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Renal and Electrolyte Disorders

Chapter 31

OLIGURIA AND ACUTE RENAL FAILURE

Lack of urine output in the acute hypvolemic patient is renal success, not renal failure.
Ronald V. Maier, MD

An acute decrease in urine output can represent a functional adaptation, as Dr. Maier points out, but more often it represents trouble. The trouble is acute renal failure, which develops in about 5% of patients admitted to the ICU, and has a mortality rate of 60% 0). Acute renal failure is similar to the acute respiratory distress syndrome (ARDS) in that it is not a primary disease, but is a complication of other disease processes, most notably severe sepsis and septic shock (2,3). As a result, the mortality rate in acute renal failure mirrors the mortality rate of the primary diseases. Since these primary diseases have a high mortality, it is not surprising that the mortality rate in acute renal failure has not changed in the last 50 years (4), and that acute hemodialysis has had little or no impact on mortality. This latter observation seems to have escaped the notice of the "evidence-based medicine" crowd, who preach that an intervention should be discarded if it does not improve mortality.

GENERAL CONSIDERATIONS

Oliguria

Oliguria is traditionally defined as a urine output of less than 400 mL/ day (5), but no one waits 24 hours to make the diagnosis, so this translates to a urine output of less than 16.6 mL/hr. Another definition of oliguria, based on body weight, is a urine output less that 0.5 mL/kg/hr (2).

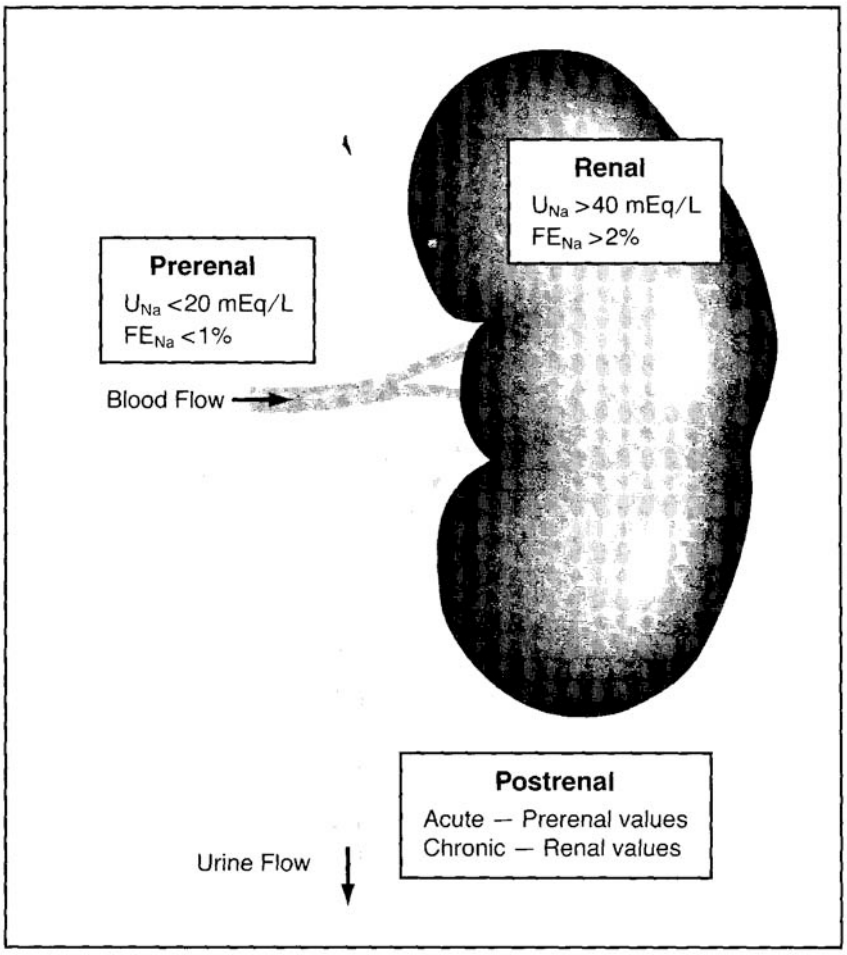

FIGURE 31.1 Classification of oliguria and acute renal failure based on the anatomic location of the problem.

The weight-based definition corresponds to a urine output of 35 to 40 mL!hr for a 70 to 80 kg adult, which is more than twice the urine output in the traditional definition of oliguria. The difference between these definitions is probably not significant (although this has never been addressed), but you should at least be aware that there is more than one definition of oliguria.

The causes of oliguria are traditionally separated into three categories, as illustrated in Figure 31.1. Each category is named according to the anatomic location of the problem responsible for the oliguria. The conditions in each category that are encountered in ICU patients are listed in Table 31.1.

TABLE 31.1 Causes of Acute 9liguria in the ICU

Prerenal Disorders	Renal Injury	Postrenal Obstruction
Hypovolemia	Circulatory shock	Papillary necrosis
Mechanical ventilation	Severe sepsis	Retroperitoneal mass
Cardiomyopathy	Muhiorgan failure	Urethral stricture
Aortic stenosis	SL!rgeryt	Prostatic hypertrophy
Dissecting aneurysm	Drugs and toxins*	
Drugs that impair renal autoregulation*	Myoglobinuria	
	Radiocontrast dye	

'Includes nonsteroidal antiinflammatory agents (ketorolac), angiotensin-enzyme inhibitors, and angiotensin receptor
t Cardiac surgery and abdominal aortic aneurysm
t Includes nephrotoxic drugs (amin,?glycosides, amphotericin, cisplatin), drugs acute interstitial nephritis (see Table 31.4), and nephrotoxins (e.g., ethylene

Pre renal Conditions

The prerenal sources of oliguria are located proximal to the kidneys and are characterized by a decrease in renovascular flow. The disorders in this category include low cardiac output from hypovolemia, mechanical ventilation, aortic stenosis, and end-stage cardiomyopathy, as well as drugs that impair renal autoregulation (e.g., angiotensin-converting enzyme inhibitors). Prerenal disorders are responsible for about 30 to 40% of cases of oliguria in the ICU (3). The oliguria in these conditions can usually be corrected by correcting the underlying disorder, but prolonged or severe prerenal conditions can lead to renal injury and oliguric renal failure.

Renal Injury

The intrinsic renal disorders encountered in the ICU usually fall into two categories: acute tubular necrosis (ATN), or acute interstitial nephritis (AIN). ATN is responsible for over 50% of cases of acute oliguria in the ICU (3), and is most often caused by inflammatory injury (including sepsis), circulatory shock, and toxic injury from drugs (e.g., aminoglycosides), radiocontrast dye, and myoglobinuria. ATN is described briefly below, while AIN is described later in the chapter.

ATN and GFR

ATN is characterized by (oxidative) injury to the renal tubular epithelial cells with sloughing of the cells into the lumen of the renal tubules (see Fig. 31.2). The sloughed cells create an obstruction that increases the pressure in the proximal tubules. This decreases the net filtration pressure across the glomerular capillaries and reduces the glomerular filtration rate (GFR). This process is called *tubulo-glomerular feedback.*

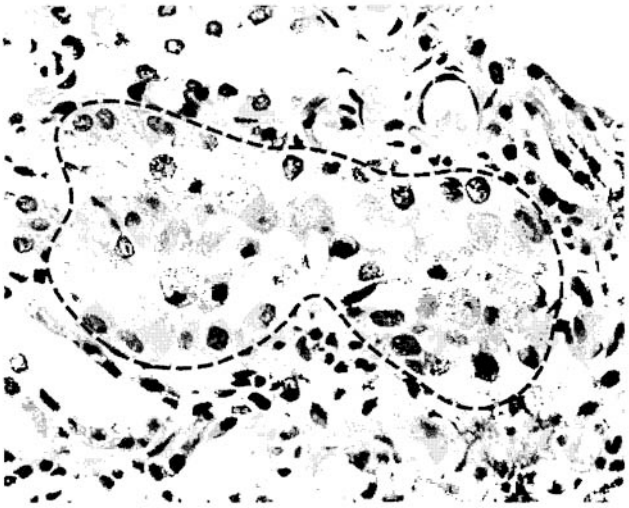

FIGURE 31.2 Photomicrograph of acute tubular necrosis (ATN) showing a proximal tubule (outlined by the dotted line) filled with exfoliated epithelial cells. (From Racusen LC. Histopathology of acute renal failure. New Horiz 1995;3:662–668.)

Postrenal Obstruction

Obstruction distal to the renal parenchyma is responsible for only about 10% of cases of oliguria in the ICU (3). The obstruction can involve the most distal portion of the renal collecting ducts (papillary necrosis), the ureters (extraluminal obstruction from a retroperitoneal mass), or the ureters (strictures or extraluminal obstruction from prostatic enlargement). Ureteral obstruction from stones does not cause oliguria unless there is a solitary functional kidney.

EVALUATION OF OLIGURIA

The initial evaluation of the oliguric patient should be aimed at identifying prerenal or reversible causes of oliguria. Prompt evaluation is necessary because prolonged or severe prerenal conditions can lead to oliguric renal failure, which is not immediately reversible. The following measurements can help to distinguish between prerenal and renal causes of oliguria.

Central Venous Catheters

Most patients in the ICU will have a central venous catheter, and these catheters permit 2 measurements that are useful in the evaluation of oliguria. The first measurement is the central venous pressure (CVP). The CVP will overestimate cardiac filling volumes in critically ill patients (as described in Chapter 12), but a central venous pressure that is very low 0-2 mm Hg) can be used as evidence of hypovolemia. In ventilatordependent patients, a CVP as high as 10 to 12 mm Hg could represent

hypovolemia and, in these patients, the respiratory variation in blood pressure should be examined for evidence of hypovolemia (see below). The other measurement available with CVP catheters is the *central venous oxyhemoglobin saturation* ($Scv0_2$), which is described in Chapter 11. An $Scv0_2$ that is below 50% can indicate a low cardiac output (when the arterial O_2 saturation and hemoglobin levels are normal), and an $Scv0_2$ that is close to 25 or 30% is probable ~vidence of a low cardiac output (unless the patient is severely anemic). In patients with systemic sepsis, an $Scv0_2$ below 70% is considered abnormal (6).

Respiratory Variation in Blood Pressure
As explained in Chapters 1 and 24, positive-pressure lungs inflations during mechanical ventilation will augment cardiac stroke output and increase the systolic blood pressure (see Fig. 1.5), but only when cardiac filling volumes are adequate. When cardiac filling volumes are inadequate, positive-pressure lung inflations will reduce the cardiac stroke output and decrease the systolic blood pressure. Therefore in ventilatordependent patients, a decrease in blood pressure shortly after each lung inflation can be used as evidence of inadequate cardiac filling.

Evaluation of the Urine
Urine Microscopy
Microscopic examination of the urine sediment is the easiest and least expensive diagnostic procedure. The presence of abundant tubular epithelial cells with epithelial cell casts is virtually pathognomonic of ATN. In addition, the presence of white cell casts identifies an interstitial nephritis, and the presence of pigmented casts identifies myoglobinuria. If urine microscopy is unrevealing, measuring the sodium concentration in a spot urine sample can be useful.

Spot Urine Sodium
When renal perfusion is diminished, sodium reabsorption increases and urinary sodium excretion decreases. On the other hand, intrinsic renal disease is usually accompanied by a decrease in sodium reabsorption and an increase in sodium excretion in the urine. Therefore, in the setting of oliguria, a urine sodium below 20 mEq/L usually indicates a prerenal condition (5). However, a urine sodium above 40 mEq/L does not rule out a prerenal condition when it is superimposed on an underlying case of chronic renal insufficiency (where there is obligatory sodium loss in the urine), or when there is ongoing diuretic therapy. Elderly patients can also have an obligatory loss of sodium in the urine. Therefore, a urine sodium above 40 mEq/L must be interpreted according to the clinical setting.

Fractional Excretion of Sodium
The fractional excretion of sodium (FE_{Na}) is the fraction of sodium filtered at the glomerulus that is excreted in the urine. This is equivalent to the sodium clearance divided by the creatinine clearance, as shown in

TABLE 31.2 Quantitative Assessment of Renal Function

Creatinine Clearance (Men):

CL (Cr mL/ min) = (140 - age) x weight (kg) / 72 x Serum creatinine (mg/dL)

Creatinine Clearance (Women):'

CLCr (mL/min) = 0.85 x CLCr for men

Fractional Excretion of Sodium:
FE_{Na} = Urine [Na] / Plasma [Na] / Urine [Cr] / Plasma [Cr] x 100

Table 31.2 (7). The FE_{Na} is normally less than 1 %; i.e., less than 1 % of the filtered sodium is excreted in the urine. In the setting of oliguria, the FEN. provides the following information:
FEN_{Na} < 1 % = probable prerenal condition

FE_{Na} > 2% = probable renal injury

There are some exceptions to these criteria: e.g., the FE_{Na} can be less than 1 % in ATN due to myoglobinuria (5). Despite the occasional exception, the FE_{Na} is one of the most reliable urinary parameters for distinguishing prerenal from renal causes of oliguria. However, it is a cumbersome determination to perform, and this limits its popularity.

Serum Creatinine Concentration

A *change* in the serum creatinine concentration can be used to identify patients with renal injury and renal failure (2) as shown in Table 31.3. The serum creatinine can also be used to calculate the creatinine clearance, as shown in Table 31.2 (8). The creatinine clearance overestimates the GFR because creatinine is secreted by the renal tubules. However, changes in creatinine clearance can be used to track changes in GFR. The changes in creatinine clearance expected in acute renal failure are shown in Table 31.3.

TABLE 31.3 Criteria for the Diagnosis of Acute Renal Injury and Acute Renal Failure

Condition	Serum Creatinine	Creatinine Clearance
Renal Injury	2 x baseline	>50% decrease
Renal Failure	3 x baseline or acute rise >=0.5 mgldL to >=4 mgldL	>= 75% decrease

From Reference 2.

INITIAL MANAGEMENT

The principal task in the early management of the oliguric patient is to identify and correct volume deficits and discontinue any drugs that could be a source of oliguric renlll failure.

Fluid Challenge

If there is evidence or suspicion of inadequate ventricular filling based on the evaluation described in the last section, then immediate volume infusion is warranted. Fluid challenges of 500 mL to 1,000 mL for crystalloid fluids and 300 mL to 500 mL for colloid fluids, infused over 30 minutes, have been proposed for patients with severe sepsis and septic shock (9), and these recommendations can be applied to all patients who require volume infusion. The fluid challenges are continued until there is a response or until you are concerned about volume overload.

There is no evidence to favor crystalloid or colloid fluids for volume infusions. Colloid fluids are more likely to expand the plasma volume and less likely to expand the extracellular fluid volume than crystalloid fluids (see Chapter 13). In patients with hypoalbuminemia, 5% albumin should be seriously considered for volume resuscitation.

Don't Use Low-Dose Dopamine

Despite more than thirty years of use as a renal vasodilator, low-dose dopamine (2 μg/kg/min) has shown no evidence of benefit in patients with acute oliguric renal failure. In fact, low-dose dopamine can have deleterious effects on hemodynamics (decreased splanchnic blood flow) immune function (inhibition of T-cell lymphocyte function) and endocrine function (inhibition of thyroid-stimulating hormone release from the pituitary) (1). For these reasons, the use of low-dose dopamine in patients with acute oliguria is (borrowing the title from reference 11) *bad medicine.*

Furosemide

In patients with acute oliguric renal failure, there is little or no chance of increasing urine output with furosemide because less than 10% of the injected drug will reach the site of action in the renal tubules (2). If furosemide is used in an attempt to promote urine flow, it should be given by continuous infusion as described in Chapter 14.

