Fluid/Electrolyte/Acid-Base Abnormalities

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Contents

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Learning Objectives

- Identify the major causes of dehydration.
- Identify specific therapies for dehydration disease processes focusing on rehydration of the dehydrated patient.
- Classify the causes of hypernatremia.
- Differentiate between potential therapies of hypernatremia.
- Describe the pathophysiology, diagnosis, and treatment of patients with diabetes insipidus.
- Classify the causes of hyponatremia.
- Differentiate between potential therapies of hyponatremia.
- Summarize the pathophysiology, diagnosis, and treatment of patients with SIADH.
- Summarize the pathophysiology, diagnosis, and treatment of patients with cerebral salt wasting.
- State the inherited causes of hypocalcemia and their potential treatment.
- State the causes of acquired hypocalcemia.
- Discuss the clinical signs associated with hypocalcemia.
- Discuss the treatment of hypocalcemia including when it is necessary to treat.
- Discuss the normal "handling" of and requirements for potassium in the pediatric patient.
- Recognize that because of the predominantly intracellular location of potassium, serum potassium is not a reliable indicator of total body potassium.
- Discuss the potential clinical effects associated with a low serum potassium.
- Discuss the treatment of a low serum potassium in the PICU patient including when it is necessary to treat.
- Discuss the causes and management of hypokalemia (total body potassium deficiency) in the PICU patient.
- Identify groups of patients who are at risk for hyperkalemia.
- Describe the potential ill effects associated with a high serum potassium.
- State the ECG changes associated with hyperkalemia and describe how to use the ECG to diagnose increased serum potassium.
- Describe the short-term and long-term treatment of hyperkalemia.
- Describe the clinical correlates of high and low serum magnesium.
- Define the treatment of hypomagnesemia.
- Describe the clinical correlates of high and low serum phosphorus.
- Define the treatment of hypo- and hyperphosphatemia.
- Describe the pathophysiologic effects caused by metabolic acidosis.
- Describe the basis for classifying metabolic acidosis by:
  - Acute versus chronic.
  - Presence or absence of abnormally large anion gap.
- Formulate the differential diagnosis for each of the above subgroups.
- Describe the arguments for and against the treatment of metabolic acidosis with bicarbonate for each of the groups described above.
- Summarize the pathophysiologic effects caused by metabolic alkalosis.
- Identify the major causes of acute and chronic metabolic alkalosis.
- Describe the general treatment of metabolic alkalosis including when acute treatment is indicated.

30.1 Volume Depletion (Dehydration)

Volume depletion, commonly referred to as dehydration, occurs whenever water and salt losses exceed intake. If oral intake remains adequate, dehydration is usually avoided. Infants are especially prone to dehydration because they have higher proportional body fluid turnover than older children or adults. If an infant develops anorexia or vomiting, dehydration develops sooner than in the older child because of the higher proportion of obligatory losses. Diarrhea in conjunction with vomiting is the most common cause of dehydration in children. Dehydration can also occur from increased sweating produced by fever; acute infections that decrease oral intake, such as pneumonia or meningitis; or conditions that cause increased renal losses of salt and water such as pyelonephritis or excess diuretic use.

The clinical signs of dehydration are a manifestation of extracellular volume depletion. Signs of extracellular volume depletion in children include an elevation in heart rate, delayed capillary refill, diminished tearing, dry mucous membranes, a sunken fontanel, poor skin turgor, decreased peripheral pulses, cool peripheries, and ultimately a fall in blood pressure when volume depletion is severe. Three factors determine the amount of extracellular volume depletion and therefore the severity of dehydration: (1) the fluid deficit, (2) the electrolyte deficit, and (3) the speed at which dehydration occurs.

The fluid deficit or antecedent deficit is the total amount of body water lost. It is expressed as the percent decrease in body weight and can be estimated based on physical findings (Table 30.1). In general, the larger the fluid deficit, the more severe the degree of dehydration. The clinical signs of dehydration are also affected by the electrolyte deficit, which usually parallels extracellular fluid losses. Therefore, for the same fluid deficit, the severity of clinical signs of extracellular volume depletion is inversely proportional to the serum sodium concentration. Stated differently, given the same volume loss, hyponatremic dehydration is clinically more severe than hypernatremic dehydration. Signs of volume depletion are less pronounced in patients with hypernatremia due to better preservation of the extracellular volume. This is the basis for classifying dehydration according to the serum sodium as hyponatremic, isonatremic, or hypernatremic. The rate at which dehydration occurs also affects the severity of extracellular volume depletion. Initial fluid losses typically come primarily from the intravascular space. Over time, fluid is mobilized from the interstitial and intracellular space to maintain intravascular volume. If fluid depletion of the intravascular space occurs rapidly, this compensatory process is less complete, and signs of intravascular volume depletion predominate. Therefore, dehydration occurring over several days to a week is better tolerated than dehydration occurring over hours or a day.

The most important determinant of serum sodium concentration in the presence of dehydration is the type and volume of fluid intake.

The most common cause of dehydration in children is infectious diarrhea, particularly rotavirus. The diarrheal losses are usually hypotonic to serum; stool [Na and K] is between 80 and 130 mEq/L. The most important factor in determining the type of dehydration is the amount and type of oral intake. In most instances, the amount of free water losses and free water ingested are of similar magnitude, resulting in little change in serum sodium. In infants where water intake may be decreased due to limited access or vomiting, free water losses result in hypernatremic dehydration. In older children who may be able to satisfy their thirst or who are taking very hypotonic oral fluids, free water intake in excess of free water losses results in hyponatremic dehydration.

Table 30.1 Clinical signs of dehydration

	Mild	Moderate	Severe
Weight loss	3–5%	6–9%	>10%
Skin turgor	Normal	Tenting	None
Skin: Touch	Normal	Dry	Clammy
Capillary refill (s)	<2	>2	>2
Mucous membranes	Moist	Dry	Parched
Eyes	Normal	Intermediate	Sunken
Tears	Present	Absent	Absent
Pulse	Full	Decreased	Weak or absent
Heart rate	Regular	Rapid	Rapid
Blood pressure	Normal	Normal–low	Hypotensive shock
Urine output	Decreased	Oliguria	Anuria
Fontanel (if present)	Normal	Sunken	Markedly sunken
Sensorium	Clear	Lethargic	Listless

30.1.1 Treatment

The primary goal of rehydration is to reestablish hemodynamic stability and tissue perfusion. In severe dehydration with hemodynamic compromise, very rapid administration of 20–40 mL/kg of an isotonic solution, such as 0.9% sodium chloride, Plasma-Lyte, lactated Ringer's, or Hartmann's solution, is warranted. Further fluid resuscitation should continue until the child is hemodynamically stable. This requires close serial examination of distal perfusion, measurement of urinary output, and analysis of serum chemistries to guide ongoing fluid replacement. Volume depletion can generally be corrected by administering 40 mL/kg of an isotonic solution over 2–4 h, followed by the remainder of the deficit and ongoing maintenance as 0.9% sodium chloride with appropriate amounts of dextrose and potassium added. Hypotonic fluids such as 0.45% and 0.22% sodium chloride have no role in the initial therapy of a volume-depleted child. Hypotonic fluids may be necessary after the initial phase of fluid therapy if there is hypernatremia, ongoing free water losses from high fever or voluminous diarrhea, or a renal concentrating defect such as congenital nephrogenic diabetes insipidus or renal dysplasia. Hypotonic fluids may also be required in a child with severe hyponatremic dehydration after initial therapy with 0.9% sodium chloride to prevent rapid correction of hyponatremia from a free water diuresis.

30.1.1.1 Isotonic Solution Versus Balanced Solution for Fluid Resuscitation

There has been a growing concern that 0.9% saline has a supraphysiological chloride concentration and may result in untoward complications such as hyperchloremic metabolic acidosis, renal vasoconstriction, delayed micturition, hyperkalemia, an increased incidence of acute kidney injury, and need for renal replacement therapy. The benefit of balanced solutions over isotonic saline seems to be primarily in critically ill adult patients with sepsis and those with preceding acute kidney injury and previous renal replacement therapy. It

Isotonic solutions should be used for parenteral volume expansion in the dehydrated child.

Hypotonic fluids should not be administered rapidly to a dehydrated child. Slow correction of hypernatremia may require the judicious use of hypotonic fluids to correct free water losses.

is unclear if this is applicable to children with volume depletion. Balanced solutions differ from normal saline primarily in having variable amounts of a buffering agent, such as lactate, acetate, or gluconate. Balanced solutions do not have bicarbonate as it is not stable in polyvinyl chloride bags. Balanced solutions also have variable amounts of potassium, calcium, and magnesium and have a lower sodium concentration and osmolarity in comparison to normal saline (Table 30.2). A 0.9% saline solution (Na 154 mmol/L) has a higher sodium concentration than plasma but results in normal osmolarity, whereas Plasma-Lyte (Na 140 mmol/L) and lactated Ringer's (Na 130 mmol/L) are slightly hypotonic in relationship to plasma. Lactated Ringer's in particular may aggravate hyponatremia and should be avoided in hyponatremic patients or those at high risk for cerebral edema.

30.2 Hypernatremia

Hypernatremia is defined as a serum sodium >145 mEq/L. Hypernatremia occurs in children and adults often in the presence of restricted access to water for a variety of reasons. In most instances, these patients either are debilitated by an acute or chronic illness or neurologic impairment or are at the extremes of age. Hypernatremia is also not uncommon in children in the intensive care unit. Contributing factors for hypernatremia in the intensive care setting are excess sodium administration, renal concentrating defects, gastrointestinal fluid losses, increased insensible water losses, restricted access to oral fluids, and dialysis-related complications. Excess administration of sodium can occur via hypertonic solutions, blood products, and sodium bicarbonate administration. Increased insensible water losses occur with fever, tachypnea, and burns. Hypernatremia can result from intentional salt poisoning, in particular in children with gastrostomy tubes. A serum sodium greater than 145 mEq/L should always be considered abnormal and evaluated thoroughly in order to prevent the development of significant hypernatremia.

30.2.1 Pathogenesis

The body has two defenses to protect against developing hypernatremia: the ability to produce concentrated urine by reabsorbing filtered water and a powerful thirst mechanism. Antidiuretic hormone (ADH) release occurs when the plasma osmolality exceeds 275–280 mOsm/kg and results in a maximally concentrated urine when the plasma osmolality exceeds 290–295 mOsm/kg. Thirst is the body's second line of defense but provides the ultimate protection against hypernatremia. If the thirst mechanism is intact and there is unrestricted access to free water, it is rare for someone to develop sustained hypernatremia from either excess sodium ingestion or a renal-concentrating defect.

30.2.2 Diagnosis

Less than maximally concentrated urine (<800 mOsm/kg) in a hypernatremic patient signifies a renal concentrating defect.

The cause of hypernatremia is usually multifactorial and a systematic approach is required to determine the underlying etiology (Fig. 30.1). Serum sodium, glucose, and osmolality must be simultaneously evaluated. Elevated serum sodium is always associated with hyperosmolality and should be considered abnormal. In association with significant hyperglycemia, the serum sodium concentration is depressed due to the associated translocation of fluids from the

Table 30.2 Composition of commonly used resuscitation fluids

Fluid	Sodium mEq/L	Chloride mEq/L	Potassium mEq/L	Calcium mEq/L	Magnesium mEq/L	Buffer mEq/L	Osmolarity mOsm/L	Osmolality mOsm/kg[a]
Human plasma	135–144	95–105	3.5–5.3	4.4–5.2	1.6–2.4	23–30 bicarbonate	308	287[b]
Normal saline								
0.9% NaCl	154	154	0	0	0	0	308	287
Balanced solutions								
Hartmann's	131	111	5	4	0	29 lactate	278	256
Lactated Ringer's	130	109	4	3	0	28 lactate	273	254
Plasma-Lyte	140	98	5	0	3	27 acetate and 23 gluconate	294	273

[a]Calculated osmolality = (0.93 X osmolarity)
[b]The range of osmolality for plasma is 275–295 mOsm/kg

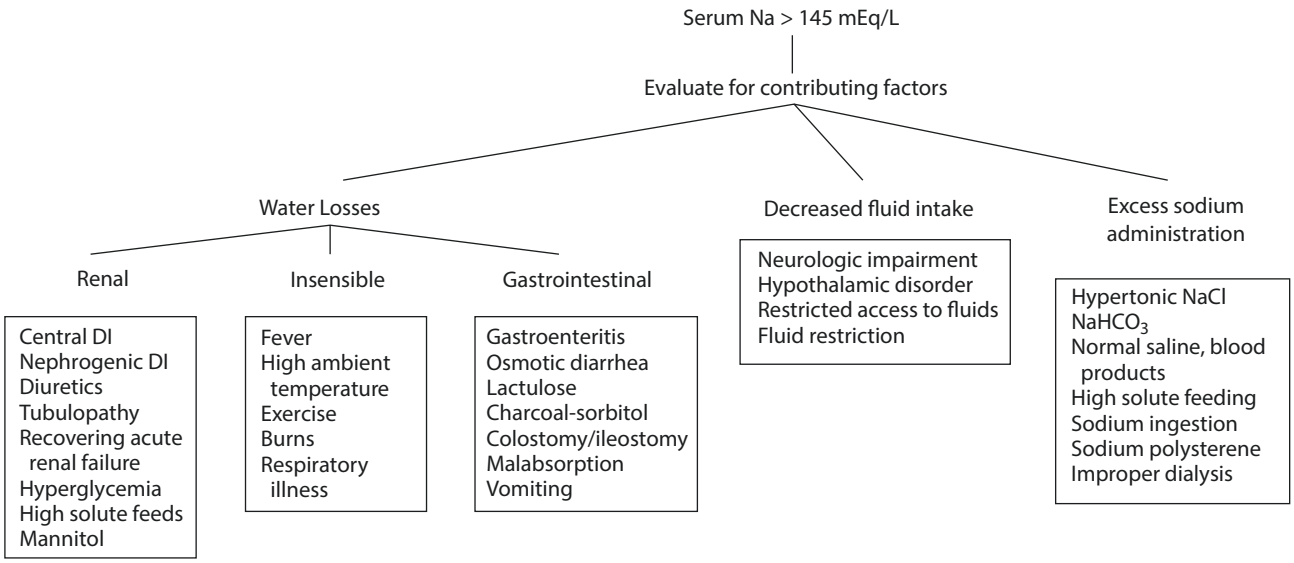

Fig. 30.1 Diagnostic approach to hypernatremia

intracellular to extracellular space, and therefore, true hypernatremia will be masked. Once the diagnosis of hypernatremia is established, a detailed history and review of fluid intake should be obtained to determine if the patient has an intact thirst mechanism, had restricted access to fluids, or was not provided adequate free water in intravenous fluids. The following should be evaluated: gastrointestinal losses, urinary output, dermal losses from fever or burns, diet history (including tube feedings), medication history (including diuretics), and sources of exogenous sodium. Urine volume should be measured and compared to fluid intake. The urine osmolality and electrolytes should be determined to assess if the renal concentrating ability is appropriate and to quantify the urinary free water losses. Less than maximally concentrated urine (<800 mOsm/kg) in the face of hypernatremia associated with signs of dehydration is a sign of a renal concentrating defect as hypernatremia is a maximal stimulus for ADH release. A useful test for distinguishing central from nephrogenic diabetes insipidus is plasma copeptin testing. Copeptin, the C-terminal segment of the pre-pro-hormone for arginine vasopressin, can be used as a surrogate marker of ADH as it is easier and more reliable to measure than ADH. Salt poisoning should be considered in cases of severe and unexplained hypernatremia. A gastric or stool sodium concentration higher than plasma sodium is virtually diagnostic of salt poisoning. Pseudohypernatremia has been reported to occur with vecuronium and esmolol due to interference with ion-selective electrodes.

