it developed as a result of the treatment regimen used for peptic ulcer disease. Introduction of modern treatments for peptic ulcers led to a marked reduction in the frequency of this disorder. Now milk-alkali syndrome is again being commonly diagnosed. There are several important differences between the syndrome currently encountered and the disorder that was seen in the early 1900s.

Which ONE of the following statements about the modern milk-alkali syndrome is CORRECT?
A. The calcium levels now are lower than in the past.
B. The degree of kidney dysfunction now is worse than in the past.
C. The inorganic phosphorous levels now are lower than in the past.
D. The degree of alkalosis now is worse than in the past.

19. Aminoglycosides can produce a clinical syndrome that mimics which ONE of the following tubule disorders?
A. Gittelman syndrome
B. Liddle syndrome
C. Bartter syndrome
D. Pseudohypoaldosteronism type II
E. Gordon syndrome

20. A 58-year old man with CKD (eGFR 29 ml/min) as a result of hypertension is placed on bicarbonate supplements to reduce his risk for progression of his CKD.

Which ONE of the following effects of bicarbonate administration is MOST likely to explain the beneficial effect?
A. Reduced ammonia synthesis
B. Reduced renal tubular energy expenditure
C. Reduced intrarenal BP
D. Reduced angiotensin formation

21. A 60-year-old man presents to the ED with severe cellulitis of the right arm. He remembers falling down and lacerating his elbow several days before. He has no other history, and he is on no medications. Physical examination reveals marked erythema of the lower half of his right arm. He is febrile to 102°F. BP is 90/70 mmHg, and white blood cell count is 18,000/mm³ with a left shift. A presumptive diagnosis of severe sepsis is made. Chemistries reveal the following: Na 136 mEq/L, K 4.0 mEq/L, Cl 100 mEq/L, HCO₃ 17 mEq/L, and lactate 6 mEq/L. Treatment with antibiotics and aggressive intravenous fluid therapy is begun, and 2 hours later, a repeat lactate level is still 6 mEq/L.

Which ONE of the treatment options is the BEST choice?
A. Administer NaHCO₃
B. Start continuous venovenous hemofiltration
C. Give fomepazole
D. Give insulin and glucose
E. Maintain current therapy

22. You are asked to evaluate a 40-year-old man who was hospitalized after he sustained severe head trauma in a motor vehicle accident. He was admitted to the intensive care unit, intubated, and sedated. He was started on a morphine infusion for pain and a propofol infusion at 2 mg/kg per h for sedation and to help control intracranial hypertension. The propofol dosage was titrated up to 5 mg/kg per h to maintain cerebral perfusion pressure above 70 mmHg. On the fifth day of hospitalization, several new biochemical abnormalities were noted. He had developed an anion gap metabolic acidosis and high triglyceride levels, and creatine phosphokinase was 15,000 IU/ml. At this time, his vital signs were acceptable with a BP of 150/90 mmHg and pulse of 110/min.
Which ONE of the following is the MOST likely acid that is accumulating?
A. L-lactic acid
B. Keto acids (acetoacetic and beta-hydroxyl butyric)
C. D-lactic Acid
D. Glyoxalic acid
E. Pyroglutamic acid (5-oxoproline)

23. A 24-year-old patient with a seizure disorder is treated with topiramate. After 2 weeks, a biochemical profile reveals the following results: Serum Na 141 mmol/L, serum K 3.4 mmol/L, serum Cl 110 mmol/L, and serum HCO₃ 16 mmol/L.

Which ONE of the following is the MOST likely cause of this electrolyte pattern?
A. Distal renal tubular acidosis as a result of a membrane backleak of hydrogen ion
B. A primary defect in renal ammoniagenesis
C. Inhibition of carbonic anhydrase
D. Stimulation of the respiratory center
E. Secondary hyperaldosteronism

24. A 45-year-old man presents with flank pain and hematuria and is found to have a right-sided kidney stone. He has a history of severe migraine headaches managed with triptans. In addition, his physician has prescribed a number of medications for him in the past, including calcium channel blockers and β-adrenergic antagonists, in an attempt to prevent the headaches from occurring so frequently. More recently, topiramate was found to be effective, and the patient has been taking this medication for the past year.