SPECIFIC RENAL DISORDERS

Inflammatory Renal Injury

Acute, oliguric renal failure is reported in about 25% of patients with severe sepsis and 50% of patients with septic shock (3). It also occurs in patients with systemic inflammation without evidence of infection

(see Chapter 40). In these clinical settings, acute renal failure appears to be just one part of a more widespread systemic illness associated with dysfunction and failure in multiple organs (4). The culprit in these conditions is the inflammatory response, which has been called *malignant intravascular inflammation* (5). The management of this condition is supportive, and is described in Chapter 40.

Contrast-Induced Renal Failure

Iodinated radiocontrast agents can produce acute renal injury and renal failure, and contrast-induced nephropathy is now considered the third leading cause of acute renal failure in hospitalized patients (6). The renal injury usually becomes apparent as a rising serum creatinine within 72 hours after the procedure. Predisposing conditions include diabetes, hypertension, pre-existing renal disease, congestive heart failure, and the osmolality and volume of iodinated contrast agent used during the procedure. Oliguria is uncommon, but can occur in patients with preexisting renal disease. Most cases resolve within 2 weeks, and few require hemodialysis (6). The mechanism of renal injury is multifactorial, and includes hyperosmolar injury to the endothelium of small vessels in the kidney, and oxidative injury to the renal tubular epithelial cells.

Prevention

The most effective strategy for prevention of contrast-induced nephropathy in high-risk patients is intravenous hydration (if permitted) combined with the antioxidant N-acetylcysteine. The following regimen is recommended 06,17):

Volume infusion: Isotonic saline at 100 to 150 mL/hr started at 3 to 12 hours before the procedure. For emergent procedures, at least 300 to 500 mL isotonic saline should be infused just prior to the procedure. Urine output should be maintained at 150 mL/hr for at least 6 hours after the procedure (6).

N-acetylcysteine: 600 mg by mouth twice daily from 24 hours before, to 24 hours after, the procedure (6), or for emergent procedures such as primary angioplasty, 600 mg IV just before the procedure and 600 mg orally twice daily for 48 hours after the procedure (8).

N-acetylcysteine is an intracellular glutathione surrogate that is used as the antidote for acetaminophen hepatotoxicity (see Chapter 53). Oral administration of N-acetylcysteine is poorly tolerated because the sulfur content has a pungent taste (like rotten eggs). Irrtravenous N-acetylcysteine was recently approved for use in acetaminophen overdose, and is considered safe except for rare cases of anaphylaxis.

The physician performing the contrast procedure should be informed when patients are at risk for contrast-induced nephropathy. Although contrast agents with reduced osmolality are now used routinely to limit the risk of contrast-induced nephropathy, limiting the volume of the contrast agent to 100 mL is also beneficial (6).

TABLE 31.4 Drugs That Can Cause Interstitial Nephritis

Antibiotics	*CNS Drugs*	*Diuretics*
Aminoglycosides	Carbamazepine	Acetazolamide
Amphotericin B	Phenobarbital	Furosemide
Cephalosporins	Phertttoin	Thiazides
Fluoroquinolones	*NSAIDs*	*Others*
Penicillins	Aspirin	Acetaminophen
Sulfonamides	Ibuprofen	ACE Inhibitors
Vancomycin	Ketorolac	Iodinated dyes
	Naproxen	Ranitidine

NSAIDs = nonsteroidal antiinflammatory drugs, *ACE* = angiotensin-converting

Acute Interstitial Nephritis (AIN)

AIN is an inflammatory condition that involves the renal interstitium and presents as acute renal failure, usually without oliguria. Most cases are the result of a hypersensitivity drug reaction, but infections (usually viral or atypical pathogens) can also be involved. The drugs most often implicated in AIN are listed in Table 31.4. Antibiotics are the most common offenders, particularly the penicillins.

AIN can be difficult to distinguish from ATN. In cases of druginduced AIN, the characteristic signs of a hypersensitivity reaction (e.g., fever, rash, eosinophilia) may not be present. The onset of renal injury usually occurs within 2 weeks after starting the drug, but delayed reactions occurring months after the onset of drug therapy have been reported (7). The presence of eosinophils and leukocyte casts on urine microscopy are the most characteristic diagnostic findings. A renal biopsy can secure the diagnosis, but is rarely obtained.

In suspected cases of AIN, any possible offending agents should be discontinued. Oral prednisone at a dose of 0.5 to 1 mg/kg daily for one to four weeks may help to speed recovery 09,20). Complete resolution can take months.

Myoglobinuric Renal Failure

Acute renal failure develops in about one-third of patients with diffuse muscle injury (rhabdomyolysis) (21,22). The culprit is myoglobin, which is released by the injured muscle and is capable of damaging the renal tubular epithelial cells after it is filtered through the glomerulus. The source of cell injury may be the iron moiety in heme (23), which is capable of oxidative cell injury via the production of hydroxyl radicals (see Chapter 21, Fig. 21.5). This would also explain why hemoglobin can produce a similar type of renal tubular injury.

The common causes of rhabdomyolysis are trauma, infection, immobility (in alcoholics), drugs (e.g., lipid lowering agents) and electrolyte abnormalities (e.g., hypophosphatemia). The risk of renal failure is not related to any single abnormality, but is more likely when there is a combination of abnormalities. For example, one study of trauma victims with rhabdomyolysis revealed that the best predictor of acute renal failure was the combination of a serum creatinine> 1.5, a creatine kinase (CPK) >5,000 IU /L, a base deficit <=4, and myoglobin in the urine (23). The serum creatinine is not an accurate index of renal function in rhabdomyolysis because the enhanced creatine release from skeletal muscle adds to the serum creatinine. The principal conditions that predispose to renal injury are hypovolemia and acidosis.

Myoglobin in Urine

Myoglobin can be detected in urine with the orthotoluidine dipstick reaction (Hemastix) that is used to detect occult blood in urine. If the test is positive, the urine should be centrifuged (to separate erythrocytes) and the supernatant should be passed through a micropore filter (to remove hemoglobin). A persistently positive test after these measures is evidence of myoglobin in urine.

The presence of myoglobin in urine does not identify patients with a high risk of renal injury, but the absence of myoglobin in urine identifies patients with a low risk of renal injury (22).

Management

The plasma levels of potassium and phosphate must be monitored carefully in rhabdomyolysis because these electrolytes are released by injured skeletal muscle and the concentration in plasma can increase dramatically, especially when renal function is impaired. Aggressive volume resuscitation to prevent hypovolemia and maintain renal blood flow is one of the most effective measures for preventing or limiting the renal injury in rhabdomyolysis. Alkalinizing the urine can also help to limit the renal injury, but this is difficult to accomplish and is often not necessary. About 30% of patients who develop myoglobinuric renal failure will require dialysis (22).

RENAL REPLACEMENT THERAPY

About 70% of patients with acute renal failure will require some form of renal replacement therapy (RRT). The usually indications for RRT are volume overload, uremic encephalopathy, and difficult-to-control hyperkalemia and metabolic acidosis. There is a growing body of RRT techniques, including hemodialysis, hemofiltration, hemodiafiltration, high flux dialysis, and plasma filtration. Each employs a different method of water and solute transport. The presentation that follows is limited to the techniques of hemodialysis and hemofiltration.

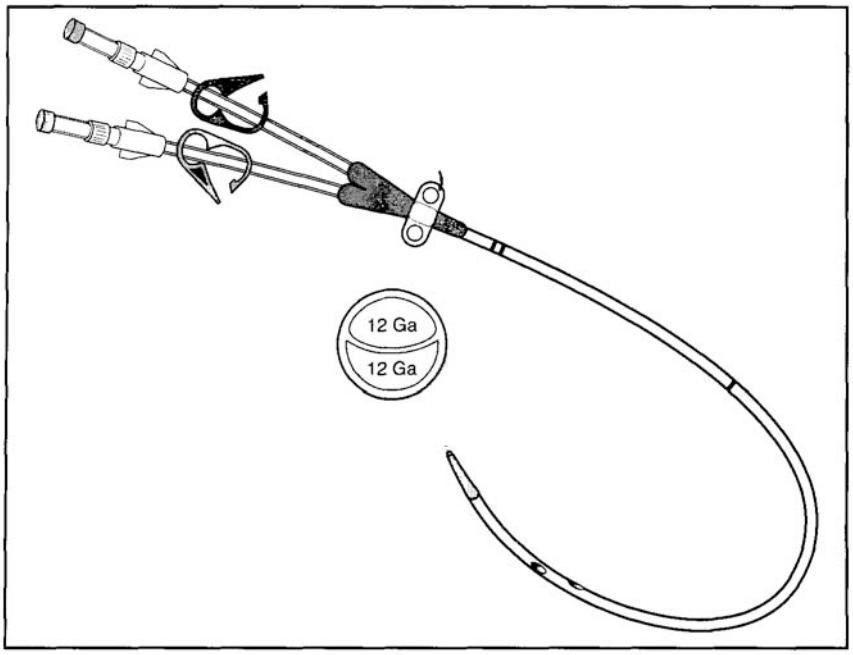

FIGURE 31.3 A double lumen venous catheter used for hemodialysis. The internal diameter of each lumen is about twice the diameter of each lumen in a triple-lumen central venous catheter (see Figure 6.4).

Hemodialysis

Hemodialysis removes solutes by diffusion, which is driven by the concentration gradient of the solutes across a semipermeable membrane. To maintain this concentration gradient, blood and dialysis fluid are driven in opposite directions across the diffusional barrier (dialysis membrane): this technique is known as *countercurrent exchange* (24). A blood pump is used to move blood in one direction across the dialysis membrane at a rate of 200 to 300 mL/min. The dialysis fluid on the other side of the membrane moves twice as fast, or at 500 to 800 mL/min (24).

Vascular Access

A large-bore, double-lumen vascular catheter like the one shown in Figure 31.3 is required to perform intermittent hemodialysis. Each lumen of the catheter in this figure has a diameter that is roughly twice the diameter of each lumen in a standard central venous catheter (see the triplelumen catheter in Figure 6.4 and compare lumen sizes using Table 6.1). Because flow through rigid tubes varies directly with the fourth power of the radius (see the Hagen-Poiseuille equation in Figure 1.6), a catheter lumen that is doubled in size will allow ($2^4 = 16$) a 16-fold greater flow

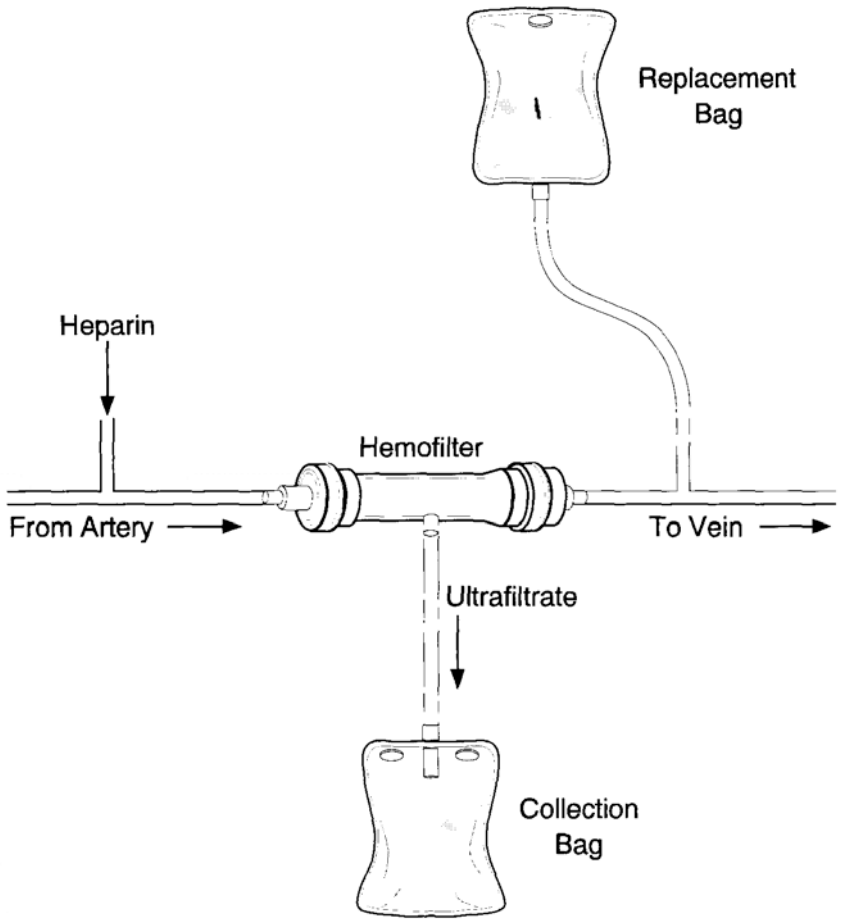

FIGURE 31.4 The technique of continuous arteriovenous hemofiltration (CAVH).

rate. The large-bore catheter in Figure 31.3 is thus well-suited for the high flow needed to perform intermittent hemodialysis. Blood is withdrawn from one lumen of the catheter, pumped through the dialysis chamber, and then returned to the patient through the other lumen.

The large-bore dialysis catheters are placed in either the internal jugular vein or the femoral vein. The subclavian vein is not recommended because there is a high incidence of vascular stenosis and this makes the ipsilateral arm veins unsuitable for chronic dialysis access if renal function does not recover (25). The internal jugular vein is preferred because of the risk for venous thrombosis with femoral vein cannulation (see Table 6.3), but awake patients are intolerant of the limited neck mobility associated with cannulation of the internal jugular vein with these largebore catheters.

BenifIts and Risks
The benefit of hemodialysis is rapid clearance of solutes. Only a few hours of dialysis is needed to remove a day's worth of accumulated nitrogenous waste. The disadvantage of dialysis is the need to maintain a blood flow of at least 300 mL/min through the dialysis chamber. This creates a risk of hypotension, which occurs in about one-third of intermittent hemodialysis treatments (24).

Hemofiltration
Whereas hemodialysis removes solutes by diffusion, hemofiltration uses *convection* for solute transport. Convection is a method where a solute-containing fluid is driven across a permeable membrane by exerting a pressure difference across the membrane. The solutes are cleared by the movement of the fluid across the membrane. Since the fluid "drags" the solute across the membrane, this method of solute transport is known as *solvent drag* (24). Because the removal of solutes by convection is relatively slow, hemofiltration is performed continuously.

Continuous Hemofiltration
One technique of continuous hemofiltration is illustrated in Figure 31.4. In this case, the hemofilter is placed between an artery and a vein, and the technique is called *continuous arteriovenous hemofiltration* (CAVH). No pumps are required for CAVH. The arteriovenous pressure difference is the pressure gradient for flow through the filter. The pressure gradient for water movement across the filter is the mean blood pressure on one side, and the vertical distance between the filter and the ultrafiltrate collection bag on the other side. If the collection bag is lowered, the filtration pressure will increase.
Hemofiltration can remove large volumes of fluid (up 3 liters per hour) so a replacement fluid is needed to prevent hypovolemia. This is shown in the CAVH circuit in Figure 31.4. The replacement fluid also decreases the plasma concentration of waste products that are removed in the ultrafiltrate. That is, the concentration of solutes in the ultrafiltrate is the same as in the blood, so the plasma concentration of waste products will not decrease unless a waste-free fluid is used to replace the fluid that is removed.

Benefits
Since hemofiltration is driven by pressure and not flow, high flow rates are not needed, and there is a much less risk of hypotension with CAVH. The removal of solutes is also more gradual and more physiological with continuous hemofiltration. One shortcoming of CAVH is that it is not suitable for use in patients with hypotension. The technique of *continuous venovenous hemofiltration* (CVVH) uses a pump to generate a pressure, and can be used in hypotensive patients.
In general, the benefits of continuous renal replacement therapy are leading to a gradual disappearance of intermittent hemodialysis in the ICU.