30.2.3 Clinical Manifestations of Hypernatremia

Hypernatremia results in an efflux of fluid from the intracellular space to the extracellular space to maintain osmotic equilibrium. This leads to transient cerebral dehydration with cell shrinkage. Brain cell volume can acutely decrease by as much as 10–15% but then quickly adapts. In response to extracellular hyperosmolarity, within 1 hour, brain cells significantly increase their intracellular content of sodium and potassium, amino acids, and unmeasured organic substances called idiogenic osmoles. Within 1 week, brain cells regain approximately 98% of their water content. If severe hypernatremia develops acutely, the brain may not be able to increase its intracellular solute sufficiently to pre-

serve its volume, and the resulting cellular shrinkage can cause structural changes. Cerebral dehydration from hypernatremia can result in functional changes and a physical separation of the brain from the meninges leading to a rupture of the delicate bridging veins and extra-axial or intracerebral hemorrhages. Venous sinus thrombosis leading to infarction can also develop. Acute hypernatremia has also been shown to cause cerebral demyelinating lesions in both animals and humans. Patients with hepatic encephalopathy are at the highest risk for developing demyelinating lesions, especially if hypernatremia is a result of rapid overcorrection of preexisting hyponatremia.

Children with hypernatremia are usually agitated and irritable but can progress to lethargy, listlessness, and coma. On neurologic examination, they frequently have increased tone, nuchal rigidity, and brisk reflexes. Myoclonus, asterixis, and chorea can be present; tonic-clonic and absence seizures have been described. Hyperglycemia is a particularly common consequence of hypernatremia in children. Severe hypernatremia can also result in rhabdomyolysis. While earlier publications reported that hypocalcemia was associated with hypernatremia, this was not observed in more recent literature. The degree of central nervous system depression appears to correlate with the severity of hypernatremia.

Patients with hepatic encephalopathy are at highest risk for developing cerebral demyelination from iatrogenic hypernatremia due to rapid overcorrection of preexisting hyponatremia.

30.2.4 Treatment

The cornerstone of hypernatremia management is providing adequate free water to correct the serum sodium concentration but doing this at a rate that limits the risk of brain injury. Hypernatremia is frequently accompanied by volume depletion; if hemodynamic instability is present, fluid resuscitation with an isotonic solution should be instituted to establish more normal hemodynamics prior to slowly correcting the free water deficit. Following initial volume expansion, the composition of parenteral fluid therapy largely depends on the etiology of the hypernatremia. Patients with sodium overload or a renal concentrating defect require a more hypotonic fluid than patients with volume depletion and intact renal concentrating ability. Oral hydration should be instituted as soon as it can be safely tolerated. Plasma electrolytes should be checked frequently until adequate correction is achieved.

A simple way of estimating the minimum amount of fluid necessary to correct the serum sodium is by the following equation:

$$\text{Free water deficit}(\text{mL}) = 4\text{mL} \times \text{lean body wt}(\text{kg}) \times [\text{Desired change in serum Na in mEq/L}]$$

Larger amounts of fluid are required depending on the fluid composition. To correct a 3 L free water deficit, approximately 4 L of 0.2% sodium chloride in water or 6 L of 0.45% sodium chloride in water would be required as they contain approximately 75% and 50% free water, respectively. The calculated deficit does not account for insensible losses or ongoing urinary or gastrointestinal losses. Maintenance fluids, which include replacement of urine volume with hypotonic fluids, are given in addition to the deficit replacement. Glucose containing replacement fluids should be limited as they can result in significant hyperglycemia.

The rate of correction of hypernatremia is largely dependent on the severity of the hypernatremia and the etiology. Due to the brain's relative inability to extrude unmeasured organic substances (idiogenic osmoles), rapid correction of hypernatremia can lead to cerebral edema. While there are no definitive

studies that document the optimal rate of correction without developing cerebral edema, empirical data have shown that unless symptoms of hypernatremic encephalopathy are present, a rate of correction not exceeding 1 mEq/h or 15 mEq/24 h is reasonable. In severe hypernatremia (>170 mEq/L), serum sodium should not be corrected to below 150 mEq/L in the first 48–72 h. If the patient is at high risk for developing cerebral edema, such as with head trauma or encephalitis, the rate of correction of hypernatremia should be slower.

Seizures occurring during the correction of hypernatremia are not uncommon in children and may be a sign of cerebral edema. Hypotonic fluid infusion should be ceased, and hypertonic saline should be administered when cerebral edema is suspected during the correction of hypernatremia. The presence of signs of intracranial hypertension, such as headache, hypertension, bradycardia, abnormal respiratory pattern, and coma, warrants rapid treatment including securing the airway, osmolar therapy, and hyperventilation if herniation seems imminent. In symptomatic children, assessment of progressive cerebral edema by computed tomography of the head is indicated. Seizures not associated with concomitant cerebral swelling are usually self-limited and not a sign of long-term neurological sequelae.

Certain forms of therapy for hypernatremia require special mention.

In the setting of hemodynamic compromise, fluid resuscitation with 0.9% sodium chloride should precede the correction of the free water deficit in hypernatremic dehydration.

30.2.5 Central Diabetes Insipidus

Patients with central diabetes insipidus typically have a high urine output with hypotonic urine compared with the serum osmolality and a greater than 50% increase in urine osmolality in response to the first dose of dDAVP.

Central diabetes insipidus (CDI) is an important cause of hypernatremia in the intensive care setting that must be recognized early as it requires specific therapy. CDI results from inadequate arginine vasopressin (AVP) secretion. CDI in the intensive care setting typically presents with abrupt polyuria and free water diuresis. Severe hypernatremia can develop in an individual who has restricted access to fluids and is receiving sodium-containing parenteral fluids. Common causes of CDI in the intensive care setting include traumatic brain injury, brain tumors, pituitary surgery (e.g., postoperative craniopharyngioma resection), central nervous system infections, and cerebral hemorrhages or infarcts. CDI occurs most commonly in the setting of brain death. Because patients with CDI conserve sodium appropriately, they typically do not manifest signs of volume depletion unless the diagnosis is delayed. Polyuria and a urine osmolality that is not maximally concentrated in the presence of hypernatremia suggest a renal concentrating defect. In CDI, the urine osmolality is typically much less than the plasma osmolality. The treatment of CDI includes the correction of free water deficit and the administration of the AVP synthetic analog, desmopressin acetate (dDAVP). Desmopressin can be administered subcutaneously, intranasally, or intravenously. In critically ill patients, edema and peripheral vasoconstriction may preclude effective subcutaneous administration; therefore, intravenous administration of dDAVP or vasopressin may be required. In CDI, there will typically be a greater than 50% increase in urine osmolality in response to dDAVP concomitant with a reduction in urinary output.

30.2.6 Hypernatremia in the Edematous Patient

While hypernatremia is usually associated with volume depletion, some patients in the intensive care setting may have hypernatremia with edema. This typically occurs in patients with either multisystem organ failure or acute renal insufficiency. These patients initially present with a normal serum sodium and become increasingly edematous following the administration of large amounts of volume in the form of saline, colloid, or blood products to restore circula-

tory volume. Iatrogenic hypernatremia then develops if the patient has either urinary or gastrointestinal free water losses in combination with fluid restriction and ongoing saline administration. The free water diuresis is usually due to loop diuretics, renal insufficiency, an osmotic diuresis, or tubular dysfunction from medications. This clinical scenario must be recognized early as the hypernatremia can be prevented if sodium is removed from all continuous infusions. If the patient is receiving multiple medications in IV fluid, the type of fluid used may need to be changed to a low or no sodium formulation, such as D_5W. It may not be possible to correct hypernatremia in the edematous patient with free water alone if there is severe renal insufficiency or marked fluid overload leading to congestive heart failure or pulmonary congestion. In this situation, renal replacement therapy may be required to correct both fluid overload and hypernatremia.

30.3 Hyponatremia

30.3.1 Pathogenesis

Hyponatremia usually signifies impaired free water excretion due to excess AVP production.

Hyponatremia typically develops when a relative excess of free water is accompanied by an underlying condition that impairs the kidney's ability to excrete free water.

There are hemodynamic and non-hemodynamic stimuli for AVP production that place the ICU patient at risk for hyponatremia.

Hyponatremia is defined as a serum sodium <135 mEq/L. The body's primary defense against developing hyponatremia is the kidney's ability to generate dilute urine and excrete free water. Excess ingestion of free water alone is rarely the cause of hyponatremia. However, infants are at increased risk for hyponatremia due to water intoxication as a result of inappropriate administration of free water or overly dilute formula preparation. It is also rare to develop hyponatremia from excess urinary sodium losses in the absence of free water ingestion except for children with cerebral salt wasting, as described later. In order for hyponatremia to develop, it typically requires a relative excess of free water in conjunction with an underlying condition that impairs the kidney's ability to excrete free water (► Box 30.1). Thus, there is a component of impaired water excretion in hyponatremic states. Renal water handling is primarily under the control of AVP, which is produced in the hypothalamus and released from the posterior pituitary. AVP inhibits water diuresis by increasing the permeability to water in the collecting tubule. There are osmotic, hemodynamic, and non-hemodynamic stimuli for AVP release. In most cases of hyponatremia, there is a stimulus for vasopressin production that results in impaired free water excre-

Box 30.1 Disorders with Impaired Renal Water Excretion

1. Effective circulating volume depletion.
   (a) Gastrointestinal losses: Vomiting, diarrhea.
   (b) Skin losses: Cystic fibrosis.
   (c) Renal losses: Salt wasting nephropathy, diuretics, cerebral salt wasting, hypoaldosteronism.
   (d) Edematous states: Heart failure, cirrhosis, nephrosis, hypoalbuminemia.
2. Thiazide diuretics.
3. Renal failure.
   (a) Acute.
   (b) Chronic.
4. Non-hypovolemic states of ADH excess.
   (a) SIADH.
   (b) Cortisol deficiency.
   (c) Hypothyroidism.

Table 30.3 Common causes of SIADH

Central nervous system disorders	Carcinomas
Infection: Meningitis, encephalitis	Bronchogenic carcinomas
Neoplasms	Oat cell of the lung
Vascular abnormalities	Duodenum
Psychosis	Pancreas
Hydrocephalus	Neuroblastoma
Postpituitary surgery	
Head trauma	
Pulmonary disorders	**Medications**
Pneumonia	Vincristine
Tuberculosis	Intravenous Cytoxan
Asthma	Carbamazepine
Positive pressure ventilation	Oxcarbazepine
Pneumothorax	Serotonin reuptake inhibitors

tion. It is important to recognize that the body will attempt to preserve extracellular volume at the expense of the serum sodium; therefore, a hemodynamic stimulus for AVP production overrides the inhibitory effect of hyponatremia. There are numerous stimuli for AVP production (Table 30.3) that make many hospitalized children at risk for hyponatremia due to the syndrome of inappropriate ADH (SIADH).

30.3.2 Diagnosis

Hyperglycemia causes a hyperosmolar hyponatremia due to a translocation of water from the intracellular to the extracellular space. The serum sodium falls by 1.6 mEq/L for every 100 mg/dL rise in blood glucose concentration above normal.

Before embarking on an aggressive therapeutic regimen, it is vital to confirm that hyponatremia is in fact associated with hypoosmolality. Hyponatremia can be associated with either a normal or an elevated serum osmolality (Fig. 30.2). The most common reasons for the latter are hyperglycemia, severe hyperproteinemia, or hyperlipidemia. Hyperglycemia results in hyperosmolality with a translocation of fluid from the intracellular space to the extracellular space, resulting in a 1.6 mEq/L fall in the serum sodium for every 100 mg/dL elevation in the serum glucose concentration above normal. Severe hyperlipidemia, hypercholesterolemia, hyperproteinemia, or radiocontrast and intravenous immunoglobulin infusions can displace plasma water, resulting in a decreased sodium concentration (pseudohyponatremia) with a normal serum osmolality. Serum sodium is currently measured by either direct or indirect-reading ion-selective electrode potentiometry. The direct method will not result in a diagnosis of pseudohyponatremia as it measures the activity of sodium in the aqueous phase of serum only. Conversely, the indirect method can result in pseudohyponatremia as the specimen is diluted with a reagent prior to measurement. The indirect method is currently performed in approximately 60% of chemistry labs in the United States; therefore, clinicians need to be aware of pseudohyponatremia. If hyponatremia is associated with hypoos-