On the basis of this history, the composition of the kidney stone is MOST likely to be which ONE of the following?
A. Calcium phosphate
B. Calcium carbonate
C. Uric acid
D. Calcium oxalate
E. Cysteine

25. A 45-year-old man is admitted to the hospital with an acute asthma attack. After treatment with glucocorticoids and β agonist inhalants, his condition improved so that mechanical ventilation was not necessary. His BP is 150/80 mmHg.

Which ONE of the following sets of arterial blood gases is MOST likely to be obtained for this patient?

Table 1.

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For all questions highlighted in green, access to related UpToDate topic reviews is available on the ASN website (www.asn-online.org). See the CME Information page for instructions.
Core Knowledge Questions

Fluid, Electrolyte, and Acid-Base Disturbances

1. A 65-year-old man presents with the chief complaint of progressive weakness over the past several months. He is normotensive, and his physical examination is unremarkable. Laboratory studies reveal the following: Na 135 mmol/L, Cl 105 mmol/L, K 3.0 mmol/L, HCO₃ 18 mEq/L, creatinine 1.8 mg/dl, BUN 22 mg/dl, glucose 110 mg/dl, PCO₂ 28 Torr, pH 7.33, hematocrit 25%, white blood cell count 5600/mm³, and platelets 340,000/mm³; urinalysis shows trace protein, 1+ glucose, normal sediment, and 24-h urine protein of 4.8 g.

Which ONE of the following is a CHARACTERISTIC of the renal abnormality present in this patient?

A. Evidence of nephrocalcinosis on kidney ureters-bladder x-ray of the abdomen.
B. The serum HCO₃ concentration will increase after the administration of oral bicarbonate at 80 mEq/d but then decrease to 18 mmol/L after the therapy is discontinued.
C. Bicarbonate therapy will cause the serum K to decline slightly as a result of a shift into cells.
D. The urine pH will be persistently alkaline.
E. The urine anion gap will be negative.

2. A 78-year-old Caucasian woman is brought to the emergency department secondary to abdominal pain. During the past 2 months, she has noticed periumbilical pain that is brought on by food ingestion. As a result of worsening pain, the patient began taking acetaminophen 4 g/d for the past week. Medical history is significant for stable two-block claudication and transient ischemic attack.

Physical examination reveals the following: Temperature of 38.1°C, pulse 98 bpm, BP of 158/88 mmHg, left-sided carotid bruit, normoactive bowel sounds, abdominal bruit, and pain to deep palpation in the mid-epigastrium without rebound.

Admission laboratory studies reveal the following: Na 138 mmol/L, K 4.9 mmol/L, Cl 102 mmol/L, HCO₃ 7 mEq/L, creatinine 1.4 mg/dl, BUN 30 mg/dl, glucose 126 mg/dl, serum osmolality 295 mOsm/L. Arterial blood gas shows pH of 7.17, Pco₂ of 18 Torr, and Po₂ of 104 Torr; urinalysis shows pH of 5.5, trace ketones, and negative sediment.

The anion gap acidosis in the presence of vascular disease and history consistent with intestinal angina led to a diagnosis of ischemic bowel. The patient was taken to the operating room for an exploratory laparotomy. No evidence of ischemic bowel was found. A lactate level sent earlier came back at 2.8 mEq/L.

Which ONE of the following is the MOST likely cause of the metabolic acidosis in this patient?

A. Pyroglutamic acidosis resulting from the administration of acetaminophen.
B. α-Lactic acidosis as a result of bacterial overgrowth.
C. Malignant hyperthermia with secondary lactic acidosis.
D. Diabetic ketoacidosis.
E. Salicylate toxicity.