A FINAL WORD

A sudden and precipitous drop in urine output\is rarely a sign of simple dehydration that will be corrected with fluids. Instead, it is usually an ominous sign of failure involving of one of the major organ systems in the body. In the setting of sepsis, the appearance of oliguria usually heralds the beginning of multiple organ failure, which often has a fatal outcome. This condition of multiorgan failure, which can be viewed as the gradual process of dying (the more organs that fail, the closer the patient is to death), is described in Chapter 40.

REFERENCES

Chapter 32

HYPERTONIC AND HYPOTONIC CONDITIONS

This chapter describes the diagnosis and management of conditions associated with abnormalities in total body water. These conditions typically present with abnormalities in the plasma sodium concentration (hypernatremia and hyponatremia) that are sometimes mistaken as problems in sodium balance (1,2). This chapter presents a very simple approach to hypematremia and hyponatremia based on a clinical assessment of the extracellular volume. The very first part of the chapter contains a quick review of the determinants of water movement between fluid compartments.

BASIC CONCEPTS

The following is a description of the forces that determine the movement of water between the intracellular and extracellular fluid compartments.

Osmotic Activity

The activity (concentration) of solute particles in a solution is inversely related to the activity (concentration) of water molecules in the solution. The solute activity in a solution is also called the *osmotic activity* and is expressed in osmoles (osm). The total osmotic activity in a solution is the sum of the individual osmotic activities of all the solute particles in the solution. For monovalent ions, the osmotic activity in milliosmoles (mOsm) per unit volume is equivalent to the concentration of the ions in milliequivalents (mEq) per unit volume. Thus, the osmotic activity in isotonic saline (0.9% sodium chloride) is as follows:

0.9% NaCl = 154 mEq *Na/L* + 154 mEq Cl/L
= 154 mOsm *Na/L* + 154 mOsm Cl/L
= 308mOsm/L

Osmolarity is the osmotic activity per volume of solution (solutes plus water) and is expressed as *mOsm/L* (3,4). Osmolality is the osmotic activity per volume of water and is expressed as mOsm/kg H_20. The osmotic activity of body fluids usually is expressed in relation to the volume of water (i.e., osmolality). However, the volume of water in body fluids is far greater than the volume of solutes, so there is little difference between the osmolality and osmolarity of body fluids. Thus, the terms osmolality and osmolarity can be used interchangeably to describe the osmotic activity in body fluids.

Tonicity

When two solutions are separated by a membrane that allows the passage of water but not solutes, the water passes from the solution with the lower osmotic activity to the solution with the higher osmotic activity. The *relative* osmotic activity in the two solutions is called the effective osmolality, or tonicity. The solution with the higher osmolality is described as hypertonic, and the solution with the lower osmolality is described as hypotonic. Thus, the tendency for water to move into and out of cells is determined by the relative osmolality (tonicity) of the intracellular and extracellular fluids.

When the membrane separating two fluids is permeable to both solutes and water, and a solute is added to one of the fluids, the solute equilibrates fully across the membrane. In this situation, the solute increases the osmolality of both fluids, but there will be no movement of water between compartments (because there is no difference in osmolality between the two compartments). A solute that behaves in this manner is urea, which is freely permeable across cell membranes. Therefore, an increase in the urea concentration in extracellular fluid (i.e., an increase in the blood urea nitrogen or BUN) will increase the osmolality of the extracellular fluid, but this does not draw water out of cells because urea does not create a difference in osmolality between extracellular and intracellular fluid. Thus, azotemia (increased BUN) is a hyperosmotic condition, but not a hypertonic condition.

Plasma Osmolality

The osmolality of the extracellular fluids can be measured in the clinical laboratory using the freezing pDInt of plasma (a solution containing *1 osm/L* will freeze at -1.86° C). This is the *freezing pDInt depression* method for measuring osmolality.

The osmolality of the extracellular fluids can also be calculated using the concentrations of sodium, chloride, glucose, and urea in plasma (these are the major solutes in extracellular fluid). The calculation below uses a plasma sodium (Na+) of 140 mEq/L, a plasma glucose of 90 mg/dL, and a BUN of 14 mgldL (3,5).

Plasma osmolality = (2 X Plasma Na+) + Glucose/18 + BUN/2.8

= (2 X 140) + 90/18+ 14/2.8
= 290 mOsm/kg HzO

The sodium concentration is doubled to include the osmotic contribution of chloride. The serum glucose and urea are measured in milligrams per deciliter, and the factors 18 and 2.8 (the atomic weights divided by 10) are used to convert *mg/* dL to mOsm/kg H_2O.

Osmolal Gap

Because solutes other than sodium, chloride, glucose, and urea are present in the extracellular fluid; the measured plasma osmolality will be greater than the calculated plasma osmolality. This osmolar gap (i.e., the difference between the measured and calculated plasma osmolality) is normally as much as 10 mOsm/kg H_2O (3,5). An increase in the osmolar gap occurs when certain toxins (e.g., ethanol, methanol, ethylene glycol, or the unidentified toxins that accumulate in renal failure) are in the extracellular fluid (6). Therefore, the osmolar gap has been proposed as a screening test for identifying the presence of tdxins in the extracellular fluid. In the case of renal failure, the osmolar gap has been recommended as a reliable test for distinguishing acute from chronic renal failure: the osmolar gap is expected to be normal in acute renal failure and elevated in chronic renal failure (7). In reality, the osmolar gap is used infrequently.

Plasma Tonicity

Because urea passes freely across cell membranes, the effective osmolality or tonicity of the extracellular fluid can be calculated by eliminating urea (BUN) from the plasma osmolality equation.

Plasma tonicity = (2 X Plasma Na+) +Glucose/18
= (2 X 140) + 90/18
= 285 mOsm/kg H2O

Because the concentration of urea contributes little to the total solute concentration in extracellular fluids, there is little difference between the osmolality and tonicity of the extracellular fluid. This equation establishes the plasma sodium concentration as the principal determinant of the effective osmolality of extracellular fluid. Because the effective osmolality determines the tendency for water to move into and out of cells, the plasma sodium concentration is the principal determinant of the relative volumes of the intracellular and extracellular fluids.

HYPERNATREMIA

The normal plasma (serum) sodium concentration is 135 to 145 mEq/L. Therefore, hypematremia (i.e., a serum sodium concentration above 145 mEq/L) can be the result of loss of fluid that has a sodium

TABLE 32.1 Change in Total Body Sodium and Water in Hypernatremia and Hyponatremia

Condition	Extracellular Volume	Total Body Sodium	Total Body Free Water
Hypernatremia	Decreased	decrease	decrease
	Normal	-	decrease
	Increased	increase +	increase
Hyponatremia	Decreased	decrease +	decrease
	Normal	-	increase
	Increased	increase	increase

concentration below 135 mEq/L (hypotonic fluid loss) or gain of fluid that has a sodium concentration above 145 mEq/L (hypertonic fluid gain). Each of these conditions can be identified by assessing the state of the extracellular volume as shown in Table 32.1 (1,8,9).

Extracellular Volume

If invasive hemodynamic monitoring is available, the state of the intravascular volume can be evaluated by the relationship between the cardiac filling pressures and the cardiac output. For example, the combination of reduced cardiac filling pressures and a low cardiac output is evidence of hypovolemia (see the section on *Hemodynamic Subsets* in Chapter 9). In the absence of hypoproteinemia (which shifts fluids from the intravascular to extravascular space), the state of the intravascular volume can be used as a reflection of the state of the extracellular volume (ECV).

If invasive hemodynamic monitoring is not available, the evaluation of hypovolemia described in Chapter 12 can be used to detect a decreased ECV. The clinical detection of an increased ECV can be difficult because the absence of edema does not exclude the presence of a high ECV (edema may not be apparent until the ECV has increased 4 to 5 liters) and the presence of edema can be misleading because edema in ICU patients can be the result of immobility, hypoalbuminemia, or venous congestion from high intrathoracic pressures (in ventilatordependent patients).

Once the state of the ECV is determined, the strategies shown in Figure 32.1 can be applied.

Low ECV indicates loss of hypotonic fluids. Common causes are excessive diuresis, vomiting, and diarrhea. The management strategy is to replace the sodium deficit quickly (to maintain plasma volume) and to replace the free water deficit slowly (to prevent intracellular overhydration).

Normal ECV indicates a net loss of free water. This can be seen in diabetes insipidus, or when loss of hypotonic fluids (e.g., diuresis) is

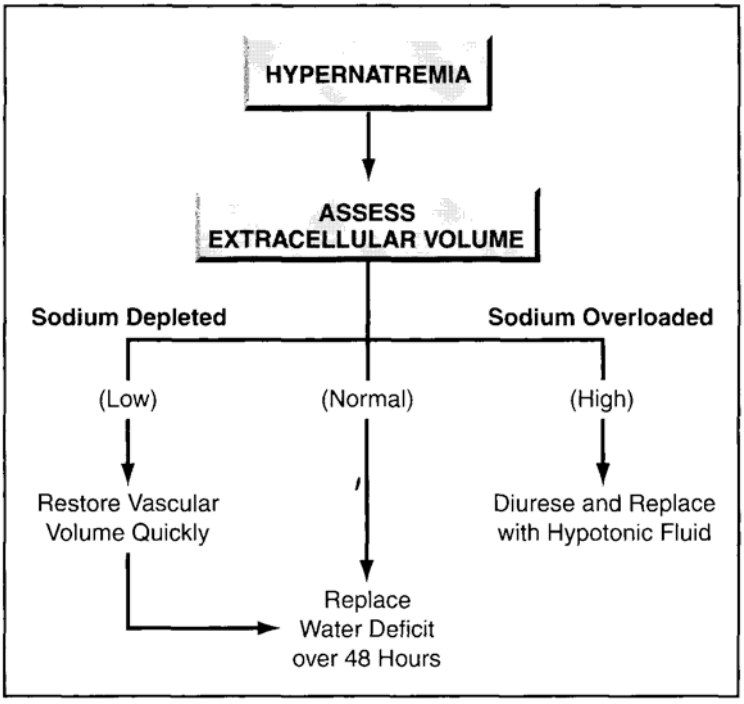

FIGURE 32.1 Management of hypernatremia based on the extracellular volume.

treated by replacement with isotonic saline in a 1:1 volume-to-volume ratio. The management strategy is to replace the free water deficit slowly (to prevent intracellular overhydration).

High ECV indicates a gain of hypertonic fluids. This is seen with aggressive use of hypertonic saline or sodium bicarbonate solutions. The management strategy is to induce sodium loss in the urine with diuresis and to replace the urine volume loss with fluids that are hypotonic to the urine.

Each of these conditions is described in more detail in the following sections.

HYPOVOLEMIC HYPERNATREMIA

The most common cause of hypernatremia is loss of hypotonic body fluids. The concentration of sodium in body fluids that are commonly lost is shown in Table 32.2. With the exception of small bowel and pancreatic secretions, loss of any of these body fluids will result in hypernatremia.

Consequences

All of the body fluids listed in Table 32.2 contain sodium, so the loss of these fluids will be accompanied by deficits in total body sodium as well

TABLE 32.2 Sodium Concentration in Body Fluids

Fluids Commonly Lost	Sodium Concentration (mEq/L)
Urine*	<10
Diarrhea	40
Gastric secretions	55
Sweat	80
Furosemide diuresis	75
Pancreatic secretions	145
Small bowel secretions	145

*Urinary sodium concentration varies according to daily sodium intake.

as total body water (TBW). The sodium deficits predispose to hypovolemia, whereas the free water deficits predispose to hypertonicity in the extracellular\fluids. Therefore, the two consequences of hypotonic fluid loss are hypovolemia and hypertonicity.

Hypovolemia
The most immediate threat with hypotonic fluid loss is hypovolemia, which predisposes to hypoperfusion of the vital organs (8,9). Fortunately, hypovolemia is not as prominent when hypotonic fluids are lost as when whole blood is lost. This is because the resultant hypertonicity draws water out of cells, and this helps maintain the volume of the extracellular (intravascular) fluid compartment.

Hypertonicity
The hypertonicity of the extracellular fluids predisposes to cellular dehydration. The most serious consequence of hypertonic hypernatremia is a metabolic encephalopathy (10). Clinical findings include depressed consciousness that can progress to frank coma, generalized seizures, and focal neurological deficits (10). Hypematremic encephalopathy has an associated mortality of up to 50% (10), but management should proceed slowly.

Volume Replacement
The most immediate concern in hypovolemic hypernatremia is to replace volume deficits and maintain the cardiac output. Volume replacement can be guided by the cardiac filling pressures, cardiac output, urine output, etc. When solute losses are severe and hemodynamic compromise is present, infusions of collDId fluids (5% albumin or 6% hetastarch) will restore the intravascular volume much more effectively than infusion of crystallDId fluids, as described in Chapter 13. When crystallDId fluids are used for volume resuscitation in hypertonic dehydration, isotonic fluids (e.g., 0.9% sodium chloride) are preferred to hypotonic fluids (e.g., halfnormal saline) to reduce the risk of cellular edema.

Free Water Replacement
When hypovolemia has been corrected, the next step is to calculate and replace the free water deficit. The calculation of free water deficit is based on the assumption that the product of TBW and plasma sodium concentration (P Na) is always constant.

Current TBW x Current P Na = Normal TBW x Normal P Na (

Substituting 140 mEq/L for a normal P_{Na} and rearranging terms yields the following relationship:

Current TBW = Normal TBW X (140/Current P_N) (32.5)

The normal TBW (in liters) is usually 60% of lean body weight (in kg) in men and 50% of lean body weight in women (11). However, in hypernatremia associated with free water deficits, the normal TBW should be approximately 10% less than usual (11). Thus in men, the normal TBW is 0.5 X body weight (kg), and in women, the normal TBW is 0.4 X body weight (in kg). Once the current TBW is calculated, the water deficit is taken as the difference between the normal and current TBW.

TBW deficit (L) = Normal TBW - Current TBW

Sample Calculation
Assume that an adult man with a lean body weight of 70 kg has a plasma sodium of 160 mEq/L. The normal TBW will be 0.5 X 70 = 35 L. The current TBW will be 35 X *140/160* = 30.5 L. The TBW deficit will be 35 - 30.5 = 4.5 L.
The volume needed to correct the water deficit is determined by the concentration of sodium in the replacement fluid. This volume can be determined as follows (12):

Replacement volume (L) = TBW deficit X *(1/1* - X)

where X is the ratio of the sodium concentration in the resuscitation fluid to the sodium concentration in isotonic saline (154 mEq/L). If the water deficit is 4.5 L and the resuscitation fluid is half-normal saline (Na = 75 mEq/L), the replacement volume will be 4.5 X *(1/0.5)* = 9 liters (or twice the free water deficit)

Cerebral Edema
The brain cells initially shrink in response to a hypertonic extracellular fluid, but cell volume is restored within hours. This restoration of cell volume is attributed to the generation of osmotically active substances called idiogenic osmoles (8). Once the brain cell volume is restored to normal, the aggressive replacement of free water can predispose to cerebral edema and seizures. To limit the risk of cerebral edema, **free water**

deficits should be replaced slowly so that serum sodium decreases no faster than 0.5 mEq/L per hour (typically requires 48 to 72 hours) (8,10).

HYPERTONIC SYNDROMES

Diabetes Insipidus

The most noted cause for hypernatremia without apparent volume deficits is diabetes insipidus (01), which is a condition of impaired renal water conservation (1,13,14). This condition results in excessive loss of urine that is almost pure water (devDId of solute). The underlying problem in 01 is related to antidiuretic hormone (ADH), a hormone secreted by the posterior pituitary gland that promotes water reabsorption in the distal tubule. Two defects related to ADH can occur in DI:

Central DI is caused by failure of ADH release from the posterior pituitary (15). Common causes of central or in critically ill patients include I:{aumatic brain injury, anoxic encephalopathy, meningitis, and brain death (16). The onset is heralded by polyuria that usually is evident within 24 hours of the inciting event.