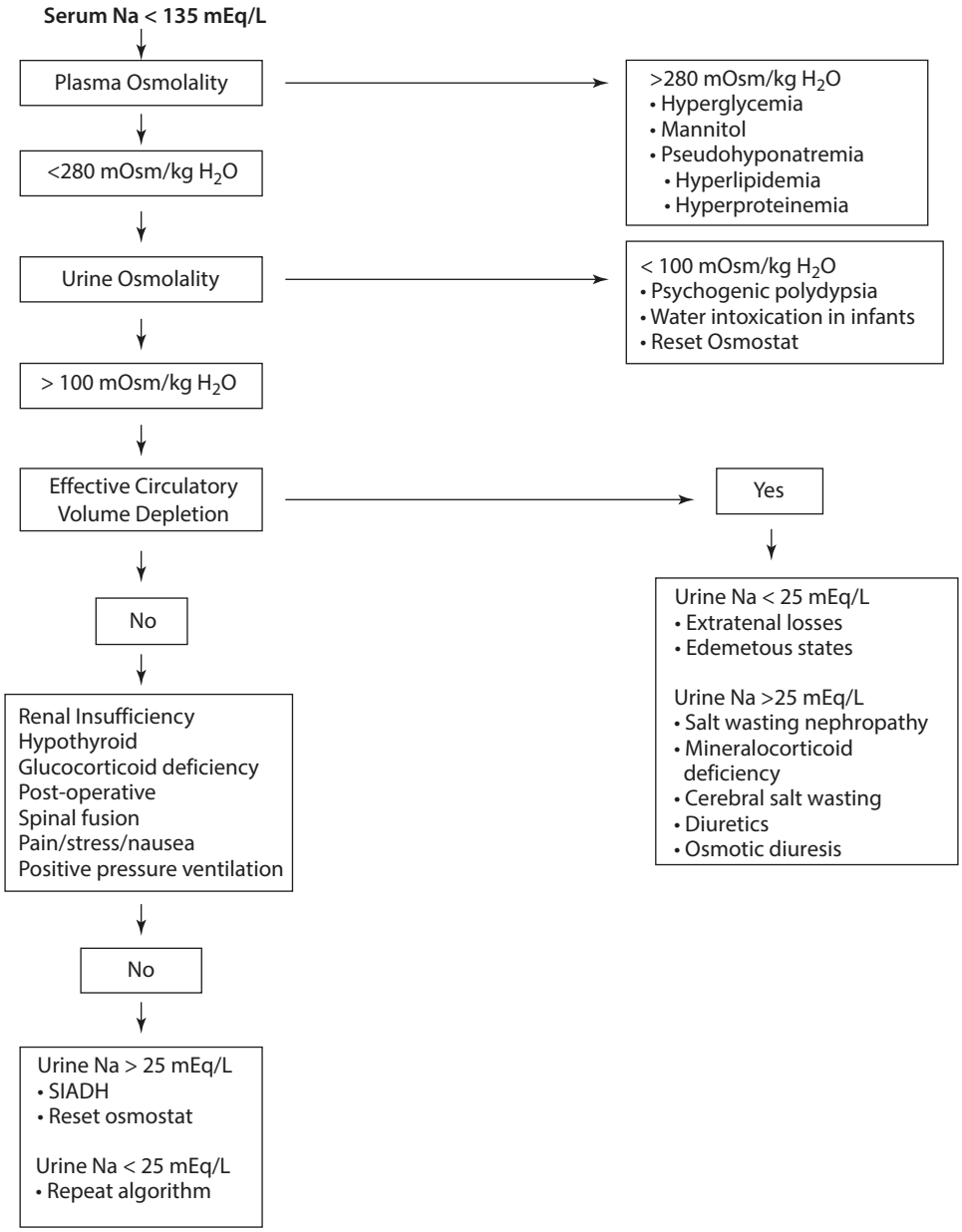

Fig. 30.2 Diagnostic approach to hyponatremia

molality (true hyponatremia), the next step is to measure the urinary osmolality to determine if there is an impaired ability to excrete free water ($Urine_{Osm}$ > 100 mOsm/kg).

The information that is most useful in arriving at a correct diagnosis of hyponatremia is a detailed history of fluid balance, weight changes, medications (especially diuretics), and underlying medical illnesses. Hyponatremia is usually a multifactorial disorder, and a detailed history helps identify sources of salt and water losses, free water ingestion, and underlying illnesses that cause a nonosmotic stimulus for vasopressin production. An assessment of the volume status on physical examination and measuring the urinary electrolytes and osmolality can be extremely helpful, but both can be misleading. In patients in whom hyponatremia is due to salt losses, such as diuretics, signs of volume depletion may be absent on physical examination as the volume defi-

cit may be nearly corrected due to oral intake of hypotonic fluids if the thirst mechanism is intact or in NPO children receiving hypotonic IV fluids.

In general, a urinary sodium concentration less than 25 mEq/L is consistent with effective circulating volume depletion, while a urine sodium greater than 25 mEq/L is consistent with renal tubular dysfunction, use of diuretics, or the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Numerous factors can affect the urine sodium concentration, making interpretation difficult; therefore, the timing of the urinary measurements in relation to dosages of diuretics, intravenous fluid boluses, or fluid and sodium restriction are also important. In some cases, estimation of intravascular volume status by the measurement of a central venous pressure may be helpful.

Before SIADH can be diagnosed, diseases causing decreased effective circulating volume, renal impairment, adrenal insufficiency, and hypothyroidism must be excluded. Cortisol deficiency in particular should be ruled out as it can be clinically indistinguishable from SIADH and can manifest in times of stress. Glucocorticoid hormones exert an inhibitory effect on AVP synthesis, which is why patients with glucocorticoid deficiency have markedly elevated AVP serum concentrations that are rapidly reversed by physiologic hydrocortisone replacement. A serum cortisol concentration in the normal range does not rule out adrenal insufficiency as the cause of hyponatremia as the appropriate adrenal response to hyponatremia would be to increase cortisol production. An adrenocorticotropic hormone (ACTH) stimulation test should be considered if the cortisol serum concentration is not appropriately elevated in the setting of hyponatremia. Hypothyroidism can also resemble SIADH in infants.

30.3.3 Hospital-Acquired Hyponatremia and its Prevention

Hospital-acquired hyponatremia is of concern in children as the standard of care in pediatrics had been to administer hypotonic maintenance fluids containing 0.2–0.45% sodium chloride. The safety of this approach had never been established. Hospitalized children have numerous nonosmotic stimuli for increased vasopressin production that place them at risk for developing hyponatremia. Critically ill children are at higher risk as most have multiple nonosmotic stimuli for AVP secretion (e.g., pulmonary disorders, mechanical ventilation, intracranial injury). There are over 50 reported cases in the past 10 years of neurologic morbidity and mortality resulting from hospital-acquired hyponatremia in children receiving hypotonic parenteral fluids. Over half of these cases occurred in the postoperative setting in previously healthy children undergoing minor elective surgeries. Hyponatremia is especially dangerous in children with underlying CNS injury such as encephalitis, wherein even mild hyponatremia (sodium >130 mEq/L) may result in cerebral edema and even herniation. In 2018, the American Academy of Pediatrics issued a Clinical Practice Guideline on maintenance intravenous fluids stating that the most important measure to prevent hyponatremia is to avoid using hypotonic fluids in children who have clear risks for nonosmotic AVP secretion and to initially administer isotonic saline (0.9% sodium chloride) unless otherwise clinically indicated. These recommendations were based on over 20 prospective trials in almost 3000 patients demonstrating that isotonic fluids decrease the incidence of hyponatremia three- to sixfold in comparison with hypotonic fluids. The serum sodium should be followed in any patient receiving continuous parenteral fluid and adjustments to the composition of intravenous fluids made accordingly.

Clinical indications to not use 0.9% sodium are primarily in disease states associated with increased free water losses, such as renal concentrating defects, voluminous diarrhea, or severe burns. Furthermore, children with neurosurgical disorders, significant congenital or acquired heart disease, hepatic or renal dysfunction, fluid overload, or edema, children undergoing or who recently received chemotherapy, or children <28 days old or in the NICU may require a different maintenance fluid composition and infusion rate.

The most important factor resulting in hospital-acquired hyponatremia is the administration of hypotonic fluids to patients with compromised ability to excrete free water.

30.3.4 Hyponatremic Encephalopathy

30.3.4.1 Clinical Symptoms

A major consequence of hyponatremia is the influx of water into the intracellular space resulting in cellular swelling, leading to cerebral edema and encephalopathy. The symptoms of hyponatremic encephalopathy can be quite variable, with the only consistent symptoms being headache, nausea, vomiting, emesis, and weakness. As cerebral edema worsens, patients develop behavioral changes, with impaired response to verbal and tactile stimuli. Advanced symptoms are consequences of cerebral herniation, with seizures, respiratory arrest, dilated pupils, and decorticate posturing. Not all patients have the usual progression of symptoms such that advanced symptoms can present with sudden onset.

Headache, nausea, and vomiting are the most consistent symptoms of hyponatremic encephalopathy.

30.3.4.2 Risk Factors for Developing Hyponatremic Encephalopathy

Age

Children under 16 years of age are at increased risk for developing hyponatremic encephalopathy due to their relatively larger brain to intracranial volume ratio as compared to adults. A child's brain reaches adult size by 6 years of age, whereas the skull does not reach adult size until 16 years of age. Consequently, children have less room available in their rigid skulls for brain expansion and are likely to develop brain herniation from hyponatremia at higher serum sodium concentrations than adults. Immediate initiation of appropriate therapy is crucial to prevent significant morbidity.

Children develop hyponatremic encephalopathy at higher serum sodium concentrations than adults as a result of the child's large brain to intracranial volume ratio.

Hypoxia

Hypoxemia is a significant contributor to the development of hyponatremic encephalopathy and long-term neurological sequelae. The combination of systemic hypoxemia and hyponatremia is more deleterious than is either factor alone because hypoxemia impairs the ability of the brain to adapt to hyponatremia. Hyponatremia alone leads to a decrement of cerebral blood flow. Additionally, patients with symptomatic hyponatremia can develop hypoxemia by at least two different mechanisms resulting from cerebral edema: neurogenic pulmonary edema and hypercapnic respiratory failure secondary to obtundation/coma. Respiratory failure can occur suddenly; severe neurologic morbidity is seen in patients with hyponatremia who suffered a respiratory arrest as a feature of their hyponatremic encephalopathy.

Syndrome of Inappropriate Antidiuretic Hormone Production (SIADH)

SIADH is one of the most common causes of hyponatremia in the hospital setting and frequently leads to severe hyponatremia (plasma Na <120 mEq/L). It is caused by elevated ADH secretion in the absence of an osmotic or hypovolemic stimulus. SIADH can occur due to a variety of illnesses but most often occurs due to central nervous system disorders, pulmonary disorders, and

medications (Table 30.3). Among the latter, the chemotherapeutic drugs vincristine and Cytoxan and the antiepileptic drug, carbamazepine, are especially common causes. SIADH is essentially a diagnosis of exclusion (Fig. 30.2). Before SIADH can be diagnosed, diseases causing decreased effective circulating volume, renal impairment, adrenal insufficiency, and hypothyroidism must be excluded. The hallmarks of SIADH are mild volume expansion with low to normal plasma concentrations of creatinine, urea, uric acid, and potassium; impaired free water excretion with normal sodium excretion which reflects sodium intake; and hyponatremia that is relatively unresponsive to sodium administration in the absence of fluid restriction. The biochemical parameters most suggestive of SIADH in adults are a spot urine sodium concentration > 30 mEq/L, a fractional excretion of sodium >0.5%, fractional excretion of urea >55%, fractional excretion of urate (FEUrate) >11%, and plasma uric acid <4 mg/dl. The specificity and sensitivity of these biomarkers have not been evaluated in children.

SIADH is usually of short duration and resolves with treatment of the underlying disorder and discontinuation of the offending medication. Fluid restriction is the cornerstone therapy of SIADH. However, fluid restriction results in slow correction of hyponatremia and is frequently impractical in infants who receive most of their nutrition as liquids. Intravenous fluids should be of tonicity greater than or equal to normal saline. Should this not be sufficient to correct the plasma sodium, 3% sodium chloride may be given as needed. If a more rapid correction of hyponatremia is needed, the addition of a loop diuretic in combination with hypertonic saline is useful.

For children with chronic asymptomatic hyponatremia from SIADH that does not respond to fluid restriction, the next step is to increase the oral sodium intake or give oral urea in order to increase the renal solute load, thereby inducing an osmotic diuresis. Oral urea has been successful in treating chronic hyponatremia in both children and adults who did not respond to conservative measures. A once-daily dose of 15–30 g of urea in an adult appears to be effective and well tolerated. A commercially available lemon-flavored urea powder drink (Ure-Na by Nephcentric LLC) is now available in the United States.

SIADH occurs when normal extracellular volume is maintained at the expense of serum sodium.

Vasopressin-2 antagonists (vaptans) represent a relatively new class of medication for the management of SIADH. These agents selectively antagonize the antidiuretic effect of AVP and result in a urinary free water diuresis (aquaresis) without increasing loss of electrolytes. Vaptans produce an aquaresis within 1–2 h of administration which abates within 12–24 h. When used to treat hyponatremia, vaptans result in an approximately 5–7 mEq/L increase in serum sodium within the first 24 h of administration, but the effect is highly variable. The most common side effects of vaptans are increased thirst, polyuria, and dry mouth. There are currently two vaptans that are FDA approved in the United States: tolvaptan, which is available in an oral formulation, and conivaptan, which is available in an intravenous preparation. There are safety concerns with vaptans as they have been associated with alanine aminotransferase elevation and severe hepatotoxicity with long-term use, and serious overcorrection of hyponatremia has been reported. Overcorrection is of particular concern in neurologically impaired or critically ill children with restricted access to water. These agents are inhibitors of cytochrome P450 and should not be used in conjunction with other drugs known to be metabolized by this pathway. At the present time, vaptans cannot be recommended as a first-line agent in the management of SIADH as they are expensive, are not always necessary, and present safety concerns. Vaptans do appear to be a suitable second-line agent for short-term use in patients with SIAD after conservative measures have failed.

Cerebral Salt Wasting (Also See ▶ Chap. 43)

In the setting of CNS injury or following a neurosurgical procedure, hyponatremia is usually attributed to SIADH, a condition whose hallmark is euvolemia to mild hypervolemia, with the cornerstone of management being fluid restriction. More recently, it has become apparent that an increasing number of neurosurgical patients with hyponatremia have a distinct clinical entity called cerebral salt wasting (CSW), a condition whose hallmark is renal sodium loss leading to extracellular volume depletion. The cornerstone of management is volume expansion and salt supplementation. Because these two diseases have many clinical similarities, it can be difficult to confirm a diagnosis of CSW, but it is essential to distinguish between these two conditions as their management is completely different, and fluid restriction would be harmful in the presence of CSW.

The pathogenesis of CSW is not completely understood, but it appears to be due to the release of natriuretic peptides, such as atrial natriuretic peptide, brain natriuretic peptide, and C-type natriuretic peptide. These peptides cause a natriuresis via a complex mechanism of (1) hemodynamic effects leading to an increased GFR, (2) inhibition of the renin-angiotensin system, and (3) inhibition of the secretion and action of AVP. This complex mechanism can lead to laboratory values that are indistinguishable from SIADH with a low uric acid, plasma renin, aldosterone, and vasopressin levels despite volume depletion. The key distinguishing feature between CSW and SIADH is extracellular volume depletion. Careful documentation of trends in urinary output and central venous pressure is particularly useful. An algorithm using changes in the fraction excretion of urate (FEUrate) has recently been validated for distinguishing SIADH from CSW. While both SIADH and CSW are associated with hypouricemia and an elevated FEUrate of >11%, the FEUrate normalized following the correction of hyponatremia in SIADH, whereas the FEUrate remains persistently elevated following the correction of serum sodium in CSW.