3. A 32-year-old man is brought to the emergency department and is described as combative and agitated. A friend describes the patient as “into alcohol and all kinds of drugs and inhalants” but is unable to specify what specifically he may have taken. On physical examination, the patient is uncooperative and is slightly disoriented. Laboratory studies reveal the following: Na 140 mmol/L, K 3.1 mmol/L, Cl 111 mmol/L, HCO₃ 190.
21 mEq/L. Arterial blood shows pH of 7.5, Pco₂ 21 Torr, Po₂ of 86 Torr, serum ketones present in 1:4 dilution, urine ketones 4+, and urine glucose 1+.

Which ONE of the following is the MOST likely cause of the clinical syndrome?
A. Toluene inhalation.
B. Ethylene glycol intoxication.
C. Diabetic ketoacidosis.
D. Isopropyl alcohol ingestion.
E. Alcoholic ketoacidosis.

4. A 71-year-old woman who has had nocturia for several years is admitted to the hospital secondary to increasing weakness and frequency of urination. She has been well until 2 days ago, when she felt weak and could not climb the stairs to her apartment. She has a history of duodenal ulcer many years ago that responded to intensive antacid therapy. She currently takes calcium carbonate for treatment of osteoarthritis, and she takes bicarbonate of soda for heartburn. She has a 40 pack-year history of smoking.
On physical examination, she is frail and oriented only to person. Pulse is 106/min, and BP is 110/80 supine and 90/70 mmHg sitting. The remainder of the examination is normal.
Laboratory studies reveal the following: Hematocrit 41, Na 152 mmol/L, K 3.0 mmol/L, Cl 100 mmol/L, HCO₃ 39 mEq/L, BUN 98 mg/dl, creatinine 7.1 mg/dl, Ca 14.4 mg/dl, phosphate 6.3 mg/dl, serum 1,25-dihydroxyvitamin D 30 pg/ml (35 to 85 pg/ml), parathyroid hormone 16 pg/ml (30 to 50 pg/ml). Urinalysis shows specific gravity of 1.007, trace protein, Na of 49 mmol/L, creatinine of 70 mg/dl, and urine osmolality of 260 mOsm/kgH₂O. Renal ultrasound shows normal-sized kidneys and no hydronephrosis.

The clinical and laboratory findings are MOST consistent with which ONE of the following?
A. Vitamin D intoxication.
B. Chronic kidney disease as a result of longstanding hypertension.
C. Multiple myeloma.
D. Milk-alkali syndrome.
E. Primary hyperparathyroidism.

5. A 38-year-old woman with a strong family history of cardiovascular diseases and hypertension recently received a diagnosis of essential hypertension. Her BP, on three separate measurements, averages 154/94 mmHg. Current medications include a daily multivitamin and birth control pills. The physical examination and laboratory examination are normal. Because the patient is using birth control pills, her primary care physician was comfortable prescribing lisinopril 10 mg/d. One month later, the patient returns for follow-up. BP is 142/88 mmHg. Laboratory examination shows the following: Na 140 mEq/L, K 5.5 mEq/L, Cl 100 mEq/L, HCO₃ 22 mEq/L, creatinine 0.8 mg/dl, and BUN 10 mg/dl. The physician refers the patient to a nephrologist for hyperkalemia evaluation.

Which ONE of the following is the MOST likely risk factor for hyperkalemia development after prescribing an angiotensin-converting enzyme inhibitor for this patient?
A. High-grade bilateral renal artery stenosis.
B. Pseudohypoaldosteronism type II.
C. Acquired adrenal insufficiency.
D. Mineralocorticoid-blocking activity in birth control pill.
E. Daily ingestion of bananas.
Answers and Explanations

1. Answer: B. The serum HCO₃ concentration will increase after the administration of oral bicarbonate at 80 mEq/d but then decrease to 18 mmol/L after the therapy is discontinued.