Nephrogenic DI is caused by defective end-organ responsiveness to ADH. Possible causes of nephrogenic or in critically ill patients include amphotericin, dopamine, lithium, radio contrast dyes, hypokalemia, aminoglycosides, and the polyuric phase of ATN (14,17). The defect in urine concentrating ability in nephrogenic DI is not as severe as it is in central 01.

Diagnosis

The hallmark of or is a dilute urine in the face of hypertonic plasma. In central DI, the urine osmolarity is often below 200 *mOsm/L,* whereas in nephrogenic DI, the urine osmolarity is usually between 200 and *500 mOsmlL* (16). The diagnosis of or is confirmed by noting the urinary response to fluid restriction. Failure of the urine osmolarity to increase more than 30 *mOsm/L* in the first few hours of complete fluid restriction is diagnostic of DI. The fluid losses can be excessive during fluid restriction in or (particularly central DI), and thus fluid restriction must be monitored carefully. Once the diagnosis of DI is confirmed, the response to vasopressin (5 units intravenously) will differentiate central from nephrogenic DI. In central DI, the urine osmolarity increases by at least 50% almost immediately after vasopressin administration, whereas in nephrogenic DI, the urine osmolarity is unchanged after vasopressin.

Management

The fluid loss in DI is almost pure water, so the replacement strategy is aimed at replacing free water deficits only. The water deficit is calculated as described previously, and the free water deficit is corrected slowly (over 2 to 3 days) to limit the risk of cerebral edema. In central DI, vasopressin administration is also required to prevent ongDIng free water losses. The usual dose is 2 to 5 units of aqueous vasopressin subcutaneously every

4 to 6 hours (14). The serum sodium must be monitored carefully during vasopressin therapy because water intoxication and hyponatremia can occur if the central DI begins to resolve.

Non-Ketotic Hyperglycemia

The formula for plasma tonicity presented earlier predicts that hyperglycemia will be accompanied by a hypertonic extracellular fluid. When progressive hyperglycemia does not result in ketosis, the major clinical consequence is a hypertonic encephalopathy similar to the one described for hypernatremia (10). The syndrome of nonketotic hyperglycemia (NKH) usually is seen in patients who have enough endogenous insulin to prevent ketosis. The condition usually is precipitated by a physiological stress (e.g., infection, trauma), and the patients mayor may not have a prior history of diabetes mellitus (11). The plasma glucose is often 1000 mg/dL or higher (11) (whereas in ketoacidosis, the plasma glucose is usually below 800 *mgl* dL. The persistent loss of glucose in the urine produces an bsmotic diuresis that can lead to profound volume losses.

Clinical Manifestations

Patients with NKH usually have an altered mental status and may show signs of hypovolemia. The altered mental status can progress to frank coma when the plasma tonicity rises above 330 mOsmlkg H_2O (11). Advanced cases of encephalopathy can be accompanied by generalized seizures and focal neurological deficits, as described for hypernatremic encephalopathy.

Fluid Management

The fluid management of NKH is similar to that described for hypovolemic hypernatremia. Volume deficits tend to be more profound in NKH than in simple hypovolemic hypernatremia because of the osmotic diuresis that accompanies the glycosuria. Therefore, rapid correction of the plasma volume (i.e., with 5% albumin or isotonic saline) may be necessary.

Free Water Diflcit

Once the plasma volume is restored, free water deficits are estimated and replaced slowly. However when calculating the free water deficit that accompanies hyperglycemia, it is necessary to correct the plasma sodium for the increase in plasma glucose. This is because the hyperglycemia draws water from the intracellular space, and this creates a dilutional effect on the plasma sodium concentration. The decrease in plasma sodium in hypernatremia can vary according to the state of the ECV. In general, for every 100 mgldL increment in the plasma glucose, the plasma sodium should fall by 1.6 to 2 mEq/L (11,18). Therefore, for a patient with a plasma glucose of 1000 *mgl* dL and a measured plasma sodium of 145 mEqlL, the actual or corrected plasma sodium will average 145 + *(900/100* X 1.8) = 161 mEq/L (the factor 1.8 is taken as the average value between 1.6 and 2 mEq/L.

The restoration of brain cell volume can occur rapidly in hypertonic states due to hyperglycemia (11). Therefore, the free water replacement should be particularly judicious in NKH.

Insulin Therapy
Because insulin drives both glucose and water into cells, insulin therapy can aggravate hypovolemia. Therefore, in patients who are hypovolemic, insulin should be withheld until the vascular volume is restored. Once this is accomplished, insulin therapy can be given as advised for diabetic ketoacidosis (see Chapter 29). The insulin requirement will diminish as the hypertonic condition is corrected, so plasma glucose concentrations should be monitored hourly during intravenous insulin therapy in NKH.

HYPERVOLEMIC HYPERNATREMIA
Hypernatremia from hypertonic fluid gain is uncommon. Possible causes are hypertonic salinF resuscitation, sodium bicarbonate infusions for metabolic acidosis (see Table 37.1), and ingestion of excessive amounts of table salt (19).

Management
In patients with normal renal function, excess sodium and water are excreted rapidly. When renal sodium excretion is impaired, it might be necessary to increase renal sodium excretion with a diuretic (e.g., furosemide). Because the sodium concentration in urine during furosemide diuresis is approximately 75 mEq/L, excessive urine output will aggravate the hypernatremia (because the urine is hypotonic to plasma). Therefore, urine volume losses must be partially replaced with a fluid that is hypotonic to the urine.

HYPONATREMIA
Hyponatremia (serum sodium less than 135 mEq/L) (20) has been reported in 50% of hospitalized patients with neurologic disorders (21), 40% of hospitalized patients with acquired immunodeficiency syndrome (22), 5% of hospitalized elderly patients (23) and 1 % of postoperative patients (24). Hyponatremic patients can have twice the mortality rate of patients with a normal plasma sodium (22,23), but a causal link is unproven.

Pseudohyponatremia
Plasma is 93% water by volume, and sodium is restricted to this aqueous phase of plasma. The traditional method of measuring the sodium

concentration in plasma (flame photometry) uses the entire volume of the sample, which includes both the aqueous and nonaqueous phases of plasma. Sodium is present only in the aqueous phase of plasma, so the measured sodium concentration in plasma will be lower than the actual sodium concentration. Plasma is normally 93% water by volume, so the difference in measured and actual plasma sodium is negligible in normal subjects.

Extreme elevations in plasma lipids or proteins will increase the volume of the nonaqueous phase of plasma. In this situation, the measured plasma sodium concentration can be significantly lower than the actual (aqueous phase) sodium concentration. This condition is called *pseudohyponatremia(1,25)*.

Ion-Specific Electrodes

Many clinical laboratories now have ion-specific electrodes that measure sodium activity in water only. Therefore, for patients with marked elevations in plasma lipids or plasma proteins, ask the hospital laboratory to use an ion-specific electrode to measure the plasma sodium concentration.

HYPOTONIC HYPONATREMIA

True or hypotonic hyponatremia represents an increase in free water relative to sodium in the extracellular fluids. **It** does *not* necessarily represent an increase in the volume of extracellular fluids. As shown in Table 32.1, the ECV can be low, normal, or high in patients with hyponatremia. The diagnostic approach to hyponatremia can begin with an assessment of the ECV, as shown in Figure 32.2 (1,8,21). (The assessment of ECV is described earlier, for the assessment of hypernatremia.)

Hypovolemic Hyponatremia

This condition is characterized by fluid losses combined with volume replacement using a fluid that is hypotonic to the lost fluid (e.g., diuresis replaced by drinking tap water). The result is a net loss of sodium relative to free water, which decreases both the ECV and the extracellular sodium concentration. The concentration of sodium in a random (spot) urine sample can sometimes help determine **if** the sodium loss is renal or extrarenal in origin.

Site of Sodium Loss	Urine Sodium
Renal	>20 mEq/L
Extrarenal	<10 mEq/L

Renal sodium losses would be seen in diuretic overuse, adrenal insufficiency and in cerebral salt-wasting syndrome; whereas extrarenal sodium losses can occur with diarrhea and persistent vomiting.

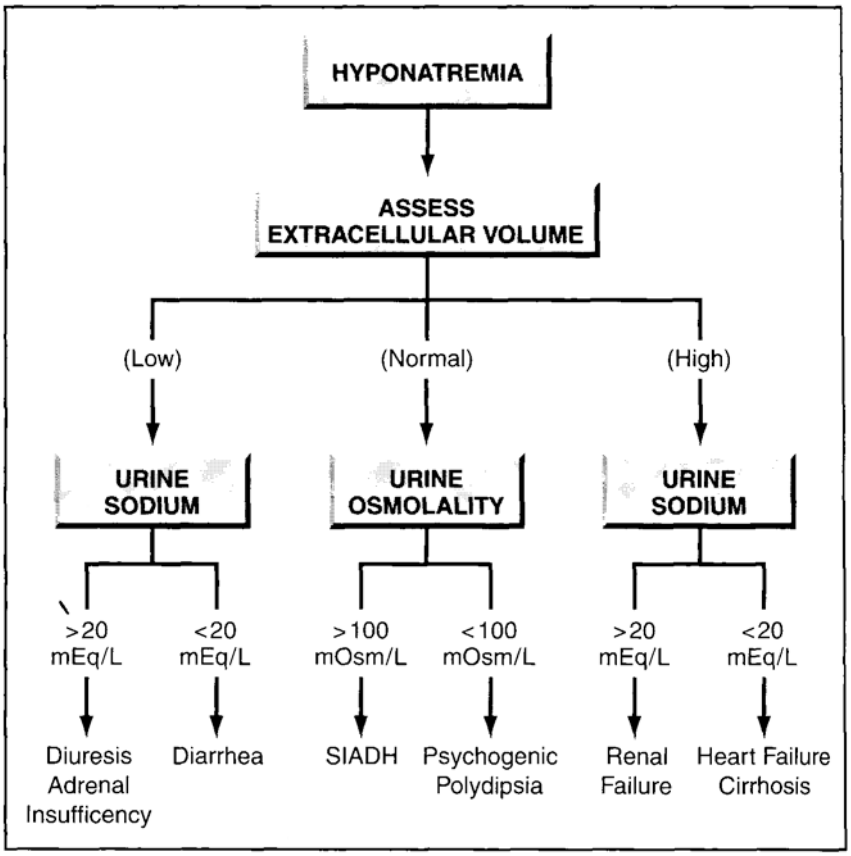

FIGURE 32.2 Diagnostic approach to hyponatremia. *SIADH* = syndrome of inappropriate antidiuretic hormone.

Isovolemic Hyponatremia

Isovolemic hyponatremia is characterized by a small gain in free water, but not enough to be clinically detected (approximately 5 L of excess water is necessary to produce detectable peripheral edema in the averagesize adult). In this situation, the major disorders to consider are inappropriate (non osmotic) release of ADH and acute water intoxication (psychogenic polydipsia). The urine sodium and urine osmolality will help distinguish between these two disorders.

Clinical Disorder	Urine Sodium	Urine Osmolality
Inappropriate ADH	>20 mEq/L	>100 mOsm/kg H_2O
Water intoxication	<10 mEq/L	<100 mOsm/kg H_2O

The inappropriate (nonosmotic) release of ADH is characterized by an inappropriately concentrated urine (urine osmolality above 100 mOsm/kg

H,O) in the face of a hypotonic plasma (plasma tonicity below 290 *mOsm*/ kg H_20). This condition can be seen in certain groups of "stressed" patients, such as patients who have undergone recent surgery. It can also be produced by a variety of tumors and infections. This latter condition is known as the *syndrome of inappropriate ADH* (SIADH), and it can be accompanied by severe hyponatremia (plasma sodium below 120 mEq/L).

Hypervolemic Hyponatremia

Hypervolemic hyponatremia represents an excess of sodium and water, with the water gain exceeding the sodium gain. In this situation, the urine sodium can sometimes help identify the source of the problem.

Common Causes	Urine Sodium
Heart failure	<20 mEq/L
Renal failure	>20 mEq/L
Hepatic failure	<20 mEq/L

The urine sodium can be misleading if the patient is also receiving diuretics (which are commonly used in these conditions). The clinical picture is usually helpful, although these conditions can co-exist in critically ill patients.

Hyponatremic Encephalopathy

The most feared complication of hyponatremia is a life-threatening metabolic encephalopathy that is often associated with cerebral edema, increased intracranial pressure, and seizures, and can be accompanied by the adult respiratory distress syndrome (27-29). Severe cases can progress to respiratory arrest.

Correction of the hyponatremia can also be associated with an encephalopathy that is characterized by demyelinating lesions, pituitary damage, and oculomotor nerve palsies (28). This is usually seen when the sodium concentration is corrected too rapidly. A specific demyelinating disorder known as *central pontine myelinolysis* has also been attributed to rapid correction of hyponatremia (30). These conditions can be irreversible and even fatal, and the next section contains some recommendations to limit the risk of central nervous system injury.

MANAGEMENT STRATEGIES

The management of hyponatremia is determined by the state of the ECV (i.e., low, normal, or high) and by the presence or absence of neurological symptoms. Symptomatic hyponatremia requires more aggressive corrective therapy than asymptomatic hyponatremia. However, to limit the risk of a demyelinating encephalopathy, the rate of rise in plasma sodium should not exceed 0.5 mEq/L per hour and the final plasma sodium

concentration should not exceed 130 mEq/L (27). The general management strategies based on the ECV are as follows:
Low ECV: Infuse hypertonic saline (3% NaCl) in symptomatic patients, and isotonic saline in asymptomatic patients.
Normal ECV: Combine furosemide diuresis with infusion of hypertonic saline in symptomatic patients, or isotonic saline in asymptomatic patients.
High ECV: Use furosemide-induced diuresis in asymptomatic patients. In symptomatic patients, combine furosemide diuresis with judicious use of hypertonic saline.

Sodium Replacement

When corrective therapy requires the infusion of isotonic saline or hypertonic saline, the replacement therapy can be guided by the calculated sodium deficit. This is determined as follows (using a plasma sodium of 130 mEq/L as the desired end-pDInt of replacement therapy):

Sodium deficit (mEq) = Normal TBW X (130 - Current P Na)

The normal TBW (in liters) is 60% of the lean body weight (in kg) in men, and 50% of the lean body weight in women. Thus, for a 60 kg woman with a plasma sodium of 120 mEq/L, the sodium deficit will be 0.5 X 60 X (130 - 120) = 300 mEq.

Because 3% sodium chloride contains 513 mEq of sodium per liter, the volume of hypertonic saline needed to correct a sodium deficit of 300 mEq will be *300/513* = 585 mL. Using a maximum rate of rise of 0.5 mEq/L per hour for the plasma sodium (to limit the risk of a demyelinating encephalopathy), the sodium concentration deficit of 10 mEq/L in the previous example should be corrected over at least 20 hours. Thus, the maximum rate of hypertonic fluid administration will be *585/20* = 29 mL/hour. If isotonic saline is used for sodium replacement, the replacement volume will be 3.3 times the replacement volume of the hypertonic 3% saline solution.

A FINAL WORD

To design an effective approach to hypernatremia and hyponatremia, it is essential to understand that these conditions are the result of a problem with water balance more than sodium balance. The approach in this chapter shows you how to identify the problem with water and sodium balance in any patient using one determination: i.e., an assessment of the extracellular volume.

References

Chapter 33

POTASSIUM

Early sea-living organisms exhibited a preference for intracellular potassium and a disdain for intracellular sodium, which eventually changed the composition of the oceans from a potassium salt solution to a sodium salt solution. This behavior is also found in mammalian organisms, in whom potassium is the major intracellular cation and sodium is the major extracellular cation. This pattern is the result of the sodium-potassium exchange pump on cell membranes, which sequesters potassium and extrudes sodium. In humans, only 2% of the total body potassium stores are found outside cells. This lack of extracellular representation limits the value of the plasma (extracellular) potassium concentration as an index of total body potassium stores.