From a practical standpoint, the administration of normal saline should be an adequate prophylaxis against developing clinically significant hyponatremia, <130 mEq/L, in SIADH. If clinically significant hyponatremia develops in a patient with a CNS disorder receiving only normal saline, then the diagnosis of CSW should be strongly considered. If there are no signs of extracellular volume depletion, then a brief period of fluid restriction can be tried. If there are signs of volume depletion or a lack of response to fluid restriction with a further fall in the serum sodium concentration, then the patient should be managed as CSW. Patients with CSW should be volume expanded with normal saline, followed by sufficient quantities of normal saline and 3% NaCl, to maintain fluid balance and normal serum sodium. The administration of fludrocortisone may be beneficial as aldosterone production is relatively decreased in CSW.

30.3.4.3 Treatment of Hyponatremic Encephalopathy

There are two aspects of the treatment of hyponatremic encephalopathy generally accepted by experts in the field: (1) treatment should be based on the neurological involvement and not the absolute serum sodium, and (2) hypertonic saline is not indicated in the asymptomatic patient who is neurologically intact, regardless of the serum sodium concentration. In general, rapid correction with hypertonic saline is unnecessary and potentially harmful if there are no neurological symptoms. Conversely, symptomatic hyponatremia is a medical emergency. Treatment of hyponatremic encephalopathy should precede any neuroimaging studies to confirm cerebral edema and should occur in a monitored setting where the airway can be secured and serum sodium level measured frequently. Fluid restriction alone has no place in the treatment of

symptomatic hyponatremia. If symptomatic hyponatremia is recognized and treated promptly, prior to the development of a hypoxic event, the neurological outcome is good.

Patients with symptomatic hyponatremia should be treated with hypertonic saline (3% sodium chloride); children without symptoms should not receive hypertonic saline.

Patients with symptomatic hyponatremia need aggressive management with 3% NaCl (Na = 513 mEq/L). In general, 1 mL/kg of 3% NaCl will increase the serum sodium level by about 1 mEq/L. Children with severe symptoms such as seizures, respiratory arrest, or neurogenic pulmonary edema should receive 2 mL/kg of 3% NaCl, with a maximum of 150 mL, as a bolus over 10 min to rapidly reverse brain edema. This dose might need to be repeated once or twice until symptoms subside, with the remainder of therapy delivered via continuous infusion. Patients with less severe symptoms, such as headache, nausea, vomiting, or lethargy, can be treated via an infusion pump to achieve a sodium correction of 4–8 mEq/L in the first 4 h. To prevent complications arising from excessive therapy, 3% NaCl should be discontinued when symptoms subside. The rate of Na correction should not exceed 20 mEq/L in the first 48 h, and correction should be to mildly hyponatremic values, avoiding normalization of serum sodium or hypernatremia in the first 48 h. A continuous infusion of 3% NaCl at a rate of 1–2 mL/kg/h administered over 4 h is usually sufficient to reverse symptoms.

Cerebral Demyelination Complicating the Correction of Hyponatremia

Cerebral demyelination is a rare complication associated with symptomatic hyponatremia. Animal data has shown that correction of hyponatremia by greater than 20–25 mEq/L over 24 hours can result in cerebral demyelination. These observations have resulted in a mistaken belief that a rapid rate of correction alone is likely to result in cerebral demyelination. More recent data demonstrated that the development of cerebral demyelinating lesions is more likely due to comorbid factors such as severe liver disease, hypoxemia, hypokalemia, or chronic thiazide diuretic use rather than rate of correction alone. Cerebral demyelination following the correction of hyponatremia has primarily been described in patients with chronic hyponatremia (>48 h) and is an extremely unusual occurrence in acute symptomatic hyponatremia. Also, cerebral demyelination appears to be a less common occurrence in children than in adults.

When symptomatic cerebral demyelination follows the correction of hyponatremia, it typically follows a biphasic pattern. There is initial clinical improvement of the hyponatremic encephalopathy associated with correction of the serum sodium, which is followed by neurological deterioration 2–7 days later. Cerebral demyelination can be both pontine and extrapontine. Classic features of pontine demyelination include mutism, dysarthria, spastic quadriplegia, pseudobulbar palsy, a pseudocoma with a "locked-in stare," and ataxia. The clinical features of extrapontine lesions are more varied, including behavior changes and movement disorders. Radiographic features of cerebral demyelination typically lag behind the clinical symptoms. Cerebral demyelination is best diagnosed by MRI approximately 14 days following hyponatremia correction. The classic MRI findings are symmetrical hypointense lesions on T1-weighted images and hyperintense lesions on T2-weighted images. Some data suggest that cerebral demyelination can be detected earlier on MRI with diffusion-weighted imaging.

The outcome of cerebral demyelination is not as severe as was previously believed. Cerebral demyelination has been noted as an incidental finding on neuroimaging and at autopsy in patients with chronic illnesses. In most reported cases of cerebral demyelination attributed to dysnatremias, long-term follow-up demonstrated improvement in neurological symptoms and regres-

sion of radiographic findings. Thus, the primary cause of brain damage in patients with hyponatremia is not cerebral demyelination but results from cerebral edema and herniation. Most brain damage occurs in untreated patients and is not a consequence of therapy.

Patients with hyponatremia due to water intoxication, diarrheal dehydration, thiazide diuretics, or dDAVP are at high risk for overcorrection of hyponatremia and require extreme care and monitoring. In these illnesses, once volume depletion is corrected or when the offending medication is discontinued, there often is a rapid reversal of the urine osmolality from concentrated to dilute, resulting in a free water diuresis with potentially rapid correction of hyponatremia if saline-containing fluids are continually administered. The serum sodium can be therapeutically relowered in patient with overcorrection of severe chronic hyponatremia having other risk factors for demyelination by using a combination of dDAVP and 5% dextrose in water.

The major risk factors for developing cerebral demyelination following the correction of hyponatremia are (1) overcorrection of chronic hyponatremia, (2) inadvertent hypernatremia, (3) hypoxia, and (4) preexisting liver disease.

The primary cause of brain injury in children with hyponatremia is not cerebral demyelination but results from cerebral edema and herniation.

30.3.5 Hyponatremia in Edematous States

Edema is a common clinical finding in ICU patients and can occur in a variety of disease states including hypernatremia as previously described. Edema is defined as palpable swelling due to the expansion of the interstitial space. The common conditions that lead to edema are congestive heart failure, hepatic cirrhosis, nephrotic syndrome, sepsis, and acute kidney injury. The mechanism of edema formation and its treatment is different in each of these conditions, but all have in common an impaired ability to excrete free water, which makes hyponatremia a common associated complication. These patients rarely have symptomatic hyponatremia, but even mild hyponatremia is a major comorbidity factor which should be prevented and treated.

30.3.5.1 Pathophysiology

The development of edema requires an alteration in one or more of the Starling forces. Starling's law depicts the relationship between net filtration from the vascular space based on alterations in hydrostatic pressure, plasma oncotic pressure, and capillary permeability.

30.3.5.2 Increased Capillary Hydraulic Pressure

The most common causes of edema due to increased capillary hydraulic pressure are congestive heart failure and cirrhosis. In congestive heart failure, there is decreased cardiac output impairing renal perfusion and thus urine output leading to fluid retention with increased ventricular end-diastolic pressures. This results in a compensatory response including (a) increased sympathetic tone leading to peripheral and renal vasoconstriction, (b) increased activity of the renin-angiotensin-aldosterone system which increases renal sodium retention, and (c) increased AVP production which results in water retention. These factors expand the vascular space and retain water leading to hyponatremia. As venous pressures increase, capillary hydrostatic pressure increases leading to interstitial expansion and edema.

The primary event leading to edema in cirrhosis is increased hepatic resistance to portal flow which results in increased capillary hydrostatic pressure leading to bowel edema. As liver injury progresses, there is inappropriate arterial vasodilation leading to low blood pressure and intravascular volume relative to the capacity of the vascular space, which activates the renin-angiotensin-aldosterone system and increases vasopressin release leading to fluid and sodium retention (similar to the neurohumoral response seen in heart failure patients).

In addition, as ascites progresses, intra-abdominal pressure increases, leading to compression of the inferior vena cava which increases the likelihood for lower extremity edema.

30.3.5.3 Decreased Plasma Oncotic Pressure

Hypoalbuminemia due to renal loss is a significant, but not the only, contributing factor to edema formation in children with nephrotic syndrome. In severe hypoalbuminemia, the low capillary oncotic pressure favors fluid movement into the interstitial space. In nephrotic syndrome, the renal disease itself can lead to sodium retention, which may be the main contributing factor to edema formation. In liver disease, decreased production of proteins such as albumin leads to a fall in oncotic pressure.

30.3.5.4 Increased Capillary Permeability

Increased capillary permeability due to conditions such as burns, trauma, or sepsis can lead to edema. Edema formation is due to both fluid movement across blood vessels and to decreased capillary oncotic pressure from albumin leaking into the interstitial space.

30.3.5.5 Treatment of Hyponatremia in Edema-Forming States

Hyponatremia in edema-forming states can be difficult to treat. The cornerstone of management is treating the underlying condition, which differs by etiology. As a general rule, patients with hyponatremia and edema should be fluid restricted, and hypotonic fluids should not be given. Thiazide diuretics are a major contributing factor to the development of hyponatremia in edematous states, and their use should be limited if significant hyponatremia is present. Thiazide diuretics act at the distal convoluted tubule causing sodium and potassium loss without impairing urinary concentration. Loop diuretics are the preferred agents in the hyponatremic patient as they impair urinary concentration and lead to urinary free water loss. The administration of 25% albumin in the treatment of edema is controversial, but in all likelihood, it is beneficial when the serum albumin is <2 g/dL and may facilitate the correction of hyponatremia. Vasopressin-2 antagonists have been used in adults to correct edematous hyponatremia.

30.4 Hypocalcemia

30.4.1 Calcium Homeostasis

Approximately 1% of total body calcium resides in the extracellular volume, with the remaining 99% residing in the bone as calcium phosphate apatite. Extracellular calcium occurs in three fractions: ~40% protein bound, ~50% ionized, and ~10% in a chelated form. The majority of calcium that is protein bound is bound to albumin. Ionized (i.e., free) calcium is the biologically important fraction. A change in serum albumin concentration or pH can cause the total serum calcium and ionized calcium to fluctuate independently of each other. The total serum calcium falls by 0.8 mg/dL (0.2 mmol/L) for every 1 g/dL decrease in serum albumin concentration without affecting the ionized calcium concentration. Ionized calcium concentration rises with acidemia and falls with alkalemia (an increase in pH of 0.1 unit leads to a fall in ionized calcium by 0.16 mg/dL) without affecting the total serum calcium. These changes are mediated by proton competition for the calcium-albumin binding sites. For these reasons, ionized calcium must be measured to evaluate hypocal-

cemia as the total serum calcium does not adequately reflect the physiologically relevant ionized calcium.

The serum calcium is tightly regulated by an interplay of the calcium sensing receptor, parathyroid hormone (PTH), and 1,25 dihydroxyvitamin D_3 ($1,25(OH)D_3$). The calcium sensing receptor is primarily located on the cell surface of the parathyroid gland, where it responds to low ionized calcium by causing a prompt release of PTH; the latter results in a rapid release of calcium from the bone, increased renal tubular calcium reabsorption and phosphorous excretion, and the 1-hydroxylation of $25(OH)D_3$. 1,25 dihydroxyvitamin D_3 increases intestinal calcium absorption and bone resorption, further increasing serum calcium.

The total serum calcium falls by 0.8 mg/dL (0.2 mmol/L) for every 1 g/dL decrease in the serum albumin concentration.

Ionized calcium is the biologically important fraction of serum calcium and must be measured to evaluate and monitor hypocalcemia.

30.4.2 Etiology of Hypocalcemia (Table 30.4)

Severe hypocalcemia is a medical emergency. Symptoms of hypocalcemia can include seizures, tetany, muscle cramps, laryngospasm, neuromuscular irritability, and paresthesias. It can also contribute to hypotension in the critically ill child. The cardiac manifestations of hypocalcemia include a prolonged Q-Tc interval as hypocalcemia prolongs myocardial repolarization. Untreated hypocalcemia may lead to ventricular fibrillation or heart block. There are numerous causes of hypocalcemia in children; many of them are quite rare and are not likely to be encountered in the critical care setting. Causes of symptomatic hypocalcemia that are sufficiently common to be encountered in the critical care setting are discussed.

Neonatal hypocalcemia is relatively common in the intensive care unit. Early neonatal hypocalcemia occurring within the first 4 days of birth represents an exaggerated normal fall in serum calcium due to insufficient PTH release from immature parathyroid glands. This is most commonly seen in premature and low-birth-weight infants, infants of diabetic mothers, and with perinatal stress or asphyxia. Late neonatal hypocalcemia occurs between days 5 and 10 of life and is often due to transient PTH resistance. This can occur in conjunction with vitamin D deficiency or excess dietary phosphorous.

Hypoparathyroidism in children most often results from agenesis or dysgenesis of the parathyroid gland. The biochemical features at presentation include a low serum calcium, elevated serum phosphorus, and decreased alkaline phosphatase. The most common cause of hypoparathyroidism is the DiGeorge anomaly and velocardiofacial syndromes, where there is maldevelopment of the third and fourth branchial pouches. The DiGeorge anomaly is most often associated with 22q11 deletion and less often a 10p13 deletion. Hypocalcemia in the setting of congenital heart disease is due to DiGeorge syndrome until proven otherwise. Up to 85% of infants with conotruncal abnormalities have the 22q11 deletion. DiGeorge syndrome has also been documented in nonconotruncal congenital heart disease. Treatment consists of calcitriol and calcium supplements. Treatment should aim to keep the serum calcium low normal as hypercalciuria can develop which can lead to kidney stones or renal insufficiency.

Vitamin D deficiency is not uncommon in patients living in poverty, on very restrictive vegetarian diets, or due to malabsorption states such as intestinal lymphangiectasia. Biochemical features at presentation include a low serum calcium and phosphorous, elevated alkaline phosphatase and PTH, and decreased $25(OH)D_3$. These children typically present between 4 months and 3 years of age with the findings of rickets, delayed linear growth, osteopenia, widening of the epiphyses, rachitic rosary, frontal bossing, leg bowing, and craniotabes. Therapy consists of vitamin D supplementation with ergocalciferol, but oral calcium may be needed until serum calcium normalizes.