The patient presents with hypokalemia and normal gap acidosis, in association with glycosuria in the setting of a normal plasma glucose concentration. These findings suggest the Fanconi syndrome and a type II or proximal renal tubular acidosis (RTA). The large amount of proteinuria but only a trace positive dipstick suggests the excretion of a cationic protein, suggesting that multiple myeloma as the underlying cause. With a proximal RTA, administration of bicarbonate will only transiently increase the serum bicarbonate concentration, and, once discontinued, the plasma concentration will fall to a lower T_max, usually approximately 16 to 18 mEq/L. Choice A is incorrect because distal and not proximal RTA is associated with nephrocalcinosis. An adverse effect of bicarbonate therapy is a worsening of hypokalemia as a result of increased renal K wasting as distal Na delivery is increased. Thus, choice C is incorrect. Choice D is incorrect because the urine will acidify in proximal RTA once the serum bicarbonate falls to the lower T_max after discontinuation of oral bicarbonate therapy. The urine anion gap is not negative in proximal RTA because proximal tubular dysfunction also impairs renal ammoniagenesis, making choice E incorrect.


2. Answer: A. Pyroglutamic acidosis resulting from the administration of acetaminophen

The patient presents with an anion gap metabolic acidosis in association with ingestion of large amounts of acetaminophen. This drug leads to depletion of glutathione, thereby altering the gamma glutamyl cycle in such a way that pyroglutamic acid is overproduced. Choice B is incorrect because the clinical setting does not suggest a bacterial overgrowth syndrome, making D-lactic acidosis unlikely. Choice C is incorrect because neither the clinical setting nor the signs and symptoms in this case suggest the presence of malignant hyperthermia. The absence of ketonuria and the normal serum glucose exclude diabetic ketoacidosis, so choice D is incorrect. Salicylate toxicity often has features of both an anion gap acidosis and respiratory alkalosis with the latter being more prominent in adults. As a result, choice E is incorrect.


3. Answer: D. Isopropyl alcohol ingestion

A patient with a history of substance abuse presents with mild hypokalemia and respiratory alkalosis. The workup is noteworthy for positive serum and urine ketones. This clinical presentation best fits with isopropyl alcohol ingestion, or choice D. Ingestion of this substance leads to acetone production, giving rise to positive ketones. There is no consumption of bicarbonate in the production of acetone, so metabolic acidosis is not a feature of this intoxication. The respiratory alkalosis is likely due to alcohol withdrawal or the underlying agitation. The hypokalemia may be due to a shift of K into cells as a result of the alkalosis. Toluene inhalation, ethylene glycol intoxication, diabetic ketoacidosis, and alcoholic ketoacidosis all are conditions associated with metabolic acidosis, which is not present in this case.

4. **Answer: D. Milk-alkali syndrome**
The patient presents with metabolic alkalosis, acute renal failure, and hypercalcemia. The history describes a patient who likely is taking large quantities of antacids for treatment of dyspepsia. These features strongly suggest a diagnosis of milk-alkali syndrome. The increased frequency of urination may be the result of a renal concentrating defect caused by hypercalcemia. Vitamin D intoxication (choice A) can be a cause of hypercalcemia but is excluded by the low levels of active vitamin D. A patient with chronic kidney disease as a result of hypertension (choice B) would be expected to present with small kidneys. A serum calcium concentration of 14.4 would not be expected in such a patient. Multiple myeloma (choice C) is a consideration but is not the best answer given the clinical features in this case. Anemia and a low anion gap are often present in patients with myeloma. Primary hyperparathyroidism is excluded by the suppressed parathyroid hormone levels, making choice E incorrect.


5. **Answer: D. Mineralocorticoid blocking activity in birth control pill**
The oral contraceptive Yasmin-28 contains the non–testosterone-derived progestin drospirenone, which possesses mineralocorticoid-blocking effects similar to what is seen with spironolactone. The product labeling recommends K⁺ monitoring in the first month after prescribing the drug for patients who are receiving K⁺ supplements, renin-angiotensin blockers, or nonsteroidal anti-inflammatory drugs. Despite this recommendation, there are many instances in which monitoring does not occur or patients are prescribed the contraceptive in the setting of other drugs that either provide a K⁺ load or interfere in renal K⁺ secretion. There is nothing in the clinical history to suggest the disease states provided in choices A, B, and C. The K⁺ load contained in bananas would be unlikely to cause hyperkalemia in the setting of normal renal function, making choice E incorrect.