POTASSIUM DISTRIBUTION

The marked discrepancy between the intracellular and extracellular content of potassium is illustrated in Figure 33.1. The total body potassium content in healthy adults is approximately 50 mEq/kg 0-3), so a 70-kg adult will have 3500 mEq of total body potassium. However, only 70 mEq (2% of the total amount) is found in the extracellular fluids. Because the plasma accounts for approximately

20% of the extracellular fluid volume, the potassium content of plasma will be about 15 mEq, which is about 0.4% of the total amount of potassium in the body. This suggests that the plasma potassium will be an insensitive marker of changes in total body potassium stores.

Serum Potassium

The relationship between changes in total body potassium and changes in serum potassium is curvilinear, as shown in Figure 33.2 (4,5). The slope of the curve decreases on the "deficit" side of the graph, indicating that the change in serum potassium is much smaller when potassium is depleted than when potassium accumulates. In an averaged-size adult with a normal serum potassium concentration (Le., 3.5 to 5.5 mEq/L), a total body potassium deficit of 200 to 400 mEg is required to produce a 1 mEq/L decrease in serum potassium, whereas a total body potassium

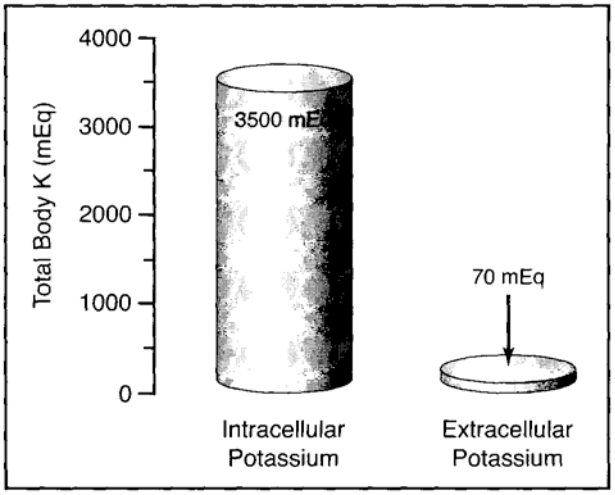

FIGURE 33.1 The intracellular and extracellular potassium content in a 70-kg adult with a total body potassium of 50 mEq/L.

excess of 100 to 200 mEq is required to produce a 1 mEq/L rise in serum potassium (5). In other words, potassium depletion must be twice as great as potassium accumulation to produce a significant (1 mEq/Ll change in the serum potassium concentration. This difference is due to the large pool of intracellular potassium, which can replenish extracellular stores when potassium is lost.

HYPOKALEMIA

Hypokalemia is a serum potassium concentration below 3.5 mEq/L. The causes of hypokalemia can be classified according to whether an intracellular shift of potassium (transcellular shift) occurred or whether a decrease in total body potassium content (potassium depletion) occurred (3,6). The following are some of the possible causes of hypokalemia that are likely to be encountered in the ICU.

Transcellular Shift

Potassium movement into cells is facilitated by stimulation of beta2-adrenergic receptors on muscle cell membranes. Inhaled beta-agonist bronchodilators (e.g., albuterol) are well known for their ability to reduce the serum potassium concentration, but this effect is mild (0.5 mEq/L or less) in the usual therapeutic doses (7). A more significant effect is seen when inhaled beta-agonists are given in combination with glucose and insulin (7) or diuretics (8). Other factors that promote the transcellular shift of potassium into cells include alkalosis (respiratory or metabolic), hypothermia (accidental or induced), and insulin. Alkalosis has a variable and unpredictable effect on the serum potassium (9). Hypothermia causes a transient drop in serum potassium that usually resolves during

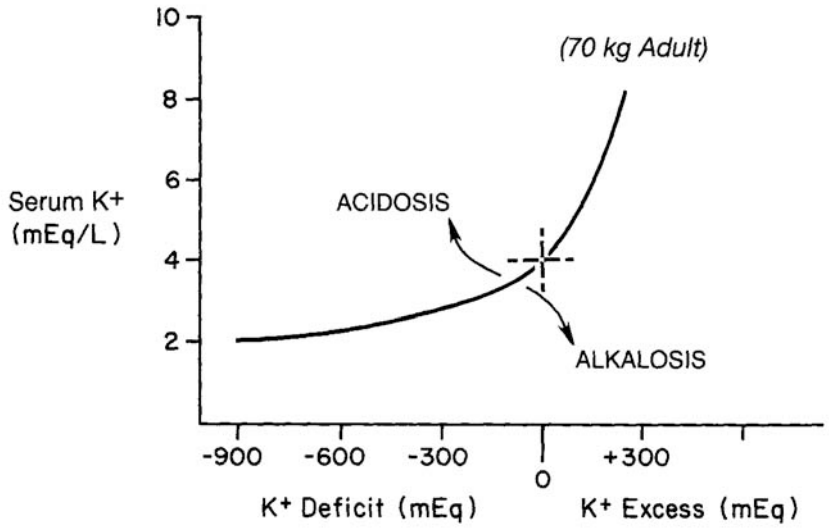

FIGURE 33.2 The relationship between the serum potassium concentration and changes in total body potassium content. (Redrawn from Brown RS. Extrarenal potassium homeostasis Kidney Int 1986;30:116–127.)

rewarming (O). Lethal cases of hypothermia can be accompanied by *hyperkalemia* because of widespread cell death (11).

Potassium Depletion

Potassium depletion can be the result of either renal or extrarenal potassium losses. The site of potassium loss can often be identified by using a combination of urinary potassium and chloride concentrations, as shown in Figure 33.3.

Renal Potassium Loss

The leading cause of renal potassium wasting is diuretic therapy. Other causes likely to be seen in the ICU include nasogastric drainage, alkalosis, and magnesium depletion. The urinary chloride is low (less than 15 mEq/L) when nasogastric drainage or alkalosis is involved, and it is high (greater than 25 mEq/L) when magnesium depletion or diuretics are responsible. Magnesium depletion impairs potassium reabsorption across the renal tubules and may playa very important role in promoting and sustaining potassium depletion in critically ill patients, particularly those receiving diuretics (2).

Extrarenal Potassium Loss

The major cause of extrarenal potassium loss is diarrhea. The potassium concentration in stool is 75 mEq/L, but because the stool volume is normally 200 mL or less each day, little potassium is lost. In diarrheal states, the daily volume of stool can be as high as 10 L, and thus severe or prolonged diarrhea can result in significant potassium depletion.

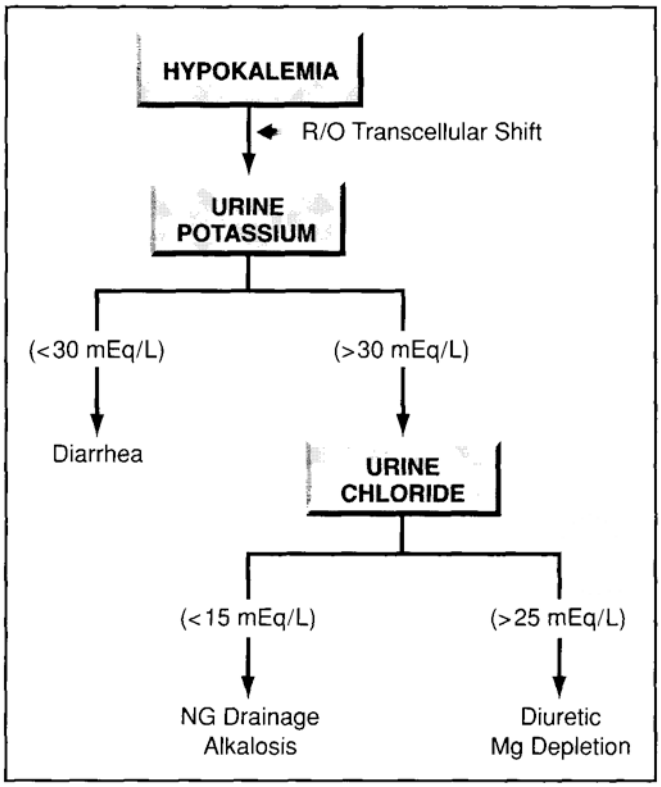

FIGURE 33.3 Diagnostic approach to hypokalemia.

Clinical Manifestations

Severe hypokalemia (serum K+ below 2.5 mEq/L) can be accompanied by diffuse muscle weakness (3). Milder degrees of hypokalemia (serum K+ 2.5 to 3.5 mEq/L) are often asymptomatic. Abnormalities in the ECG, including prominent U waves (more than 1 mm in height), flattening and inversion of T waves, and prolongation of the QT interval, can be present in more than half of the cases (13). None of these changes are specific for hypokalemia. The T wave changes and U waves can be seen with digitalis or left ventricular hypertrophy, and QT prolongation can be seen with hypocalcemia and hypomagnesemia.

Arrhythmias

There is a misconception about the ability of hypokalemia to promote cardiac arrhythmias. Hypokalemia alone does not produce serious ventricular cardiac arrhythmias (3,13). Hypokalemia is often combined with other conditions that can promote arrhythmias (e.g., magnesium depletion, digitalis, myocardial ischemia), and the hypokalemia may enhance the proarrhythmic effects of these other conditions (3).

Hypokalemia is well known for its ability to promote digitalis-induced arrhythmias.

MANAGEMENT OF HYPOKALEMIA

The first concern in hypokalemia is to eliminate or treat any condition that promotes transcellular potassium shifts (e.g., alkalosis) (3). If the hypokalemia is due to potassium depletion, proceed as described in the following section.

Potassium Deficit

If the hypokalemia is due to potassium depletion, a potassium deficit of 10% of the total body potassium stores is expected for every 1 mEq/L decrease in the serum potassium (14). The correlation between potassium deficits and the severity of hypokalemia is shown in Table 33.1. These estimates do not consider any contribution from transcellular potassium shifts, and thus they are meant only as rough guidelines for gauging the severity of potassium depletion.

Potassium Replacement

Solutions

The usual replacement fluid is potassium chloride, which is available as a concentrated solution (from 1 and 2 mEq/mL) in ampules containing 10, 20, 30, and 40 mEq of potassium. These solutions are extremely hyperosmotic (the 2 mEq/L solution has an osmolality of 4000 mOsm/L H20) and must be diluted (15). A potassium phosphate solution is also available (contains 4. 5 mEq potassium and 3 mM phosphate per mL) and is preferred by some for potassium replacement in diabetic ketoacidosis (because of the phosphate depletion that accompanies ketoacidosis).

TABLE 33.1 Potassium Deficits in Hypokalemia*

	Potassium Deficit	
Serum Potassium (mEq/L)	mEq	% Total Body K
3.0	175	5
2.5	350	10
2.0	470	15
1.5	700	20
1.0	875	25

'Estimated deficits for a 70 kg adult with a total body potassium content of 50

Infusion Rate

The standard method of intravenous potassium replacement is to add 20 mEq of potassium to 100 mL of isotonic saline and infuse this mixture over 1 hour (16). The maximum rate of intravenous potassium replacement is usually set at 20 mEq/hour (16), but dose rates up to 40 mEq/hour occasionally may be necessary (e.g., with serum K+ below 1.5 mEq/L or serious arrhythmias), and dose rates as high as 100 mEq/ hour have been used safely (17). A large central vein should be used for infusion because of the irritating properties of the hyperosmotic potassium solutions. However, if the desired replacement rate is greater than 20 mEq/hour, the infusion should not be given through a central venous catheter because of the theoretical risk of transient hyperkalemia in the right heart chambers, which can predispose to cardiac standstill. In this situation, the potassium dose can be split and administered via two peripheral veins.

Response

The serum potassium may be slow to rise at first, because of the position on the flat part of the curve in Figure 33.2. Full replacement usually takes a few days, particularly if potassium losses are ongoing. If the hypokalemia seems refractory to replacement therapy, the serum magnesium level should be checked. Magnesium depletion promotes urinary potassium losses and can cause refractory hypokalemia (18). The management of hypomagnesemia is presented in chapter 34.

HYPERKALEMIA

While hypokalemia is often well tolerated, hyperkalemia (serum K+ greater than 5.5 mEq/L) can be a serious and life-threatening condition (3,19,20).

Pseudohyperkalemia

Potassium release from traumatic hemolysis during the venipuncture can produce a spurious elevation in serum potassium. This is more common than suspected, and has been reported in 20% of blood samples with an elevated serum potassium (21). Potassium release from muscles distal to a tourniquet can also be a source of spuriously high serum potassium levels (22). Because of the risk of spurious hyperkalemia, an unexpected finding of hyperkalemia in an asymptomatic patient should always prompt a repeat measurement before any diagnostic or therapeutic measures are initiated. Potassium release from cells during clot formation in the specimen tube can also produce pseudohyperkalemia when severe leukocytosis (white blood cell count greater than 50,000/mm^3) or thrombocytosis (platelet count greater than 1 million/mm^3) is present. When this condition is suspected, the serum potassium should be measured in an unclotted blood sample.

Urine Potassium

Hyperkalemia can be caused by potassium release from cells (transcellular shift) or by impaired renal potassium excretion. If the source of the hyperkalemia is unclear, the urinary potassium concentration can be helpful. A high urine potassium (greater than 30 mEq/L) suggests a transcellular shift, and a low urine potassium (less than 30 mEq/L) indicates impaired renal excretion.

Transcellular Shift

Acidosis traditionally has been listed as a cause of hyperkalemia because of the tendency for acidosis to both enhance potassium release from cells and reduce renal potassium excretion. However, hyperkalemia does not always accompany respiratory acidosis (9), and no clear evidence exists that organic acidoses (Le., lactic acidosis and ketoacidosis) can produce hyperkalemia (9). Although hyperkalemia can accompany acidoses associated with renal failure and renal tubular acidosis, hyperkalemia in these instances may be caused by impaired renal potassium excretion.

Rhabdomyolysis can release large amounts of potassium into the extracellular fluid, but if renal function is normal, the extra potassium is promptly cleared by the kidneys. For example, severe exercise can raise the serum potassium to 8 mEq/L, but the hyperkalemia resolves with a half-time of 25 seconds (23).

Drugs that can promote hyperkalemia via transcellular potassium shifts include beta-receptor antagonists and digitalis (Table 33.2). Serious hyperkalemia (i.e., serum potassium above 7 mEq/L) is possible only with digitalis toxicity.

Impaired Renal Excretion

Renal insufficiency can produce hyperkalemia when the glomerular filtration rate falls below 10 mL/minute or the urine output falls below 1 L / day (24). Exceptions are interstitial nephritis and hyporeninemic

TABLE 33.2 Drugs That Can Cause Hyperkalemia

ACE Inhibitors'	NSAIDs
Angiotensin Recepter Blockers'	Pentamidine
Beta-Blockers	Potassium penicillin
Cyclosporine	Tacrolimus
Digitalis	TMP-SMX
Diuretics (K-sparing)	Succinylcholine
Heparin	

ACE = angiotensin converting enzyme, *NSA/Ds* = nonsteroidal antiinflammatory *TMP-SMX* = trimethoprim-sulfamethoxazole.
'Especially when combined with K-sparing diuretics.

hypoaldosteronism (24). The latter condition is seen in elderly diabetic patients who have defective renin release in response to reduced renal blood flow.

Adrenal insufficiency is a well known cause of hyperkalemia from impaired renal potassium excretion, but is not a common cause of hyperkalemia in the ICU.