Table 30.4 Etiology of hypocalcemia and treatment

Etiology	PTH	Treatment
Neonatal hypocalcemia		Intravenous calcium gluconate.
Early (days 1–4).	↓	
Infant of a diabetic mother		
Prematurity		
Perinatal asphyxia		
Late onset (days 5–10).	↑	
Dietary phosphate load		
Vitamin D deficiency		
Vitamin D deficiency	↑	Ergocalciferol (vitamin D_2).
Malabsorption.		Oral calcium supplements.
Nutritional.		
Hypoparathyroidism	↓	Calcitriol (1,25 dihydroxycholecalciferol).
DiGeorge anomaly (22q11 deletion or 10p13).		Oral calcium supplements.
CHARGE syndrome.		
Autosomal-dominant and autosomal-recessive hypoparathyroidism.		
HDR syndrome (hypoparathyroidism, deafness, renal dysplasia).		
Pseudohypoparathyroidism (type I and II)	↑	Calcitriol.
Impaired vitamin D metabolism	↑	Calcitriol.
Vitamin D-dependent rickets type I (1α-hydroxylase deficiency).		
Vitamin D-dependent rickets type II (end-organ resistance to calcitriol).		
Calcium sensing receptor defect	↓↔	No treatment unless symptomatic.
Cinacalcet (calcimimetic)	↑↔	Discontinue medication.
Calcium deficiency	↑	Oral calcium supplements.
Magnesium deficiency	↕	Magnesium supplements.
Hyperphosphatemia	↑	Phosphorous binders.
		Dialysis.
Renal failure	↑	Calcitriol.
		Calcium supplements.
Disease specific	↕	Phosphorous binders.
Sepsis.		
Acute pancreatitis.		
Rhabdomyolysis.		

Symptomatic hypocalcemia can be the first presenting sign of advanced renal insufficiency. This results from (1) decreased renal production of 1,25(OH) D_3, which reduces intestinal absorption of calcium, and (2) severe hyperphosphatemia, which decreases the serum calcium by causing calcium and phosphorous to precipitate. The administration of bicarbonate to treat acidosis in a patient with renal failure can also cause symptomatic hypocalcemia. The acidosis that is often seen in acute or chronic renal insufficiency raises the ionized calcium; an acute rise in pH following bolus bicarbonate administration causes the ionized calcium concentration to fall. Acidosis should not be treated with bicarbonate in patients with acidosis until the serum calcium is normalized.

The administration of bicarbonate to treat acidosis in patients with renal insufficiency can cause acute symptomatic hypocalcemia.

30.4.3 Hypocalcemia in the Critical Care Setting

Hypocalcemia is common in the critical care setting, occurring in 20–50% of patients, and is associated with increased mortality. The reasons for this are not fully understood, but the incidence appears to increase with disease severity, occurring in as many as 80% of patients with sepsis. Possible reasons for hypocalcemia include a disturbance in the PTH-vitamin D response pathway, with either inappropriate PTH release or resistance to and impaired vitamin D metabolism. Increased vascular permeability seen in sepsis can lead to calcium leaving the vascular space more rapidly than it can be repleted. Calcium can also be chelated by devitalized tissue, citrate in the form of blood products, lipids from parenteral nutrition, and elevated phosphorus levels from renal failure. Hypomagnesemia can also be a contributing factor as magnesium is a key cofactor for appropriate PTH release in response to hypocalcemia.

Magnesium is an essential cofactor for PTH function.

It is not clear that treating hypocalcemia without symptoms in the critically ill patient is beneficial. Some studies report that treating hypocalcemia has beneficial hemodynamic effects, while some animal studies observed increased mortality. In theory, calcium administration could be potentially harmful by increasing intracellular calcium which contributes to cell death. Reasonable indications for correcting hypocalcemia in the critical care setting include symptoms of hypocalcemia such as ECG changes and hemodynamic instability. Infants should also have hypocalcemia aggressively corrected especially in the setting of congenital heart disease. The neonatal myocardium is composed of poorly organized myocytes and a functionally immature sarcoplasmic reticulum that cannot provide sufficient cytosolic calcium for excitation-contraction coupling; hence, the immature myocardium has a greater reliance on extracellular calcium entering the cytoplasm via ion channels. Hypocalcemia should be corrected in all children requiring inotropic or vasopressor support, though recommended targets for ionized calcium levels vary from slightly below the lower limit of normal to low normal.

The value of treating asymptomatic ionized hypocalcemia in critically ill children is unclear. Hypocalcemia should be treated in children on vasoactive drug support, and neonates depend on adequate extracellular calcium concentrations to maintain normal cardiac pumping function.

30.4.4 Acute Management of Hypocalcemia

The treatment of choice for symptomatic hypocalcemia is the administration of 10% calcium gluconate. Calcium gluconate is preferred over calcium chloride as it has less potential for caustic injury when administered peripherally and is safer for prolonged infusions. Further, the chloride load associated with prolonged calcium chloride infusion can be considerable. In emergency situations, calcium can be administered over minutes, but in general, it is given as a slow infusion over 2–4 h. Rapid calcium boluses cause transient marked hypercalcemia with return to baseline level within minutes; thus, continuous infusions are more effective at managing goal-directed calcium levels. Bolus calcium

has been shown to increase blood pressure in adult cardiac patients by virtue of increased systemic vascular resistance at the expense of reduced cardiac output. Patients receiving calcium infusions should have ionized calcium levels monitored frequently. Calcium boluses and infusions should only be administered through central venous catheters (with the exception of life-threatening emergencies) to prevent destructive and disfiguring tissue injuries from the extravasation of the calcium solutions. Hypomagnesemia, if present, should also be corrected with magnesium sulfate as magnesium is an essential cofactor for calcium homeostasis. If acute hypocalcemia must be corrected by the oral route, calcium glubionate should be used as it has the best absorption.

30.5 Hypokalemia

30.5.1 Potassium Homeostasis

Potassium is the most abundant cation in the body; 98% of potassium resides in the intracellular space, and 2% is extracellular. It is the ratio of intracellular to extracellular potassium concentration that determines the resting membrane potential of excitable tissue; therefore, the body must maintain the extracellular potassium concentration in a fairly narrow range of 3.5–5.5 mEq/L to prevent neurological and cardiac conduction disturbances. Potassium can be consumed in large quantities in the diet and is absorbed rapidly in the gastrointestinal tract. Serum potassium is acutely regulated by a transcellular shift of potassium from the extracellular to intracellular compartment by the effect of insulin or stimulation of β_2-adrenoceptors. The long-term regulation of potassium is via urinary excretion which is primarily regulated by aldosterone. The serum potassium does not reflect the total body potassium content as disorders in serum potassium may be due to acute intracellular shift or more chronic potassium depletion or overload. Chronic perturbations in serum potassium are better tolerated than acute changes as the gradient in intracellular to extracellular potassium will be less severe. Chronic hyperkalemia generally reflects a disorder in renal function or decreased mineralocorticoid activity, and chronic hypokalemia represents total body potassium depletion.

Since potassium is measured in either the serum or whole blood, the normal ranges for potassium are different. When blood clots, platelets release their intracellular contents, which includes potassium, so that serum potassium is typically 0.3–0.5 mEq/L higher than whole blood or plasma potassium concentration. In thrombocytopenic patients, the difference is smaller, whereas in patients with high platelet counts, the difference in potassium concentration will be larger.

30.5.2 Clinical Effects of Hypokalemia

Mild hypokalemia can cause serious arrhythmia in the presence of underlying cardiac disease or digoxin use.

Acute serum/plasma potassium concentration changes do not accurately represent total body potassium stores.

Hypokalemia, defined as serum potassium <3.6 mEq/L, is one of the most common electrolyte abnormalities occurring in the critical care setting. Mild hypokalemia, potassium 3–3.5 mEq/L, is usually asymptomatic, and even levels of 2.5–3 mEq/L are often well tolerated in children in the absence of cardiac disease as it does not cause significant arrhythmias. With underlying cardiac disease or digoxin use, even mild hypokalemia can contribute to arrhythmias. In adults, serum potassium <3.0 mEq/L are reported to cause weakness, myopathy, constipation, and intestinal ileus, while serum potassium less than 2.5 mEq/L can cause rhabdomyolysis and ascending paralysis. These symptoms are rarely observed in children even in the critical care setting. When

hypokalemia develops, the underlying cause should be addressed and corrected as hypokalemia is associated with increased morbidity and mortality in both children and adults.

30.5.3 Causes of Hypokalemia in the Critical Care Settings (▸ Box 30.2)

The most common cause of potassium depletion in the critical care setting is from the use of loop or thiazide diuretics, which increase sodium delivery to the collecting duct. This leads to maximal sodium reabsorption in these segments and facilitates potassium excretion through sodium-potassium exchange. Chronic diuretic use may be associated with effective circulating volume depletion, which further stimulates the renin-angiotensin-aldosterone pathway, increasing urinary potassium losses. Hypochloremic metabolic alkalosis, which is a frequent complication of diuretics, contributes to hypokalemia by impairing chloride-linked sodium reabsorption, thereby increasing distal tubule sodium reabsorption in exchange for potassium excretion. Hypomagnesemia, which is a common complication of diuretic therapy, promotes urinary potassium losses by unknown mechanisms. The combination of loop plus thiazide diuretics can lead to significant hypokalemia.

Other disorders leading to hypokalemia are conditions which lead to gastrointestinal losses, transcellular shifts in potassium, or mineralocorticoid excess. Potassium is primarily excreted in the stool by the colonic epithelium;

Box 30.2 Causes of Hypokalemia

1. Inadequate intake.
2. Urinary losses.
   - (a) Diuretics.
   - (b) Salt wasting nephropathy.
     - (i) Fanconi syndrome.
   - (c) Osmotic diuresis.
     - (i) Uncontrolled diabetes.
   - (d) Transport disorder.
     - (i) Bartter's and Gitelman's syndromes.
   - (e) Mineralocorticoid excess.
   - (f) Magnesium depletion.
     - (i) Amphotericin B.
   - (g) Alkalosis.
   - (h) Non-reabsorbable anions (penicillin).
3. Extrarenal losses.
   - (a) Vomiting.
   - (b) Diarrhea.
   - (c) Malabsorption.
   - (d) Tumors.
   - (e) Dialysis.
4. Transcellular shifts.
   - (a) β_2-adrenergic agents,
   - (b) Insulin.
   - (c) Theophylline.
   - (d) Hyperthyroidism.
   - (e) Hypokalemic periodic paralysis.
   - (f) Barium poisoning.

therefore, any process that results in diarrhea can cause large potassium losses. Intestinal losses from an ileostomy or upper gastrointestinal losses from vomiting or nasogastric drainage do not contain significant amounts of potassium. Hypochloremic alkalosis induced by emesis can cause hypokalemia by increasing urinary potassium losses as the kidney attempts to maintain protons. β_2-adrenergics, theophylline, and insulin can cause hypokalemia by causing a transcellular shift in potassium. There are numerous medical conditions associated with increased mineralocorticoid production or activity that can cause hypokalemia, especially in conjunction with diuretics.

30.5.4 Treatment of Hypokalemia

Aggressive parenteral potassium is not indicated unless there are cardiac arrhythmias, severe myopathies, or paralysis.

The treatment of hypokalemia is controversial as excess potassium supplementation, especially via the intravenous route, can cause dangerous hyperkalemia. Hypokalemia is generally asymptomatic, and therapy should aim for a slow correction over a period of days, preferably by the enteral route as potassium chloride in two to three divided doses. In cases of cardiac arrhythmias, severe myopathies, paralysis, or severe hypokalemia (<2 mEq/L), aggressive intravenous administration of potassium is indicated. Potassium should be given as potassium chloride as there is generally an accompanying chloride deficit. Potassium administration should occur at a rate of 0.25–0.5 mEq/kg/h. Symptomatic hypokalemia can be corrected at a maximal rate of 1 mEq/kg/h with a maximum dose of 20 mEq. Many PICUs routinely administer 0.5–1 mEq/kg over 1 h (maximum 20 mEq) without complications as long as strict adherence to administration policy is observed. Neither repeated bolus doses of potassium nor a continuous parenteral fluid containing potassium at a concentration greater than 60 mEq/L should be administered through a peripheral intravenous line as this can sclerose the vein, and potassium infiltration can cause tissue necrosis. Magnesium depletion should be corrected as hypomagnesemia promotes urinary potassium losses. Potassium-sparing diuretics can be helpful to curtail urinary potassium losses.

30.6 Hyperkalemia

30.6.1 Patients at Risk for Hyperkalemia (▸ Box 30.3)

Hyperkalemia is defined as serum potassium greater than 6 mEq/L in newborns and greater than 5 mEq/L in infants and children. Hyperkalemia can develop as a result of either excess potassium intake, decreased potassium excretion, or a transcellular shift of potassium from the intracellular to extracellular space. There are usually multiple factors contributing to hyperkalemia; therefore, a detailed evaluation of potassium intake, renal function, and medication history is mandatory.

Patients with chronic renal insufficiency are able to maintain near normal serum potassium levels unless GFR is less than 10% of normal.

A common setting for serious hyperkalemia in children is oliguric acute kidney injury due to renal ischemia, acute glomerulonephritis, hemolytic uremic syndrome, multiple organ failure, or acute urinary tract obstruction. Patients with chronic renal insufficiency are usually able to maintain near normal potassium until the glomerular filtration rate declines to less than 10% of normal. When a patient with chronic renal insufficiency has serious hyperkalemia, there is usually a secondary cause such as an acute increase in potassium intake or a medication, such as an ACE inhibitor, calcineurin inhibitor (e.g., tacrolimus, cyclosporine), potassium-sparing diuretic, or NSAID, which is impairing the normal renal compensatory response to hyperkalemia. Mineralocorticoid deficiency or resistance can also result in hyperkalemia and should be suspected in any patient with normal renal function and sustained

hyperkalemia. Severe hyperkalemia can develop in infants with pyelonephritis due to a transient pseudohypoaldosteronism. Massive tissue breakdown from rhabdomyolysis or tumor lysis syndrome can also result in serious hyperkalemia. A hyperchloremic metabolic acidosis is the most common cause of hyperkalemia resulting from a transcellular shift in potassium in children. Serum potassium rises on average 0.6 mEq/L (0.24–1.7 mEq/L) for every 0.1 unit fall in pH. Diabetics can also develop hyperkalemia from cellular shift and impaired potassium entry into the cell secondary to insulin deficiency or resistance.

Box 30.3 Causes of Hyperkalemia

1. Factitious.
   (a) Hemolysis.
   (b) Thrombocytosis (platelets > 1,000,000/mm^3).
   (c) Leukocytosis (white blood cell count > 100,000/mm^3).
   (d) Repeated fist clenching with tourniquet in place.
2. Impaired potassium excretion.
   (a) Renal insufficiency or failure.
   (b) Mineralocorticoid deficiency.
      (i) Hereditary enzyme deficiencies.
      (ii) Addison's disease.
      (iii) Hyporeninemic hypoaldosteronism (type 4 renal tubular acidosis).
      (iv) Heparin-induced inhibition of aldosterone synthesis.
   (c) Pseudohypoaldosteronism.
      (i) Hereditary.
      (ii) Pyelonephritis.
3. Medications.
   (a) Potassium-sparing diuretics.
   (b) ACE inhibitors.
   (c) Angiotensin receptor blockers.
   (d) NSAIDs.
   (e) Cyclosporine/tacrolimus.
   (f) Pentamidine.
4. Impaired potassium entry into cells.
   (a) Insulin deficiency or resistance.
   (b) Hyperchloremic metabolic acidosis.
   (c) Hypertonicity (uncontrolled diabetes).
   (d) Massive tissue breakdown (rhabdomyolysis or tumor lysis syndrome).
   (e) Familial hyperkalemic periodic paralysis.
   (f) Medications.
      (i) β-Blockers,
      (ii) Digoxin (at toxic levels).
      (iii) Succinylcholine.
      (iv) Arginine.
      (v) Lysine.
5. Excess potassium administration.
   (a) Total parenteral nutrition.
   (b) Potassium supplements.
   (c) Diet or enteral feeds.
   (d) RBC transfusion.
   (e) Penicillin G potassium.

ACE is angiotensin converting enzyme; NSAID is nonsteroidal anti-inflammatory drug; RBC is red blood cell.

30.6.2 Clinical Effects of Hyperkalemia

The ratio of intracellular to extracellular potassium is the major determinant of the resting membrane potential. Hyperkalemia decreases resting membrane potential facilitating depolarization and impairing repolarization. The symptoms of mild to moderate hyperkalemia are usually asymptomatic; however, the first presenting symptom may be a fatal cardiac arrhythmia. Clinical manifestations that can result from membrane potential effects in striated muscle include weakness, paresthesias, and ascending paralysis. Ascending paralysis is usually seen in patients with chronic renal insufficiency when the serum potassium exceeds 7.5 mEq/L.

The most consistent ECG finding of hyperkalemia is elevation in the T waves that are best seen in the precordial leads (lead II).

The effects of potassium on cardiac conduction is of greatest concern (■ Table 30.5). Hyperkalemia interferes with atrial, ventricular, and atrioventricular conduction pathways leading to arrhythmias. The risks of arrhythmias usually correlate with the degree of hyperkalemia, but arrhythmias are more likely to occur with rapid increases in serum potassium than with gradual increases. The most consistent ECG finding of hyperkalemia is increased T waves followed by widening of the QRS complex. There is no clear cutoff where arrhythmias will develop, but patients with serum potassium >6.0 mEq/L should be considered at risk for arrhythmias, and patients with levels exceeding 6.5 mEq/L or having electrocardiographic features should receive immediate treatment.

30.6.3 Treatment of Hyperkalemia

The treatment of hyperkalemia largely depends on both the etiology and severity of hyperkalemia. The presence of ECG changes or serum potassium exceeding 6.5 mEq/L requires immediate therapy (▶ Box 30.4). Calcium can reverse cardiac conduction abnormalities and should be administered if ECG changes are present. Calcium can be administered through a properly functioning peripheral intravenous line in the urgent situation, but a central venous

■ **Table 30.5** Electrocardiographic manifestations of hyperkalemia

Serum potassium level	Expected ECG abnormality
Mild hyperkalemia 5.5–6.5 mEq/L	Tall, tent-shaped ("peaked") T waves with narrow base, best seen in precordial leads (lead II)
Moderate hyperkalemia 6.5–8.0 mEq/L	Peaked T waves.
	Prolonged PR interval.
	Decreased amplitude of P waves.
	Widening of QRS complexes.
Severe hyperkalemia >8.0 mEq/L	Absence of P wave.
	Intraventricular blocks, fascicular blocks, bundle branch blocks, QRS axis shift.
	Progressive widening of the QRS complex resulting in bizarre QRS morphology.
	Eventual "sine wave" pattern (sinoventricular rhythm), ventricular fibrillation, asystole.

Box 30.4 Emergency Management of Hyperkalemia

1. Evaluation.
   (a) Confirm that potassium value is venous and non-hemolyzed.
   (b) Place patient on cardiac monitor (lead II) and obtain ECG.
2. Conduction abnormalities.
   (a) Calcium gluconate (10%) 100 mg/kg/dose (1 mL/kg/dose) over 3–5 min. Can be repeated in 15 min.
3. Serum potassium > 6.5 mEq/L.
   (a) *Move potassium into cells.*
      (i) Regular insulin 0.1 U/kg with 25% glucose (2 mL/kg) IV over 30 min. Onset of effect is 10–20 min with duration of 2–3 h.
      (ii) Albuterol nebulization 0.5% 0.25 mg/kg/dose over 10 min. Onset of action 20–30 min, duration 2–3 h. can be used in conjunction with insulin and glucose.
      (iii) Sodium bicarbonate 1 mEq/kg, only if hyperchloremic metabolic acidosis; onset of action is 1–3 h.
   (b) *Remove potassium from body.*
      (i) Sodium polystyrene (Kayexalate) 1 g/kg/dose orally or as retention enema. Response time is 1–6 h.
      (ii) Loop diuretic.
      (iii) Hemodialysis or peritoneal dialysis.
      (iv) Fludrocortisone.

line should be placed for ongoing therapy. The acute management of hyperkalemia also includes therapies that shift potassium intracellularly. Intravenous insulin and glucose and an inhaled β_2-adrenergic agent such as albuterol are acceptable first-line therapies in the treatment of hyperkalemia. Both agents lower serum potassium by 0.6–1 mEq/L within 30 min and have an additive affect when used together. Insulin is effective in all patients but has the disadvantage of potentially causing hypoglycemia. Albuterol's main advantage is that it can be administered quickly and repeatedly without the need for vascular access with minimal side effects. The main disadvantage of albuterol is that it is ineffective in 10–20% of patients. Sodium bicarbonate has recently lost favor in the acute management of hyperkalemia as it is relatively ineffective in the absence of severe acidosis, has a delayed onset of action of 1 h, lowers ionized calcium, and can cause fluid overload and hypernatremia.

Following the acute lowering of serum potassium by causing an intracellular shift, the next objective is to remove potassium from the body via urine, stool, or dialytic therapies. The preferred method of removing potassium from the body is via urinary losses, so measures should be undertaken to improve urinary flow. Prerenal causes of acute kidney injury should be promptly treated with volume expansion, obstructive causes should be corrected, and urinary flow should be optimized with diuretics. When potassium removal via urinary losses is not possible, the sodium polystyrene resin (Kayexalate) is indicated. Kayexalate removes 0.5–1.0 mEq of potassium in exchange for 2–3 mEq of sodium. The primary site of potassium removal is the colon. Gastric administration of Kayexalate can require 6 h for potassium removal, while a retention enema can be effective in 2–3 h. Kayexalate is unpalatable, and quick delivery of a significant volume to a child will likely require nasogastric administration

or a retention enema. Kayexalate can have serious intestinal complications in the preterm infant, in patients with ileus, and in the immunosuppressed and should be used with caution. Multiple reports of bowel necrosis, intestinal perforation, bowel impaction, and intestinal bezoars have been reported. Hemodialysis is a rapid and effective means of potassium removal when there is severe renal impairment and acutely rising serum potassium.

Two other oral cation exchange resins were recently FDA approved for the treatment of hyperkalemia in adults: Lokelma (sodium zirconium cyclosilicate) and Veltassa (patiromer). Both agents are powders that are suspended in water and are safer than Kayexalate without the gastrointestinal side effects. Lokelma would appear to be the only agent suitable for the treatment of acute hyperkalemia as it has a more rapid onset of action of 1 hour in comparison to Veltassa that has a 7-hour onset of action. Lokelma has nine times the potassium binding of potassium as Kayexalate; it is highly selective for potassium binding. There is no data on the use of Veltassa in children, though it may replace Kayexalate as the first-line oral agent to treat acute hyperkalemia. Both Veltassa and Lokelma are suitable for the management of chronic hyperkalemia in adults.

β_2-adrenergics are equally effective to the administration of insulin and glucose in acutely lowering serum potassium.

The chronic treatment of hyperkalemia consists of limiting exogenous potassium from dietary sources, medications, or intravenous fluids. Medications contributing to hyperkalemia such as potassium-sparing diuretics or ACE inhibitors should be discontinued.

30.7 Magnesium

30.7.1 Hypomagnesemia

Hypomagnesemia is a common electrolyte abnormality in the critical care setting occurring in up to 60% of patients. Hypomagnesemia can develop rapidly as there are no regulatory hormones for magnesium, and there is not a rapid exchange between extracellular magnesium and bone and cellular stores. Hypomagnesemia usually results from dietary depletion, gastrointestinal losses, or urinary losses. The most common causes of hypomagnesemia in the critical care setting are malnutrition, diarrhea, nasogastric suction, diuretic use, volume expansion, diuretic phase of acute kidney injury, osmotic diuresis from diabetes, and nephrotoxic medications such as aminoglycosides, amphotericin B, cyclosporine, and tacrolimus. Hypomagnesemia frequently develops following cardiac bypass due to chelation from free fatty acids and from citrate.

Symptomatic hypomagnesemia usually occurs in conjunction with other electrolyte abnormalities, such as hypokalemia, alkalosis, or hypocalcemia. Conditions that cause hypomagnesemia also causes renal potassium wasting resulting in a hypokalemic state that is refractory to potassium repletion. Severe symptomatic hypomagnesemia is almost always associated with hypocalcemia. Hypomagnesemia impairs calcium homeostasis by decreasing PTH release and causing PTH resistance. The primary neurological symptoms of hypomagnesemia are similar to hypocalcemia with tetany, seizures, and carpopedal spasm. Magnesium depletion also affects cardiac conduction with widening of the QRS complex, prolongation of the PR interval, and diminution of the T wave. Hypomagnesemia can cause ventricular arrhythmias in the setting of ischemic heart disease or congestive heart failure.

Significant hypomagnesemia is defined as a serum magnesium less than 1.2 mg/dL (0.4 mmol/L or 1 mEq/L). Patients with hypocalcemic-hypomagnesemic tetany or hypokalemic-hypocalcemic arrhythmias should be treated with magnesium sulfate infusion. A special indication for magnesium supplementation is torsades de pointes. The American Heart Association recommends using magnesium sulfate in the treatment of torsades de pointes or refractory ventricular fibrillation. Rapid magnesium infusions over 2 h for cardiac or CNS indications or over 30 min for status asthmaticus are well tolerated and can be rapidly effective. However, rapid infusions also result in increased urinary magnesium losses; thus, continuous supplementation is the best way to provide ongoing correction when indicated. Hypomagnesemia is suspected to impair glucose metabolism, so magnesium should be supplemented in diabetics with hypoglycemia. The preferred method of replacing magnesium is the enteral route via slow-release preparations such as magnesium chloride or gluconate. Large doses of enteral magnesium can result in diarrhea.

Symptomatic hypomagnesemia usually occurs simultaneously with hypocalcemia.

Magnesium supplementation is recommended as treatment for torsades de pointes.

30.7.2 Hypermagnesemia

Hypermagnesemia is a rare clinical occurrence that is usually the result of excess magnesium administration to patients with renal impairment. Magnesium in phosphate-binding salts or magnesium-containing laxatives should be avoided in patients with renal impairment. Symptoms of severe hypermagnesemia include hypotension, bradycardia, somnolence, respiratory depression, and ECG abnormalities. In patients with normal renal function, hypermagnesemia can usually be managed by discontinuing the magnesium supplements. Severe symptoms can be reversed quickly by administering intravenous calcium as a magnesium antagonist. For severe toxicity and renal impairment, hemodialysis may be indicated.

Intravenous calcium can acutely reverse the symptoms of severe hypermagnesemia.

30.8 Phosphorus

30.8.1 Hypophosphatemia

Phosphate is the most abundant intracellular anion with less than 1% present in the plasma. Phosphate is essential for bone mineralization, energy metabolism, and cellular structure and function. Hypophosphatemia can result from an acute transcellular shift in phosphorous or from true phosphorous depletion from increased urinary losses or decreased intestinal absorption. Common causes of a transcellular shift in phosphorous are respiratory alkalosis, insulin administration, recovery phase of diabetic ketoacidosis, or the refeeding phase of malnutrition. Phosphorous depletion is common in patients post renal transplantation, with tubulopathies such as the Fanconi syndrome or X-linked hypophosphatemic rickets, with malnutrition, burns, vitamin deficiency, or diarrhea. Continuous hemofiltration can cause severe phosphorous depletion if large amounts of phosphorous are not replaced parenterally.

Symptomatic hypophosphatemia develops when the serum phosphorous falls below 1 mg/dL (0.32 mmol/L). Most of the clinical symptoms can be explained by decreased intracellular adenosine triphosphate (ATP) compounds and reduced 2,3-diphosphoglycerate (2,3-DPG). Symptoms include peripheral neuropathy, metabolic encephalopathy, seizures, proximal myopathy, dysphagia, and ileus. Respiratory depression can develop, and patients can be difficult

to wean from the ventilator due to respiratory weakness. Cardiac arrhythmias and impaired contractility can develop.

Causes of hypophosphatemia include respiratory alkalosis, insulin administration, recovery phase of diabetic ketoacidosis, or the refeeding phase of malnutrition.

Hypophosphatemia can cause respiratory fatigue and may make it difficult to wean a patient off mechanical ventilation.

Hypophosphatemia is best treated orally with either sodium or potassium phosphate. Intravenous phosphorous administration can cause severe hypocalcemia, so it must be given slowly and with caution. Intravenous phosphorous infusions are usually not given unless the serum phosphorus is less than 1.5 mg/dL (0.48 mmol/L). Serum calcium and phosphorous levels must be followed closely if phosphorous infusions are to be administered.

30.8.2 Hyperphosphatemia

Causes of hyperphosphatemia in the critical care setting are renal failure, rhabdomyolysis, tumor lysis syndrome, or hemolysis.

Severe hyperphosphatemia can cause symptomatic hypocalcemia by causing calcium and phosphorous to precipitate.

Serum phosphorous levels are higher in children than adults due to a higher bone turnover rate. Phosphorous is primarily filtered in the kidney. Hyperphosphatemia can develop from either excess exogenous administration of phosphorous, endogenous release of phosphorous from bone or cells, or reduced renal excretion of phosphorus. The main causes of hyperphosphatemia in the critical care setting are rhabdomyolysis, tumor lysis syndrome, hemolysis, or renal failure. The primary clinical feature of severe hyperphosphatemia is symptomatic hypocalcemia. Hyperphosphatemia causes calcium to precipitate when the product of the serum calcium times the phosphorous exceeds 72 mg/dL. If severe hyperphosphatemia occurs in conjunction with renal insufficiency, hemodialysis may be required. Oral phosphorus-binding salts or calcium, magnesium, or aluminum is useful in more chronic hyperphosphatemia.