Drugs that impair renal potassium excretion are considered one of the leading causes of hyperkalemia (3,25). A list of common offenders is shown in Table 33.2. The drugs most commonly implicated are angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, potassium sparing diuretics, and nonsteroidal antiinflammatory drugs (25,26). Other potential offenders in the ICU are heparin, trimethoprimsulfamethoxazole, and pentamidine (27-29). All of these agents promote hyperkalemia by inhibiting or blocking the renin-angiotensin-aldosterone system, and all promote hyperkalemia particularly when given with potassium supplements.

Blood Transfusions

Massive blood transfusions (i.e., when the transfusion volume exceeds the estimated blood volume) can promote hyperkalemia when given to patients with circulatory shock (30). Potassium leakage from erythrocytes results in a steady rise in plasma potassium levels in stored blood. In whole blood, the plasma potassium rises an average of 1 mEq/L/day. However, because one unit of whole blood contains 250 mL of plasma, this represents an increase of only 0.25 mEq/ day in the plasma potassium content per unit of whole blood. After 14 days of storage, the plasma potassium load is 4.4 mEq per unit of whole blood and 3.1 mEq per unit of packed red cells (31).

The potassium load in blood transfusions normally is cleared by the kidneys, and thus no sustained rise in plasma potassium occurs. However, in patients with circulatory shock, the extra potassium from blood transfusions can accumulate and produce hyperkalemia. Furthermore, when the volume of distribution for potassium is curtailed by widespread hypoperfusion, the potassium accumulation can be rapid and life-threatening.

Clinical Manifestations

The most serious consequence of hyperkalemia is the slowing of electrical conduction in the heart. The ECG can begin to change when the serum potassium reaches 6.0 mEq/L, and it is always abnormal when the serum potassium reaches 8.0 mEq/L (24). Figure 33.4 illustrates the ECG changes associated with progressive hyperkalemia.

The earliest change in the ECG is a tall, tapering (tented) T wave that is most evident in precordial leads V_2 and V_3• Similar "peaked T" waves have been observed in metabolic acidosis (32). As the hyperkalemia progresses, the P wave amplitude decreases and the PR interval lengthens. The P waves eventually disappear and the QRS duration becomes prolonged. The final event is ventricular asystole.

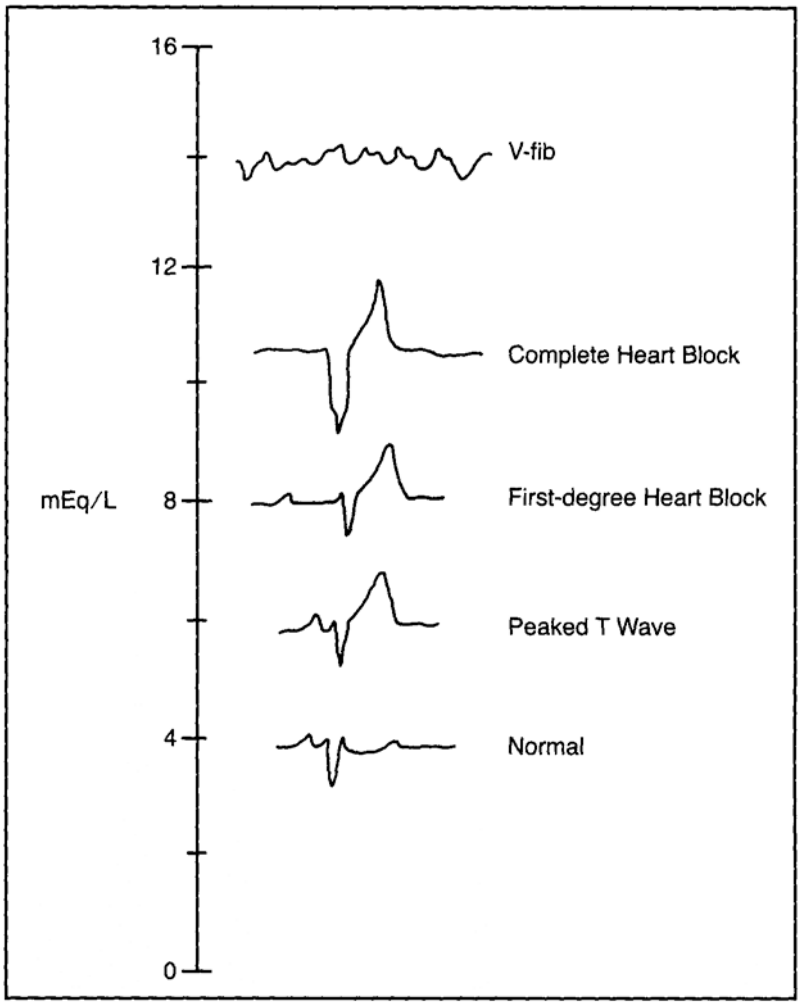

FIGURE 33.4 The ECG manifestations of progressive hyperkalemia. (Adapted from Burch GE, Winsor T. A primer of electrocardiography. Philadelphia: Lea & Febiger, 1966:143.)

MANAGEMENT OF HYPERKALEMIA

The acute management of hyperkalemia is guided by the serum potassium level and the ECG (3,20). The therapeutic maneuvers are outlined in Table 33.3.

Membrane Antagonism

Calcium directly antagonizes the membrane actions of potassium (33). When hyperkalemia is severe (i.e., above 7 mEq/L) or accompanied by advanced ECG changes (Le., loss of P waves and prolonged QRS duration), calcium gluconate is administered in the dose shown in Table 33.3. If there

TABLE 33.3 Acute Management of Hyperkalemia

Condition	Treatment	Comment
ECG changes or serum K >7 mEq/L	Calcium gluconate (10%): 10 mL IV over 3 minutes; can repeat in 5 minutes	Response lasts only 20 to 30 minutes. *Do not* give bicarbonate after calcium.
ECG changes and circulatory compromise	Calcium chloride (10%): 10 mL IV over 3 minutes	Calcium chloride contains 3 times more calcium than calcium gluconate.
AV block refractory to calcium treatment	1. 10 U regular insulin in 500 mL of 20% dextrose: infuse over 1 hour 2. Transvenous pacemaker	Insulin-dextrose treatment should drop the serum K by 1 mEq/L for 1 to 2 hours.
Digitalis cardiotoxicity	1. Magnesium sulfate: 2 g as IV bolus 2. Digitalis specific antibodies if necessary	*Do not* use calcium for the hyperkalemia of digitalis toxicity.
After acute phase or when no ECG changes	Kayexalate: oral dose of 30 g in 50 mL of 20% sorbitol, or rectal dose of 50 g in 200 mL 20% sorbitol as a retention enema	Oral dosing is preferred. Enemas poorly tolerated by patients and nurses.

is no response to calcium within a few minutes, a second dose can be given. A third dose will not be effective if there was no response to the second dose of calcium. The response to calcium lasts only 20 or 30 minutes, so other therapies should be initiated to enhance potassium clearance.

ealcium must be given cautiously to patients on digitalis because hypercalcemia can potentiate digitalis cardiotoxicity. For patients receiving digitalis, the calcium gluconate should be added to 100 mL of isotonic saline and infused over 20 to 30 minutes. If the hyperkalemia is a manifestation of digitalis toxicity, calcium is contraindicated.

When hyperkalemia is accompanied by evidence of circulatory compromise, **calcium chloride** is preferred to calcium gluconate. One ampule (10 mL) of 10% calcium chloride contains three times more elemental calcium than one ampule of 10% calcium gluconate (see Table 35.3), and the extra calcium in calcium chloride may prove beneficial in promoting cardiac contraction and maintaining peripheral vascular tone.

Transcellular Shift

Insulin-Dextrose

eombined therapy with insulin and dextrose will drive potassium into muscle cells and decrease the serum potassium by an average of 1 mEq/L.

However, this is a temporary effect, and other maneuvers aimed at enhancing potassium clearance are also required.

Sodium Bicarbonate
The administration of sodium bicarbonate (44 to 88 mEq) can also shift potassium into cells. However, the most common acidotic condition associated with hyperkalemia is renal failure, and in this condition, insulindextrose is much more effective in lowering the serum potassium than bicarbonate (34). Furthermore, bicarbonate binds calcium and should not be given after calcium is administered. For these reasons, there is little value in using bicarbonate to treat hyperkalemia.

Enhanced Clearance
Measures aimed at enhancing the removal of potassium from the body can be used alone in mild cases of hyperkalemia (i.e., serum K less than 7 mEq/L) without advanced ECG changes or can serve as a follow-up to calcium and insulin-dextrose therapy.

Exchanne Resin
Sodium polystyrene sulfonate (Kayexalate) is a cation exchange resin that can enhance potassium clearance across the gastrointestinal mucosa (gastrointestinal dialysis). This resin can be given orally or by retention enema, and it is mixed with 20% sorbitol to prevent concretion. For each mEq of potassium removed, 2 to 3 mEq of sodium are added. If there is concern about the added sodium, one or two doses of furosemide can be used to enhance natriuresis.

Loop Diuretics
The loop diuretics furosemide and ethacrynic acid enhance urinary potassium excretion. These agents can be used as a follow-up measure to calcium and insulin-dextrose. This approach is ineffective in renal failure.

Hemodialysis
Hemodialysis is the most effective method of lowering the serum potassium in patients with renal failure (3,20).

A FINAL WORD
The following points about potassium deserve emphasis:
Since only 2% of the potassium is outside cells, it is unlikely that the serum potassium concentration is an accurate reflection of total body potassium stores. However, we use the serum potassium as a reflection of total body potassium, so there's

a fundamental problem in the way we interpret and manage changes in serum potassium.
There is often a rush to correct even mild cases of hypokalemia (serum K+ between 3 and 3.5 mEq/L). This is usually not necessary, because hypokalemia is well-tolerated, and does not create a risk of arrhythmias unless there are other arrhythmogenic conditions (such as digitalis toxicity). If hypokalemia is really due to potassium depletion, don't expect an extra 40 mEq of potassium to correct the problem because for each 0.5 mEq/L decrease in serum K+, you will have to replace about 175 mEq of potassium to replenish total body K+ stores.
Don't forget that hypokalemia associated with diuretic therapy is often the result of magnesium depletion, and that potassium replacement will not correct the problem unless magnesium is also replaced.

REFERENCES

Chapter 34

MAGNESIUM

Magnesium is the second most abundant intracellular cation in the human body (potassium being the first), where it serves as a cofactor for more than 300 enzyme reactions that involve adenosine triphosphate. One of the magnesium-dependent enzyme systems is the membrane pump that generates the electrical gradient across cell membranes. As a result, magnesium plays an important role in the activity of electrically excitable tissues 0,2,5-7). Magnesium also regulates the movement of calcium into smooth muscle cells, which gives it a pivotal role in the maintenance of cardiac contractile strength and peripheral vascular tone (5).

MAGNESIUM BALANCE
The content and distribution of magnesium in the human body is shown in Table 34.1 (8). The average-size adult contains approximately 24 g (1 mole, or 2000 mEq) of magnesium; a little over half is located in bone, whereas less than 1 % is located in plasma. This lack of representation in the plasma limits the value of the plasma magnesium concentration as an index of total body magnesium stores. This is particularly true in patients with magnesium deficiency, in whom serum magnesium levels can be normal in the face of total body magnesium depletion (8,9).

Serum Magnesium
Serum is favored over plasma for magnesium assays because the anti-coagulant used for plasma samples can be contaminated with citrate or other anions that bind magnesium (8). The normal range for serum mag-nesium depends on the daily magnesium intake, which varies according to geographic region. The normal range for healthy adults residing in the United States is shown in Table 34.2 (10).

Ionized Magnesium
Only 67% of the magnesium in plasma is in the ionized (active) form, and the remaining 33% is either bound to plasma proteins (19% of the total) or che1ated with divalent anions such as phosphate and sulfate (14% of the total) (11). The standard assay for magnesium (i.e., spectrophotometry)

TABLE 34.1 Magnesium Distribution in Adults

Tissue	Weight (kg)	Magnesium Content (mEq)	Total Body Magnesium (%)
Bone	12	1060	53
Muscle	30	540	27
Soft *Tissue*	23	384	19
RBC	2	10	0.7
Plasma	3	6	0.3
Total	70 kg	2000 mEq	100%

From: Elin RJ. Assessment of magnesium status. Clin Chem 1987;33:1965-

measures all three fractions of magnesium. Therefore, when the serum magnesium is abnormally low, it is impossible to determine whether the problem is a decrease in the ionized (active) fraction or a decrease in the bound fractions (e.g., hypoproteinemia) (12). The level of ionized magnesium can be measured with an ion-specific electrode (13) or by ultrafiltration of plasma (14), but these techniques are not routinely available for clinical use. However, because the total amount of magnesium in plasma is small, the difference between the ionized and bound magnesium *content* may not be large enough to be clinically relevant.

Urinary Magnesium

The normal range for urinary magnesium excretion is shown in Table 34.2. Under normal circumstances, only small quantities of magnesium are excreted in the urine. When magnesium intake is deficient, the kidneys conserve magnesium and urinary magnesium excretion falls to negligible levels. This is shown in Figure 34.1. After the start of a magnesium deficient diet, the urinary magnesium excretion promptly falls to negligible levels and the serum magnesium remains in the normal range. This illustrates the relative value of urinary magnesium over serum magnesium levels in the detection of magnesium deficiency. This is discussed again later in this chapter.

TABLE 34.2 Reference Ranges for Magnesium*

Fluid	Traditional Units	81 Units
Serum magnesium:		
Total	1.4-2.0 mEq/L	0.7-1.0 mmol/L
Ionized	0.8-1.1 mEqlL	0.4-0.6 mmol/L
Urinary magnesium	5-15 mEq/24 hr	2.5-7.5 mmol/24 hr

·Pertains to healthy adults residing in the United States. From: Lowenstein FW. Stanton MF. Serum magnesium levels in the United States, 1971-1974. J Am 1986;5:399-414.

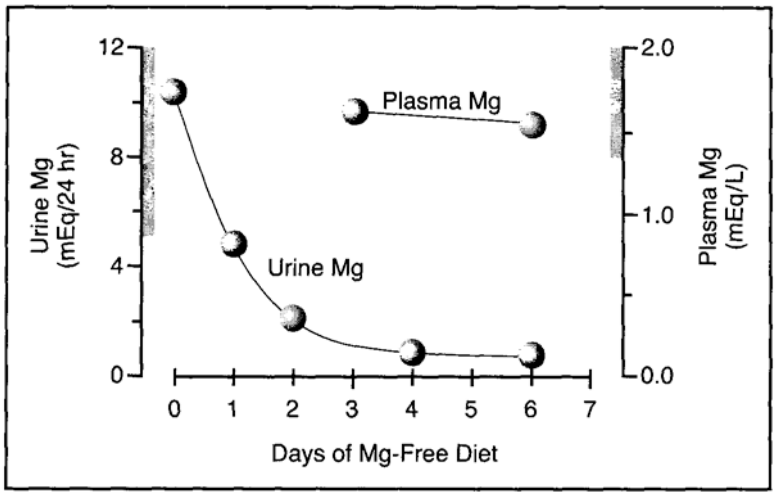

FIGURE 34.1 Urinary and plasma magnesium levels in a healthy volunteer placed on a magnesium-free diet. Solid bars on the vertical axes indicate the normal range for urine and plasma magnesium. (Adapted from Shils ME. Experimental human magnesium deficiency. Medicine 1969;48:61–82.)

MAGNESIUM DEFICIENCY

Magnesium deficiency is common in hospitalized patients. Hypomagnesemia is reported in up to 20% of patients on medical wards and in as many as 65% of patients in ICUs . Because magnesium depletion may not be accompanied by hypomagnesemia, the incidence of magnesium depletion is even higher than indicated by the surveys of hypomagnesemia. In fact, magnesium depletion has been described as "the most underdiagnosed electrolyte abnormality in current medical practice" (15).