30.9 Metabolic Acidosis

Metabolic acidosis is defined as an arterial pH below 7.36 in association with a reduced plasma bicarbonate concentration. Severe metabolic acidosis is defined as an arterial pH below 7.2. In general, metabolic acidosis stimulates a rapid ventilatory response decreasing the $PaCO_2$. The normal respiratory response to a metabolic acidosis is a decrease in $PaCO_2$ of 1.2 mmHg for every 1.0 mEq/L reduction of serum bicarbonate to a minimum $PaCO_2$ of 10 mmHg. In the presence of a normal respiratory response, a serum pH <7.20 would be observed only with serum bicarbonate <10 mEq/L. A less than expected respiratory response constitutes a mixed acid-base disturbance.

A useful way to categorize the nature of a metabolic acidosis is based on the anion gap. Metabolic acidosis can be classified as having either a normal anion gap (hyperchloremic acidosis) or an elevated anion gap. A normal anion gap acidosis results from bicarbonate loss from urine or the stool without proportional loss of chloride or with exogenous chloride loads via non-bicarbonate-containing fluids (e.g., large volumes of 0.9% NaCl). A renal tubular acidosis also produces a normal anion gap acidosis when the kidney is unable to maintain serum pH via appropriate hydrogen excretion or bicarbonate reabsorption.

An elevated anion gap acidosis indicates an increased rate of endogenous acid generation, such as ketoacids or lactate, the addition of exogenous organic acids, or decreased renal capacity to excrete an acid load as is seen in renal failure.

The anion gap is calculated as follows:

$$\text{Anion gap} = [\text{Na}] - ([\text{Cl}] + [\text{HCO}_3])$$

A normal anion is typically 7–12 mEq/L but may be as high as 15 mEq/L in children younger than 2 years of age.

The negatively charged unmeasured particles constituting the anion gap are primarily albumin; therefore, the anion gap must be corrected for a low serum albumin concentration. The anion gap decreases by 2.5 mEq/L for every 1 g/dL reduction in serum albumin from normal. When the serum albumin falls to below 2 g/dL, the anion gap can be zero or less. Thus, to correct the anion gap for low serum albumin, 2.5 mEq/L must be added to the observed anion gap for every 1 g/dL decrease in serum albumin below 4 g/dL.

The PCO_2 falls an average of 1.2 mmHg for every 1 mEq/L reduction in serum bicarbonate.

The anion gap decreases by 2.5 mEq/L for every 1 g/dL decrease in serum albumin below 4 g/dL.

30.9.1 Hyperchloremic Metabolic Acidosis (▸ Box 30.5)

Box 30.5 Non-anion Gap Acidosis

1. Gastrointestinal bicarbonate loss.
   (a) Diarrhea.
   (b) Small bowel, pancreatic, or biliary drainage.
   (c) Uterosigmoidostomy.
   (d) Cholestyramine (bile acid diarrhea).
2. Renal tubular acidosis (RTA).
   (a) Proximal renal tubular acidosis (type 2 RTA).
   (b) Classic distal RTA (type 1 RTA).
   (c) Mineralocorticoid deficiency or resistance (type 4 RTA).
   (d) Carbonic anhydrase inhibitors.
3. Other.
   (a) Dilutional acidosis (rapid saline infusion).
   (b) Post-hypocapnic state.

30.9.1.1 Gastrointestinal Losses of Bicarbonate

Gastrointestinal secretions beyond the stomach are rich in bicarbonate. Large intestinal fluid losses of bicarbonate result in a normal anion gap acidosis with hyperchloremia. The latter occurs because the fall in serum bicarbonate must be accompanied by a corresponding increase in serum chloride to maintain electroneutrality. The normal renal response to metabolic acidosis is to generate an acid urine ($pH \leq 5.5$). If hypokalemia or severe acidosis is present, significant urinary NH_4 excretion can paradoxically result in a urine pH greater than 6.0. The renal excretion of NH_4 can be estimated by measuring the urine anion gap. The equation for the urine anion gap is:

$$\text{Urine anion gap} = \text{Urine}\left(\left[\text{Na}\right]+\left[\text{K}\right]\right)-\text{Cl}$$

A negative urine anion gap indicates urinary NH_4 excretion and confirms a normal renal response to metabolic acidosis even in the face of a urine $pH > 5.5$.

The normal renal response to metabolic acidosis is to excrete NH_4 in the urine. This can be estimated by measuring the urine anion gap; a negative gap confirms NH_4 excretion.

30.9.1.2 Dilutional Acidosis

A common cause of a normal anion gap metabolic acidosis in the pediatric critical care unit is due to the rapid expansion of the extracellular space with large amount of intravenous fluids that do not contain bicarbonate. Large amounts of NaCl administration, as fluid resuscitation, can dilute the serum bicarbonate and result in acidosis. The rapid infusion of saline-containing fluids causes only a modest decrease in the serum bicarbonate despite the fact that saline-containing intravenous fluids have a pH of between 4 and 5 because of the intracellular buffering system and the renal response to acidosis.

Rapid expansion of the extracellular space with non-bicarbonate-containing fluids can result in a dilutional acidosis.

Distal renal tubular acidosis has a urine pH greater than 5.5 and a positive urine anion gap, indicating impaired urine NH_4 excretion.

30.9.1.3 Renal Tubular Acidosis

Renal tubular acidosis (RTA) describes a group of conditions characterized by either a defect in bicarbonate reabsorption or impaired hydrogen ion excretion. Renal tubular acidosis is classified in three main categories: proximal RTA (type 2), distal RTA (type 1), and hyperkalemic RTA (type 4). These conditions can be either hereditary or acquired, can result from a variety of medications or toxins, and are associated with numerous disease states. Proximal RTA is caused by impaired bicarbonate reabsorption in the proximal tubule with normal distal urine acidification. In proximal RTA, the urine pH may be lower than 5.5, and the urine anion gap is usually negative indicating normal urine NH_4 excretion. Treatment of proximal RTA typically requires large amounts of bicarbonate. Distal RTA results from impaired hydrogen ion excretion in the distal tubule. The urine pH is generally greater than 5.5, and urine anion gap is positive indicating impaired urine NH_4 excretion. The acidosis is usually corrected with relatively small doses of bicarbonate. A hyperkalemic RTA is primarily due to mineralocorticoid resistance or deficient states. The urine pH is typically greater than 5.5, and the urine anion gap is positive. Treatment consists of either mineralocorticoid or bicarbonate replacement.

30.9.2 Elevated Anion Gap Acidosis (▸ Box 30.6)

An elevated anion gap acidosis can result from three causes: increased endogenous organic acid production, impaired renal excretion of organic acids, and the ingestion of organic acids. The most common cause of elevated anion gap acidosis in the critical care setting is from endogenous organic acid production, specifically lactate and ketoacids. Diabetic ketoacidosis is discussed elsewhere in this text.

Box 30.6 Elevated Anion Gap Acidosis

1. Lactic acidosis.
   - (a) L-lactic acidosis.
     - (i) Hypoperfusion/hypoxia.
     - (ii) Inborn errors of metabolism.
     - (iii) Cyanide intoxication.
     - (iv) Seizures.
     - (v) Severe exercise.
     - (vi) Alcohol.
   - (b) D-lactic acidosis.
     - (i) Short gut syndrome.
2. Ketoacidosis.
   - (a) Diabetic ketoacidosis.
   - (b) Alcoholic ketoacidosis.
   - (c) Starvation ketoacidosis.
3. Renal failure.
4. Toxins.
   - (a) Ethylene glycol.
   - (b) Methanol.
   - (c) Salicylates.
   - (d) Paraldehyde.

30.9.2.1 Lactic Acidosis

Lactate production results from the anaerobic metabolism of pyruvate (▶ Chap. 2). The most common cause of L-lactic acidosis is from oxygen-deficient states such as hypoxia and hypoperfusion which are frequently seen in septic and cardiogenic shock. This is termed type A (fast) lactic acidosis. Lactic acidosis that occurs in the absence of hypoxia is termed type B (slow) lactic acidosis. Examples of type B lactic acidosis are inborn errors in metabolism, cyanide intoxication from nitroprusside, or severe exercise. An unusual form of lactic acidosis is D-Lactic acidosis which can be seen in short gut syndrome or malabsorption states. In these diseases, bacteria metabolize carbohydrates to D-lactic acid that is then systemically absorbed. Serum lactate levels do not measure the presence of D-lactate. The primary treatment of lactic acidosis is to treat the underlying disease state. Laboratory tests measure lactate and not lactic acid; there are other causes of increased lactate that are not associated with a metabolic acidosis, such as increased gluconeogenesis.

Cyanide intoxication from nitroprusside can result in lactic acidosis due to impaired mitochondrial oxygen utilization.

30.9.2.2 Toxic Ingestions

Life-threatening poisonings that can cause an elevated anion gap acidosis deserve specific mention. Aspirin (acetylsalicylic acid) results in both a keto-acidosis and lactic acidosis by uncoupling oxidative phosphorylation which results in anaerobic metabolism. Methanol, a common component of varnish, is metabolized to formaldehyde than to formic acid. Ethylene glycol, a common component of antifreeze, is metabolized to glycolic acid and oxalic acid. A key feature of methanol and ethylene glycol ingestion is an elevated osmolar gap, where the measured serum osmolality exceeds the calculated osmolality by greater than 25 mOsm/L.

30.9.3 Clinical Effects of Acidemia (▶ Box 30.7)

Severe acidosis is rarely lethal in an otherwise healthy individual in the absence of cardiac dysfunction. Complication-free survival has been reported in individuals with a pH less than 6.8. Severe metabolic acidosis can cause arrhythmias, hypotension, and hyperkalemia. Metabolic acidosis lowers systemic vascular resistance, but this is often offset by increased sympathetic nervous system activation. Metabolic acidosis results in an efflux of cellular potassium which may result in hyperkalemia. For reasons that are unclear, hyperkalemia is primarily seen with a hyperchloremic acidosis and not with an elevated anion gap acidosis.

Box 30.7 Clinical Effects of Acidemia

1. Cardiovascular.
   (a) Arrhythmias.
   (b) Hypotension.
   (c) Resistance to vasopressors.
   (d) Venoconstriction with centralization of blood volume.
2. Central nervous system.
   (a) Decreased sensorium.
3. Gastrointestinal.
   (a) Gastric atony.
4. Hepatic.
   (a) Reduced hepatic blood flow.
5. Metabolic.
   (a) Shift of oxyhemoglobin dissociation curve increasing tissue oxygen release.
   (b) Insulin resistance.

30.9.4 Treatment of Metabolic Acidosis with Bicarbonate: The Pros and Cons

Metabolic acidosis should not be viewed as a disease but as a symptom of an underlying disorder. As such, the primary goal of therapy is to treat the underlying condition. When severe acidosis is present (pH <7.2), bicarbonate therapy may be indicated in selected cases.

The safety and efficacy of bicarbonate therapy largely depend on the etiology of the acidosis. Bicarbonate therapy can be beneficial in severe hyperchloremic acidosis, pH <7.2, and total CO_2 < 8 mEq/L, such as that seen with either large gastrointestinal or urinary losses of bicarbonate. The body's metabolic response to hyperchloremic acidosis is the renal regeneration of bicarbonate. This can be a slow process taking days. If there are ongoing gastrointestinal losses or renal dysfunction, the body may not be capable of repairing the acidosis. Under these circumstances, addition of sodium bicarbonate to intravenous fluids is indicated both to relieve the dyspnea of respiratory compensation and to improve pH for organ function. The aim of acute treatment of severe hyperchloremic acidosis is a serum bicarbonate of 10 mEq/L, subsequently followed by a slow correction to normal.

The use of sodium bicarbonate to treat an elevated anion gap acidosis is more controversial. The main indication for using bicarbonate therapy is presumably to improve cardiac contractility. Although not supported with consistent data, the effects of endogenous or exogenous catecholamines can be depressed in the face of severe acidosis. Most data show that acute respiratory acidosis has a greater negative inotropic effect compared with metabolic acidosis. Based on observations, many intensivists believe that some bicarbonate supplementation in the presence of severe anion gap acidosis results in more rapid circulatory recovery, although to be effective, ventilation must be adequate to assure that the CO_2 generated from bicarbonate's buffering action is eliminated.

There are three conditions where bicarbonate therapy is of questionable benefit and may be deleterious: diabetic ketoacidosis, lactic acidosis, and cardiac arrest.

30.9.4.1 Diabetic Ketoacidosis

In theory, an elevated anion gap acidosis should correct rapidly once the underlying metabolic defect is corrected as the organic anion will be metabolized to bicarbonate. In diabetic ketoacidosis (DKA), acid-base balance is restored with slow hydration and insulin. The theoretical reason to use bicarbonate in DKA is that severe metabolic acidosis can cause insulin resistance, and the addition of bicarbonate may hasten the recovery. However, studies in both children and adults found no benefit from adding bicarbonate to the treatment of DKA in correcting hyperglycemia, clearing ketoacids, shortening hospital stay, or decreasing complications of DKA. In fact, bicarbonate use was found to be a risk factor for the development of cerebral edema.

30.9.4.2 Lactic Acidosis

Bicarbonate therapy in lactic acidosis can worsen cardiac function. In most clinical settings, lactic acidosis is best treated by reversing the cause rather than administration of sodium bicarbonate.

Lactic acidosis can have serious systemic effects, decreasing hepatic blood flow and cardiac output, which results in decreased lactate clearance and tissue perfusion. In theory, bicarbonate therapy might improve some of the adverse systemic effects of lactic acidosis. However, many laboratory studies found that bicarbonate administration in lactic acidosis is not beneficial and in fact has many deleterious consequences. A reasonable criticism of many animal studies is the magnitude and rapidity of the bicarbonate correction of acidosis employed, and there are clinical studies attesting to the safety of slower infu-

sions of smaller doses sodium bicarbonate. Rapid infusion of bicarbonate appears to further decrease cardiac output by worsening the intracellular pH via increased CO_2 generation, lowering the ionized calcium, and further stimulating lactate production. Indeed, at the bedside in the intubated patient with end-tidal CO_2 monitoring, one can observe the rise in CO_2 elimination in response to rapid bicarbonate administration and the lack of change in end-tidal CO_2 with slower infusion. The large amount of bicarbonate therapy necessary to correct a severe lactic acidosis can result in hypernatremia and fluid overload as sodium bicarbonate is hyperosmolar; the Na concentration in 8.4% sodium bicarbonate is 1000 mEq/L. Bicarbonate therapy in the treatment of severe lactic acidosis in conjunction with high volume hemofiltration may obviate some of these problems in that lactate removal can be achieved, and large amounts of bicarbonate can be administered without the deleterious consequences of hypernatremia and fluid overload.