Predisposing Conditions

Because serum magnesium levels have a limited ability to detect magnesium depletion, recognizing the conditions that predispose to magnesium depletion may be the only clue of an underlying electrolyte imbalance. The common predisposing conditions for magnesium depletion are listed in Table 34.3.

Diuretic Therapy

Diuretics are the leading cause of magnesium deficiency. Drug-induced inhibition of sodium reabsorption also interferes with magnesium reabsorption, and the resultant urinary magnesium losses can parallel urinary sodium losses. Urinary magnesium excretion is most pronounced with the loop diuretics (furosemide and ethacrynic acid). Magnesium deficiency has been reported in 50% of patients receiving chronic therapy

TABLE 34.3 Markers of Possible Magnesium Depletion

Predisposing Conditions	Clinical Findings
Drug therapy:*	Electrolyte abnormalities:*
Furosemide (50%)	Hypokalemia (40%)
Aminoglycosides (30%)	Hypophosphatemia (30%)
Amphotericin, pentamidine	Hyponatremia (27%)
Digitalis (20%)	Hypocalcemia (22%)
Cisplatin. cyclosporine	Cardiac manifestations:
Diarrhea (secretory)	Ischemia
Alcohol abuse (chronic)	Arrhythmias (refractory)
Diabetes mellitus	Digitalis toxicity
Acute MI	Hyperactive CNS Syndrome

'Numbers in parentheses indicate incidence of associated hypomagnesemia.

with furosemide (16). The thiazide diuretics show a similar tendency for magnesium depletion, but only in elderly patients (17). Magnesium depletion is not a complication of therapy with "potassium-sparing" diuretics such as triamterene (18).

Antibiotic Therapy

The antibiotics that promote magnesium depletion are the aminog1ycosides, amphotericin and pentamidine (19,20). The aminog1ycosides block magnesium reabsorption in the ascending loop of Henle, and hypomagnesemia has been reported in 30% of patients receiving aminoglycoside therapy (20). The other risk associated with antibiotic use occurs with antibiotic-associated diarrhea, which can be accompanied by significant magnesium losses in the stool.

Other Drugs

A variety of other drugs have been associated with magnesium depletion, including digitalis, epinephrine, and the chemotherapeutic agents cisplatin and cyclosporine (19,21). The first two agents shift magnesium into cells, whereas the latter two promote renal magnesium excretion.

Alcohol-Related Illness

Hypomagnesemia is reported in 30% of hospital admissions for alcohol abuse, and in 85% of admissions for delirium tremens (22,23). The magnesium depletion in these conditions is due to a number of factors, including generalized malnutrition and chronic diarrhea. In addition, there is an association between magnesium deficiency and thiamine deficiency (24). Magnesium is required for the transformation of thiamine into thiamine pyrophosphate, so magnesium deficiency can promote thiamine deficiency in the face of adequate thiamine intake. For

this reason, the magnesium status should be monitored periodically in patients receiving daily thiamine supplements.

Secretory Diarrhea
A high concentration of magnesium (10 to 14 mEq/L) is present in secretions from the lower gastrointestinal tract (25), and thus secretory diarrhea can be accompanied by profound magnesium depletion (23). Upper tract secretions are not rich in magnesium (1 to 2 mEq/L), so vomiting does not pose a risk for magnesium depletion.

Diabetes Mellitus
Magnesium depletion is common in insulin-dependent diabetic patients, probably as a result of urinary magnesium losses that accompany glycosuria (26). Hypomagnesemia is reported in only 7% of admissions for diabetic ketoacidosis, but the incidence increases to 50% over the first 12 hours after admission (27), probably as a result of insulin-induced movement of magnesium into cells.

Acute Myocardial Infarction
As many as 80% of patients with acute myocardial infarction (MI) can have hypomagnesemia in the first 48 hours after the event (28). The mechanism is unclear but may be due to an intracellular shift of magnesium caused by endogenous catecholamine excess.

Clinical Manifestations
Although no clinical manifestations are specific for magnesium deficiency, the following clinical findings are suggestive of an underlying magnesium deficiency (Table 34.3).

Associated Electrolyte Abnormalities
Magnesium depletion is often accompanied by depletion of other electrolytes, such as potassium, phosphate, and calcium (See Table 34.3) (29). As mentioned in Chapter 33, the hypokalemia that accompanies magnesium depletion can be refractory to potassium replacement therapy, and magnesium repletion is often necessary before potassium repletion is possible (30).
The **hypocalcemia** that accompanies magnesium depletion is due to impaired parathormone release (31) combined with an impaired endorgan response to parathormone (32). In addition, magnesium deficiency may act on bone directly to reduce calcium release, independent of parathyroid hormone (33). As with the hypokalemia, the hypocalcemia from magnesium depletion is difficult to correct unless magnesium deficits are corrected.
Hypophosphatemia is a cause rather than effect of magnesium depletion. The mechanism is enhanced renal magnesium excretion (34). Therefore, when hypophosphatemia accompanies hypomagnesemia, the

phosphate stores should be replenished to ensure adequate repletion of magnesium stores.

Arrhythmias
Because magnesium is required for proper function of the membrane pump on cardiac cell membranes, magnesium depletion will depolarize cardiac cells and promote tachyarrhythmias. Because both digitalis and magnesium deficiency act to inhibit the membrane pump, magnesium deficiency will magnify the digitalis effect and promote digitalis cardiotoxicity. Intravenous magnesium can suppress digitalis-toxic arrhythmias, even when serum magnesium levels are nOffilal (35,36). Intravenous magnesium can also abolish refractory arrhythmias (i.e., unresponsive to traditional antiarrhythmic agents) in the absence of hypomagnesemia (37). This effect may be due to a membrane-stabilizing effect of magnesium that is unrelated to magnesium repletion.
One of the most serious arrhythmias associated with magnesium depletion is torsades de pointes (polymorphous ventricular tachycardia). The role of magnesium in this arrhythmia is discussed in ehapter 18.

Neurologic Findings
The neurologic manifestations of magnesium deficiency include altered mentation, generalized seizures, tremors, and hyperreflexia. All are un-common, nonspecific, and have little diagnostic value.
A neurologic syndrome described recently that can abate with magnesium therapy deserves mention. The clinical presentation is characterized by ataxia, slurred speech, metabolic acidosis, excessive salivation, diffuse muscle spasms, generalized seizures, and progressive obtundation (38). The clinical features are often brought out by loud noises or bodily contact, and thus the term reactive central nervous system magnesium deficiency has been used to describe this disorder. This syndrome is associated with reduced magnesium levels in cerebrospinal fluid, and it resolves with magnesium infusion. The prevalence of this disorder is unknown at present.

Diagnosis
As mentioned several times, the serum magnesium level is an insensitive marker of magnesium depletion. When magnesium depletion is due to nonrenal factors (e.g., diarrhea), the urinary magnesium excretion is a more sensitive test for magnesium depletion (39). However, because most cases of magnesium depletion are due to enhanced renal magnesium excretion, the diagnostic value of urinary magnesium excretion may be limited.

Magnesium Retention Test
In the absence of renal magnesium wasting, the urinary excretion of magnesium in response to a magnesium load may be the most sensitive index of total body magnesium stores (40,41). This method is outlined

TABLE 34.4 Renal Magnesium Retention Test

Indications:

1. For suspected magnesium deficiency when the serum magnesium concentration is normal.
2. Can be useful for determining the end-point of magnesium replacement therapy.
3. Is *not* reliable in the setting of renal magnesium wasting or when renal function is impaired.

Contraindications:

1. Cardiovascular instability or renal failure.

Methodology':

1. Add 24 mmol of magnesium (6 g of $MgSO_4$) to 250 mL of isotonic saline and infuse over 1 hour.
2. Collect urine for 24 hours, beginning at the onset of the magnesium infusion.
3. A urinary magnesium excretion of less than 12 mmol (24 mEq) in 24 hours (i.e., less than 50% of the infused magnesium) is evidence of total body magnesium depletion.

"Magnesium infusion protocol. From: Clague JE, Edwards RH, Jackson MJ. magnesium loading in chronic fatigue syndrome. Lancet 1992:340:124-125.

in Table 34.4. The normal rate of magnesium reabsorption is close to the maximum tubular reabsorption rate (T_{max})' so most of the infused magnesium will be excreted in the urine when magnesium stores are normal. However, when magnesium stores are deficient, the magnesium reabsorption rate is much lower than the T max' so more of the infused magnesium will be reabsorbed and less will be excreted in the urine. When less than 50% of the infused magnesium is recovered in the urine, magnesium deficiency is *likely,* and when more than 80% of the infused magnesium is excreted in the urine, magnesium deficiency is *unlikely.* This test can be particularly valuable in determining the end-point of magnesium replacement therapy (i.e., magnesium replacement is continued until urinary magnesium excretion is at least 80% of the infused magnesium load). It is important to emphasize that this test will be unreliable in patients with impaired renal function or when there is ongoing renal magnesium wasting.

MAGNESIUM REPLACEMENT THERAPY

*Preparation*s

The magnesium preparations available for oral and parenteral use are listed in Table 34.5 (42,43). The oral preparations can be used for daily maintenance therapy (5 mg/kg in normal subjects) and for correcting

TABLE 34.5 Oral and Parenteral Magnesium Preparations

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Preparation	Elemental Magnesium
Oral preparations:	
Magnesium chloride enteric coated tablets	64 mg (5.3 mEq)
Magnesium oxide tablets (400 mg)	241 mg (19.8 mEq)
Magnesium oxide tablets (140 mg)	85 mg (6.9 mEq)
Magnesium gluconate tablets (500 mg)	27 mg (2.3 mEq)
Parenteral solutions:	
Magnesium sulfate (50%)'	*500 mg/mL* (4 mEqlmL)
Magnesium sulfate (12.5%)	*120 mg/mL* (1 mEq/mL)

"Should be diluted to a 20% solution for intravenous injection

mild, asymptomatic magnesium deficiency. However, because intestinal absorption of oral magnesium is erratic, parenteral magnesium is preferred for treating sympto~atic or severe magnesium deficiency.

Magnesium Sulfate

The standard intravenous preparation is magnesium sulfate ($MgS0_4$). Each gram of magnesium sulfate has 8 mEq (4 mmol) of elemental magnesium (6). A 50% magnesium sulfate solution (500 mg/mL) has an osmolarity of 4000 mOsm/L (43), so it must be diluted to a 10% (100 mg/mL) or 20% (200 mg/mL) solution for intravenous use. Saline solutions should be used as the diluent for magnesium sulfate. Ringer's solutions should not be used because the calcium in Ringer's solutions will counteract the actions of the infused magnesium.

Replacement Protocols

The following magnesium replacement protocols are recommended for patients with normal renal function (44).

Mild, Asymptomatic Hypomagnesemia

The following guidelines can be used for patients with mild hypomagnesemia and no apparent complications (44):

Assume a total magnesium deficit of 1 to 2 mEq/kg.

Because 50% of the infused magnesium can be lost in the urine, assume that the total magnesium requirement is twice the magnesium deficit.

Replace 1 mEq/kg for the first 24 hours, and 0.5 mEq/kg daily for the next 3 to 5 days.

If the serum magnesium is greater than 1 mEq/L, oral magnesium can be used for replacement therapy.

Moderate Hypomagnesemia
The following therapy is intended for patients with a serum magnesium level less than 1 mEq/L or when hypomagnesemia is accompanied by other electrolyte abnormalities:
Add 6 g $MgSO_4$ (48 mEq Mg) to 250 or 500 mL isotonic saline and infuse over 3 hours.
Follow with 5 g $MgS0_4$ (40 mEq Mg) in 250 or 500 mL isotonic saline infused over the next 6 hours.
eontinue with 5 g $MgS0_4$ every 12 hours (by continuous infusion) for the next 5 days.

Life- Threatening Hypomagnesemia
When hypomagnesemia is associated with serious cardiac arrhythmias (e.g., torsades de pointes) or generalized seizures, do the following:

lnfuse 2 g $MgS0_4$ (16 mEq Mg) intravenously over 2-5 minutes.

Follow with 5 g $MgS0_4$ (40 mEq Mg) in 250 or 500 mL isotonic saline infused over the next 6 hours.

Continue with 5 g $MgS0_4$ every 12 hours (by continuous infusion) for the next 5 days.

Serum magnesium levels will rise after the initial magnesium bolus but will begin to fall after 15 minutes. Therefore, it is important to follow the bolus dose with a continuous magnesium infusion. Serum magnesium levels may normalize after 1 to 2 days, but it will take several days to replenish the total body magnesium stores.

Hypornagnesemia and Renal Insufficiency
Hypomagnesemia is not common in renal insufficiency but can occur when severe or chronic diarrhea is present and the creatinine clearance is greater than 30 mL/minute. When magnesium is replaced in the setting of renal insufficiency, no more than 50% of the magnesium in the standard replacement protocols should be administered (44), and the serum magnesium should be monitored carefully.

MAGNESIUM ACCUMULATION

Magnesium accumulation occurs almost exclusively in patients with impaired renal function. In one survey of hospitalized patients, hypermagnesemia (i.e., a serum magnesium greater than 2 mEq/L) was reported in 5% of patients (45).

Predisposing Conditions

Hemolysis
The magnesium concentration in erythrocytes is approximately three times greater than that in serum (46), so hemolysis can increase the

plasma magnesium. This can occur either in vivo from a hemolytic anemia or in vitro from traumatic disruption of erythrocytes during phlebotomy. In hemolytic anemia, the serum magnesium is expected to rise by 0.1 mEq/L for every 250 mL of erythrocytes that lyse completely (46), so hypermagnesemia is expected only with massive hemolysis.

Renal Insufficiency
The renal excretion of magnesium becomes impaired when the creatinine clearance falls below 30 mL/minute (47). However, hypermagnesemia is not a prominent feature of renal insufficiency unless magnesium intake is increased.

Others
Other conditions that can predispose to mild hypermagnesemia are diabetic ketoacidosis (transient), adrenal insufficiency, hyperparathyroidism, and lithium intoxication (47).

Clinical Features
The clinical consequences of progressive hypermagnesemia are listed below (47).

Manifestation	Serum Magnesium
Hyporeflexia	>4 mEq/L
1st degree AV Block	>5 mEq/L
Complete Heart Block	> 10 mEqlL
Cardiac Arrest	>13 mEq/L

Magnesium has been described as nature's physiologic calcium blocker (48), and most of the serious consequences of hypermagnesemia are due to calcium antagonism in the cardiovascular system. Most of the cardiovascular depression is the result of cardiac conduction delays. Depressed contractility and vasodilation are not prominent.

Management
Hemodialysis is the treatment of choice for severe hypermagnesemia. Intravenous calcium gluconate (1 g IV over 2 to 3 minutes) can be used to antagonize the cardiovascular effects of hypermagnesemia *temporarily,* until dialysis is started (49). If fluids are permissible and some renal function is preserved, aggressive volume infusion combined with furosemide may be effective in reducing the serum magnesium levels in less advanced cases of hypermagnesemia.

A FINAL WORD
The following points about magnesium deserve emphasis:

Because 99% of the magnesium in the body is inside cells, the serum magnesium is not a sensitive marker of total body magnesium stores, and serum magnesium levels can be normal in patients who are magnesium depleted. The urine magnesium is a better marker of magnesium depletion (except in patients receiving furosemide, which increases urinary magnesium losses).

Magnesium depletion is probably very common in ICU patients, particularly in patients with secretory diarrhea and patients receiving furosemide and aminoglycosides.

Magnesium is a cofactor for all ATPase reactions, so magnesium depletion could lead to defects in cellular energy utilization.

Magnesium should be given daily to all ICU patients except those with renal insufficiency. Magnesium supplements are particularly important in patients receiving furosemide.

Magnesium depletion may be the cause of diuretic-associated hypokalemia, and magnesium repletion is often necessary in these cases before the serum potassium will return to normal.