30.9.4.3 Cardiac Arrest

Bicarbonate therapy had been the standard treatment in cardiac arrest, but data has revealed that it is deleterious. The American Heart Association no longer recommends bicarbonate therapy in cardiac arrest. Bicarbonate therapy is particularly dangerous in metabolic acidosis if there is an additional component of respiratory acidosis. Bicarbonate therapy increases CO_2 production resulting in increased intramyocardial and cardiac venous pCO_2, lowering intracellular pH and reducing cardiac function.

Bicarbonate therapy is not recommended in the treatment of cardiac arrest.

A central venous blood gas may be helpful to assess if bicarbonate therapy is resulting in increased CO_2 retention.

30.10 Metabolic Alkalosis

Metabolic alkalosis is defined as an arterial pH greater than 7.44 associated with an increase in plasma bicarbonate. Severe alkalosis is defined as an arterial pH exceeding 7.55. The normal respiratory response to metabolic alkalosis is to decrease ventilation, though in the absence of oxygen supplementation, this response is limited by hypoxemia from hypoventilation. In the presence of oxygen supplementation as occurs in the PICU, this hypoventilation response is not blunted. An increase in $PaCO_2$ of 0.5–0.7 mmHg can be expected for every 1 mEq/L increase in bicarbonate. For arterial pH to exceed 7.55 in the presence of a normal respiratory response in supplemental oxygen, the serum bicarbonate would have to exceed 45 mEq/L. An abnormal respiratory response would result in a mixed acid-base disorder.

Metabolic alkalosis is primarily due to two causes: either chloride depletion (chloride-sensitive alkalosis) or potassium depletion (chloride-resistant alkalosis) (► Box 30.8). Excess bicarbonate administration alone usually does not result in sustained alkalosis unless there is renal dysfunction as excess bicarbonate would be excreted in the urine. In order for a sustained alkalosis to develop, there must be both a mechanism of generating bicarbonate and an ongoing renal mechanism to reclaim bicarbonate and prevent bicarbonate excretion. An alkalosis can be generated by either proton loss via gastric acid secretion or urinary NH_4 losses or excess base gain by alkali administration or dissolution of bone apatite. Maintenance of alkalosis results from a paradoxical aciduria with ongoing renal bicarbonate reabsorption.

The normal respiratory response to metabolic acidosis is for the $PaCO_2$ to increase by 0.5–0.7 mmHg for each 1 mEq/L rise in serum bicarbonate.

Patients with a sustained metabolic alkalosis usually have a paradoxical aciduria.

Box 30.8 Etiology of Alkalosis

1. Chloride depletion (chloride-sensitive alkalosis).
   (a) Gastric losses: Repeated emesis, nasogastric suctioning, bulimia.
   (b) Chloruretic diuretics: Loop diuretic, thiazide diuretics.
   (c) Diarrheal states: Congenital chloride diarrhea, villous adenoma, post-hypercapnic state.
   (d) Dietary chloride deprivation: Chloride-deficient infant formula.
   (e) Gastrocystoplasty.
   (f) Cystic fibrosis: High sweat chloride losses.
2. Potassium depletion/mineralocorticoid excess.
   (a) Primary hyperaldosteronism.
   (b) Apparent mineralocorticoid excess: Hydroxylase deficiencies, excess licorice (glycyrrhizic acid), Liddle syndrome.
   (c) Secondary aldosteronism: Adrenal corticosteroid excess.
   (d) Bartter and Gitelman syndromes.
3. Hypercalcemic syndromes.
   (a) Milk alkali syndrome.
   (b) Hypercalcemia of malignancy.
4. Other.
   (a) Penicillin antibiotics.
   (b) Bicarbonate administration with renal failure.
   (c) Recovery from starvation.

30.10.1 Chloride-Sensitive Alkalosis

The primary cause of severe alkalosis in the critical care setting that may require immediate therapy is due to chloride depletion from either massive gastric secretion loss or diuretic administration. Bicarbonate generated as a consequence of gastric acid losses to maintain electroneutrality, such as that seen with persistent emesis, can result in severe alkalosis. Loop and thiazide diuretics, which function by inhibiting chloride reabsorption, causes urinary losses of sodium, chloride, and water resulting in severe alkalosis. Diuretics increase sodium delivery to the distal nephron, leading to increased sodium-potassium and sodium-hydrogen exchange causing accelerated urinary potassium and proton secretion. The accompanying extracellular volume depletion stimulates increased renin and aldosterone release which further causes urinary potassium and proton secretion. Potassium depletion augments bicarbonate reabsorption in the proximal tubule and stimulates urinary NH_4 excretion. Aggressive diuretic use in edematous states, with a combination of a loop diuretic and metolazone, can cause a rapid decrease in the extracellular volume and the volume of distribution of bicarbonate resulting in a "contraction alkalosis."

A urine chloride less than 10 mEq/L is suggestive of chloride-sensitive alkalosis.

In conditions of chloride depletion, the alkalosis is maintained by a combination of volume depletion, which increases proximal tubule reabsorption of bicarbonate, and chloride depletion, which results in decreased distal tubule delivery of chloride that ultimately impairs distal tubule bicarbonate excretion. Chloride depletion, and not volume depletion, is the primary mechanism sustaining the alkalosis as the alkalosis can be corrected with chloride replacement in the absence of volume repletion. Chloride depletion alkalosis can usually be diagnosed by measuring the urinary chloride concentration, which is usually less than 10 mEq/L.

30.10.2 Chloride-Resistant Alkalosis

In chloride-resistant alkaloses, chloride deficiency plays no role in accelerated tubular H+ secretion and subsequent bicarbonate reabsorption. There is no loss of chloride-rich fluid, and usually no volume depletion. The main abnormalities seen in chloride-resistant alkalosis are mineralocorticoid excess and/or hypokalemia. The combination of hypokalemia and mineralocorticoid excess results in a moderate alkalosis. In general, the alkalosis seen from mineralocorticoid excess is usually not severe. Mineralocorticoid excess can be primary, as seen with primary hyperaldosteronism with suppressed renin, or secondary, as seen with Bartter's and Gitelman's syndrome with elevated renin and aldosterone concentrations. Mineralocorticoid excess stimulates sodium reabsorption and further potassium and proton secretion. In chloride-resistant alkalosis, the urinary chloride is typically greater than 30 mEq/L, and there is hypokalemia with ongoing urinary potassium losses.

Severe hypokalemia results in potassium movement from cells and reciprocal entry of Na + and H+. This intracellular H+ entry raises plasma HCO_3-. At the tubular level, the increased intracellular H+ facilitates tubular H+ secretion that further augments the alkalosis.

Hypokalemia is the main contributing factor to metabolic alkalosis when volume expansion with saline is ineffective.

30.10.3 Post-hypercapnic Metabolic Alkalosis

Chronic respiratory acidosis results in a compensatory metabolic alkalosis whereby there is an increase in renal H^+ excretion with obligate retention of bicarbonate. In addition, co-excretion of Cl^- with H^+ may also lead to hypochloremia. This results in a state of total body HCO_3^- excess and Cl^- depletion. The rapid correction of hypercapnia results in post-hypercapnic metabolic alkalosis as the nephron is unable to rapidly excrete the previously retained bicarbonate. Thus, it is imperative that correction of chronic CO_2 retention occurs slowly. Rapid reduction of the pCO_2 may result in profound elevations in pH with concomitant deleterious physiologic effects. These include decreased coronary and cerebral blood flow, decreased oxygen release at distal tissues secondary to a leftward shift of the oxyhemoglobin dissociation curve, and decreased availability of ionized calcium. The renal response is to excrete $NaHCO_3$, but in order to achieve this, NaCl must be provided to prevent volume depletion. In the absence of NaCl administration, the alkalosis may persist as a result of volume contraction.

30.10.4 Adverse Clinical Effects of Alkalemia (▸ Box 30.9)

Severe alkalemia, arterial pH greater than 7.55, can have significant physiologic consequences. Alkalemia causes arteriolar constriction that may compromise cerebral and myocardial perfusion. Neurological symptoms include headache, tetany, seizures, confusion, apathy, and neuromuscular irritability. The systemic effects of respiratory alkalosis are more severe than metabolic alkalosis. Some of the neurological manifestations of metabolic alkalosis may be a consequence of associated electrolyte abnormalities such as hypocalcemia and hypokalemia. Severe alkalemia may also depress respiratory drive.

Severe alkalemia can decrease cerebral and cardiac perfusion.

Box 30.9 Adverse Clinical Effects of Alkalemia

1. Cardiovascular.
   (a) Arteriolar constriction with reduction in coronary artery blood flow.
   (b) Decreased ionized calcium with decreased myocardial inotropy.
   (c) Shifts oxyhemoglobin dissociation curve, reducing tissue oxygen release.
2. Respiratory.
   (a) Hypoventilation with attendant hypercapnia and hypoxemia.
3. Metabolic.
   (a) Stimulation of anaerobic glycolysis and organic acid production.
   (b) Hypokalemia.
   (c) Decreased plasma ionized calcium concentration.
   (d) Hypomagnesemia and hypophosphatemia.
4. Cerebral.
   (a) Reduction in cerebral blood flow.
   (b) CNS irritability with tetany, seizures, lethargy, delirium, and stupor.

30.10.5 Treatment of Metabolic Alkalosis

The treatment of metabolic alkalosis largely depends on the etiology. The underlying cause of alkalosis should be determined and corrected. Usual therapies include correction of volume depletion, chloride depletion, and potassium depletion and promoting bicarbonate excretion.

If volume depletion is present, then volume expansion with 0.9% sodium chloride is indicated. If alkalosis and volume depletion are due to large amounts of gastric drainage, a proton pump inhibitor may be helpful. If diuretics are the cause, then decreasing the diuretic dose or temporarily discontinuing the diuretic may be necessary. A chloride-sensitive alkalosis generally responds to sodium chloride and potassium chloride supplementation. In cases of severe life-threatening alkalemia (pH >7.6) where sodium chloride may be contraindicated, such as with congestive heart failure, hydrochloric acid (HCl) administration may be warranted. HCl is sclerosing and hyperosmolar and should not be infused through a peripheral line. A 1 mEq/kg dose of HCl lowers the plasma bicarbonate by about 2 mEq/L. Alternatively, ammonium chloride can be used to correct severe hypochloremic alkalosis. Acetazolamide, a carbonic anhydrase inhibitor, can be useful in managing a metabolic alkalosis where large amount of saline may be contraindicated such as in the edematous patient. Acetazolamide inhibits proximal sodium bicarbonate reabsorption, thereby aiding in the correction of both the alkalosis and the fluid overload.

A chloride-resistant alkalosis that is primarily due to potassium depletion generally responds well to potassium chloride supplementation. Potassium chloride should preferably be administered by the oral route divided in three to five daily doses. In the diuretic-dependent patient, the addition of a potassium-sparing diuretic such as spironolactone may be useful in preventing ongoing potassium loss.

Review Questions

1. A 10 kg child is admitted for isonatremic dehydration. Following an initial fluid bolus total of 40 mL/kg, the remaining deficit should be replaced with what type of continuous intravenous fluids?
   A. 0.2% normal saline
   B. 0.2% normal saline with 40 mEq of sodium acetate added to each liter of fluid
   C. 0.45% normal saline
   D. 0.45% normal saline with 10 mEq of sodium acetate added to each liter of fluid
   E. 0.9% normal saline.

2. A neurosurgical patient develops hypernatremia while receiving 0.9% normal saline. Which of the following is the MOST effective way of diagnosing diabetes insipidus in this setting?
   A. Measuring a plasma copeptin level.
   B. Measuring a spot urine osmolality.
   C. Measuring urine tonicity (sodium + potassium).
   D. Measuring urine volume.
   E. Performing magnetic resonance imaging (MRI) of the hypothalamus and pituitary.

3. Which of the following is the single most important factor in the development of hospital-acquired hyponatremia?
   A. Cardiac disease.
   B. Fluid retention.
   C. Hypotonic fluid administration.
   D. Renal disease.
   E. Subclinical volume depletion.

4. A 5 kg infant with bronchiolitis is transferred to the pediatric intensive care unit actively seizing and is found to have a serum sodium of 123 mEq/L. Which of the following is the MOST appropriate therapy?
   A. 0.9% normal saline bolus (10 mL/kg)
   B. 3% normal saline bolus of 10 mL over 10 min
   C. 3% normal saline infusion at 5 mL/h
   D. Intravenous lorazepam (0.5 mg).
   E. Intravenous mannitol (5 g) over 15 min.

5. A patient with nephrotic syndrome is found to have a total serum calcium level of 6.8 mg/dL with a serum albumin of 2.0 g/dL. What is the corrected total serum calcium?
   A. 6.0
   B. 7.8
   C. 8.4
   D. 9.4
   E. 10.0.

6. Hypokalemia is MOST likely to produce a serious arrhythmia in the setting of which of the following clinical conditions?
   A. Cardiac disease.
   B. Hypocalcemia.
   C. Hyponatremia.
   D. Mitochondrial disease.
   E. Sepsis.

7. A 7-year-old male with a potassium level of 6.7 mEq/L developed significant changes on his electrocardiogram consisting of peaked T waves and prolongation of his QRS interval. Which of the following interventions is the MOST appropriate immediate course of action?
   A. Hemodialysis.
   B. Inhaled beta-adrenergic agonist.
   C. Intravenous calcium administration.
   D. Intravenous insulin and dextrose infusion.
   E. Sodium polystyrene resin retention enema.

8. A patient with nephrotic syndrome also has diarrhea and is found to have a total CO_2 of 12 mEq/L, serum albumin of 1.0 g/dL, and a calculated anion gap of 5 mmol/L. What is the corrected anion gap?
   A. 6
   B. 8
   C. 10
   D. 12
   E. 16

9. A 4-month-old is admitted to the pediatric intensive care unit following cardiopulmonary arrest. Point-of-care blood testing reveals a pH 7.01, $PaCO_2$ 32 mm Hg, PaO_2 347 mm Hg, base deficit (−27 mEq/L), hemoglobin of 9.7 g/dL, and an ionized calcium level of 1.05 mmol/L. The infant receives two 20 mL/kg fluid boluses of 0.9% normal saline, is treated with sodium bicarbonate (1 mEq/kg), and is started on an infusion of dobutamine. Repeat point-of-care testing reveals a pH 7.21, $PaCO_2$ 38 mm Hg, PaO_2 163 mm Hg, and a base deficit (−12). Assuming that no calcium was administered, and based solely on the blood gas result, the ionized calcium level on that point-of-care testing should MOST closely approximate which of the following?
   A. 0.73 mmol/L
   B. 0.85 mmol/L
   C. 1.05 mmol/L
   D. 1.20 mmol/L
   E. 1.37 mmol/L.

Answers

1. E
2. B
3. C
4. B
5. C
6. A
7. C
8. D
9. A

Suggested Reading

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