In patients with hypomagnesemia, magnesium replacement will correct the serum magnesium before total body stores of magnesium are rep1eted. The best indicator of magnesium repletion is the urinary excretion of magnesium (see Table 34.4)

REFERENCES

Chapter 35

CALCIUM AND PHOSPHORUS

Calcium and phosphorus are responsible for much of the structural integrity of the bony skeleton. Although neither is found in abundance in the soft tissues, both play an important role in vital cell functions. Phosphorus participates in aerobic energy production, whereas calcium participates in several diverse processes, such as blood coagulation, neuromuscular transmission, and smooth muscle contraction. Considering the important functions of these electrolytes, it is surprising that abnormalities in calcium and phosphorus balance are so well tolerated.

CALCIUM
Calcium is the most abundant electrolyte in the human body (the average adult has more than half a kilogram of calcium), but 99% is in bone (1,2). In the soft tissues, calcium is 10,000 times more concentrated than in the extracellular fluids (2,3).

Plasma Calcium
The calcium in plasma is present in three forms, as depicted in Figure 35.1. Approximately half of the calcium is ionized (biologically active) and the remainder is complexed (biologically inactive) (1). In the inactive form, 80% of calcium is bound to albumin, while 20% is complexed to plasma anions such as proteins and sulfates. The concentration of total and ionized calcium in plasma is shown in Table 35.1. These values may vary slightly in different clinical laboratories.

Total versus Ionized Calcium
The calcium assay used by most clinical laboratories measures all three fractions of calcium, which can be misleading. The column on the right in Figure 35.1 demonstrates the effects of a decrease in the concentration of

albumin in plasma. Because albumin is responsible for 80% of the protein-bound calcium in plasma, a decrease in albumin decreases the

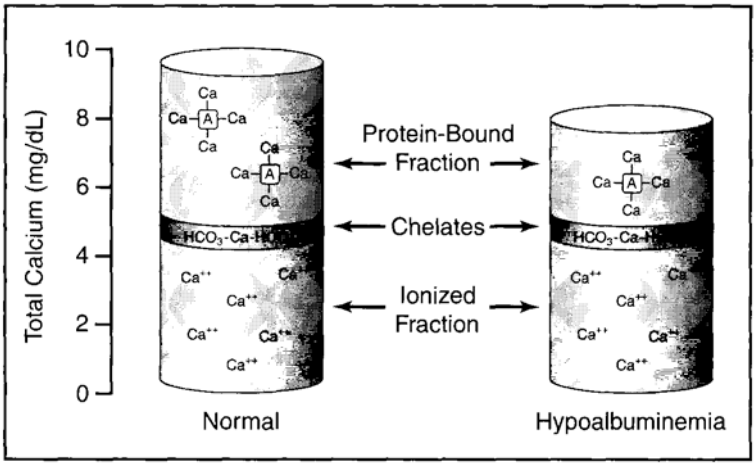

FIGURE 35.1 The three fractions of calcium in plasma and the contribution of each to the total calcium concentration. The column on the right shows how a decrease in plasma albumin can reduce the total plasma calcium without affecting the ionized calcium.

amount of calcium in the protein-bound fraction. The total calcium in plasma decreases by the same amount, but the ionized calcium remains unchanged. Because the ionized calcium is the physiologically active fraction, the hypocalcemia caused by hypoalbuminemia is not physiologically significant. The hypocalcemia that is physiologically significant is *ionized* hypocalcemia (4,5).

A variety of correction factors have been proposed for adjusting the plasma calcium concentration in patients with hypoalbuminemia. However, none of these correction factors are reliable (4,6), and the only method of identifying true (ionized) hypocalcemia in the face of hypoalbuminemia is to measure the ionized fraction of calcium in plasma.

Ionized Calcium Measurement

Ionized calcium can be measured in whole blood, plasma, or serum with ion-specific electrodes that are now available in most clinical laboratories

TABLE 35.1 Normal Ranges for Calcium and Phosphorus in Blood

Serum Electrolyte	Traditional Units (mg/dL)	Conversion Factor*	SI Units (mmol/L)
Total calcium	9.0-10.0	0.25	2.2-2.5
Ionized calcium	4.5-5.0	0.25	1.1-1.3
Phosphorus	2.5-5.0	0.32	0.8-1.6

'Multiply traditional units by conversion factor to derive 81 Units or divide 81 conversion factor to derive tranditional

(7). The normal concentration of ionized calcium in plasma is shown in Table 35.1.

Blood Collection
Several conditions can alter the level of ionized calcium in blood samples (7). Acidosis decreases the binding of calcium to albumin and increases the ionized calcium, whereas alkalosis has the opposite effect. Loss of carbon dioxide from a blood sample could falsely lower the ionized calcium, so it is important to avoid gas bubbles in the blood sample. Anticoagulants (e.g., heparin, citrate, and EDTA) can bind calcium, so blood samples should not be placed in collection tubes that contain these anticoagulants. Tubes with red stoppers ("red top" tubes) contain silicone and are adequate for measuring ionized calcium in serum samples. Heparinized syringes can be used for measuring ionized calcium in whole blood. Although heparin also binds calcium, the effect is minimal if the heparin level is less than 15 U / mL of blood (7).

Ionized Hypocalcemia
Ionized hypocalcemia has been reported in 15 to 50% of admissions to the ICU (8). The common disorders associated with ionized hypocalcemia in ICU patients are listed in Table 35.2. Hypoparathyroidism is a leading cause of hypocalcemia in outpatients, but is not a consideration in the ICU unless neck surgery has been performed recently.

Predisposing Conditions

Magnesium Depletion
Magnesium depletion promotes hypocalcemia by inhibiting para thormone secretion and reducing end-organ responsiveness to parathormone (see Chapter 34). Hypocalcemia from magnesium depletion is refractory to calcium replacement therapy, and magnesium repletion often corrects the hypocalcemia without calcium replacement.

TABLE 35.2 Causes of Ionized Hypocalcemia in the ICU

Alkalosis	Fat embolism
Blood transfusions (15%)	Magnesium depletion (70%)
Cardiopulmonary bypass	Pancreatitis
Drugs:	Renal insufficiency (50%)
Aminoglycosides (40%)	Sepsis (30%)
Cimetidine (30%)	
Heparin (10%)	
Theophylline (30%)	

Numbers in parentheses show the frequency of ionized hypocalcemia reported condition.

Sepsis
Sepsis is a common cause of hypocalcemia in the ICU (8,9). The mechanism is unclear, but it may involve an increase in calcium binding to albumin caused by elevated levels of circulating free fatty acids. Hypocalcemia is independent of the vasodilation that accompanies sepsis (9), and thus the clinical significance of the hypocalcemia in sepsis is unclear.

Alkalosis
As mentioned earlier, alkalosis promotes the binding of calcium to albumin and can reduce the fraction of ionized calcium in blood. Symptomatic hypocalcemia is more common with respiratory alkalosis than with metabolic alkalosis. Infusions of sodium bicarbonate can also be accompanied by ionized hypocalcemia because calcium directly binds to the infused bicarbonate.

Blood Transfusions
Ionized hypocalcemia has been reported in 20% of patients receiving blood transfusions (8). The mechanism is calcium binding by the citrate anticoagulant in banked blood. Hypocalcemia from blood transfusions usually is transient, and resolves when the infused citrate is metabolized by the liver and kidneys (8). In patients with renal or hepatic failure, a more prolonged hypocalcemia can result. Although hypocalcemia from blood transfusions could impede blood coagulation, this is not considered to be a significant effect and calcium infusions are no longer recommended in massive blood transfusions.

Drugs
A number of drugs can bind calcium and promote ionized hypocalcemia (8). The ones most often used in the ICU are aminoglycosides, cimetidine, heparin, and theophylline.

Renal Failure
Ionized hypocalcemia can accompany renal failure as a result of phosphate retention and impaired conversion of vitamin D to its active form in the kidneys. The treatment is aimed at lowering the phosphate levels in blood with antacids that block phosphorus absorption in the small bowel. However, the value of this practice is unproven. The acidosis in renal failure can decrease the binding of calcium to albumin, so hypocalcemia in renal failure does not imply ionized hypocalcemia.

Pancreatitis
Severe pancreatitis can produce ionized hypocalcemia through several mechanisms. The prognosis is adversely affected by the appearance of hypocalcemia, although a causal relationship has not been proven.

Clinical Manifestations

The clinical manifestations of hypocalcemia are related to enhanced cardiac and neuromuscular excitability and reduced contractile force in cardiac muscle and vascular smooth muscle.

Neuromuscular Excitability

Hypocalcemia can be accompanied by tetany (of peripheral or laryngeal muscles), hyperreflexia, paresthesias, and seizures (11). Chvostek's and Trousseau's signs are often listed as manifestations of hypocalcemia. However, Chvostek's sign is nonspecific (it is present in 25% of normal adults), and Trousseau's sign is insensitive (it can be absent in 30% of patients with hypocalcemia) (12).

Cardiovascular Effects

The cardiovascular complications of hypocalcemia include hypotension, decreased cardiac output, and ventricular ectopic activity. These complications are rarely seen in mild cases of ionized hypocalcemia (Le., ionized calcium 0.8 to 1.0 mmol!L). However, advanced stages of ionized hypocalcemia (Le., ionized calcium less than 0.65 mmol!L) can be associated with heart block, ventricular tachycardia and refractory hypotension (8).

Calcium Replacement Therapy

The treatment of ionized hypocalcemia should be directed at the underlying cause of the problem. However, symptomatic hypocalcemia is considered a medical emergency (8), and the treatment of choice is intravenous calcium. The calcium solutions and dosage recommendations for intravenous calcium replacement are shown in Table 35.3.

TABLE 35.3 Intravenous Calcium Replacement Therapy

Solution	Elemental Calcium	Unit Volume	Osmolarity
10% Calcium chloride	27 mg (1.36 mEq)/mL	10-mL ampules	2000 mOsm/L
10% Calcium gluconate	9 mg (0.46 mEq)/mL	1 O-mL ampules	680 mOsm/L

For symptomatic hypocalcemia:

1. Infuse calcium into a large central vein if possible. If a peripheral vein is used, calcium gluconate should be used.
2. Give a bolus dose of 200 mg elemental calcium (8 mL of 10% calcium chloride or 22 mL of 10% calcium gluconate) in 100 mL isotonic saline over 10 minutes.
3. Follow with a continuous infusion of 1-2 mg elemental calcium per kg per hour for 6-12 hours.

Calcium Salt Solutions

The two most popular calcium solutions for intravenous use are 10% calcium chloride and 10% calcium gluconate. Both solutions have the same concentration of calcium salt (i.e., 100 mg/mL), but calcium chloride contains three times more elemental calcium than calcium gluconate. One lO-mL ampule of 10% calcium chloride contains 272 mg (13.6 mEq) of elemental calcium, whereas one 10-mL ampule of 10% calcium gluconate contains only 90 mg (4.6 mEq) of elemental calcium (8).

Dosage Recommendations

The intravenous calcium solutions are hyperosmolar and should be given through a large central vein if possible. If a peripheral vein is used, calcium gluconate is the preferred solution because of its lower osmolarity (Table 35.3). A bolus dose of 100 mg elemental calcium (diluted in 100 mL isotonic saline and given over 5-10 minutes) should raise the total serum calcium by 0.5 mg/ dL, but levels will begin to fall after 30 minutes (8). Therefore, the bolus dose of calcium should be followed by a continuous infusion at a dose rate of 0.5 to 2 mg/kg/hr (elemental calcium) for at least 6 hours. Individual responses will vary, so calcium dosing should be guided by the level of ionized calcium in blood (8).

Caution

Intravenous calcium replacement can be risky in select patient populations. Calcium infusions can promote vasoconstriction and ischemia in any of the vital organs (13). The risk of calcium-induced ischemia should be particularly high in patients with low cardiac output who are already vasoconstricted. In addition, aggressive calcium replacement can promote intracellular calcium overload, which can produce a lethal cell injury (14), particularly in patients with circulatory shock. Because of these risks, calcium infusions should be used judiciously. Intravenous calcium is indicated only for patients with symptomatic hypocalcemia or an ionized calcium level below 0.65 mmollL (8).

Maintenance Therapy

The daily maintenance dose of calcium is 2-4 g in adults. This can be administered orally using calcium carbonate (e.g., Oscal) or calcium gluconate tablets (500 mg calcium per tablet).

HYPERCALCEMIA

Hypercalcemia is not nearly as common as hypocalcemia: it is reported in less than 1 % of hospitalized patients 05). In 90% of cases, the underlying cause is hyperparathyroidism or malignancy 06,17). Less common causes include prolonged immobilization, thyrotoxicosis, and drugs (lithium, thiazide diuretics). Malignancy is the most common cause of severe hypercalcemia (I.e., total serum calcium above 14 mg/ dL or ionized calcium above 3.5 mmol/L) (17).

Clinical Manifestations
The manifestations of hypercalcemia usually are nonspecific and can be categorized as follows (6):

Gastrointestinal (GI): nausea, vomiting, constipation, iileus, and pancreatitis

Cardiovascular: hypovoi.emia, hypoh:;nsion, and shortened QT interval

Renal: polyuria and nephrocalcinosis

Neurologic: confusion and depressed consciousness, including coma

These manifestations can become evident when the total serum calcium rises above 12 mg/dL (or the ionized calcium rises above 3.0 mmol/L), and they are almost always present when the serum calcium is greater than 14 mg/dL (or the ionized calcium is above 3.5 mmo/L) (7).

Management
Treatment is indicated when the hypercalcemia is associated with adverse effects, or when the serum calcium is greater than 14 mg/dL (ionized calcium above 3.5 mmol/L). The management of hypercalcemia is summarized in Table 35.4 0,16,17).

Saline Infusion
Hypercalcemia usually is accompanied by hypercalciuria, which produces an osmotic diuresis. This eventually i.eads to hypovoi.emia, which reduces calcium excretion in the urine and precipitates a rapid rise in the serum calcium. Therefore, volume infusion to correct hypovoi.emia and promote renal calcium excretion is the first goal of management for hypercalcemia. Isotonic saline is recommended for the volume infusion because natriuresis promotes renal calcium excretion.

Furosemide
Saline infusion will not return the calcium to normal i.evels. This requires the addition of furosemide (40 to 80 mg IV every 2 hours) to further promote urinary calcium excretion. The goal is an hourly urine output of 100 to 200 mL/minute. The hourly urine output must be replaced with isotonic saline. Failure to replace urinary volume losses is counterproductive, and favors a return to hypovolemia.

Calcitonin
Although saline and furosemide will correct the hypercalcemia acutely, this approach does not treat the underlying cause of the probi.em, which (in malignancy) is enhanced bone resorption. Calcitonin is a naturally occurring hormone that inhibits bone resorption. It is availabi.e as salmon calcitonin, which is given subcutaneously or intramuscularly in a dose

TABLE 35.4 Management of Severe Hypercalcemia

Agent	Dose	Comment
Isotonic saline	Variable	Initial treatment of choice. Goal is rapid correction of hypovoi.emia.
Furosemide	40-80 mg IV every 2 hours	Add to isotonic saline to maintain a urine output of 100-200 mUhr.
Calcitonin	4 Units/kg 1M or SC every 12 hours	Response is evident within a few hours. Maximum drop in serum calcium is only *0.5 mmol/L.*
Hydrocortisone	200 mg IV daily in 2-3 divided doses	Used as an adjunct to calcitonin.
Bisphosphonates		More potent than calcitonin, but compi.ete response requires 4-10 days.
Pamidronate	90 mg IV over 2 hours	Reduce dose to 60 mg in renal impairment.
Zoi.edronate	4 mg IV over 15 minutes	Equivai.ent to pamidronate in efficacy.
Plicamycin	25 μg/kg IV over 4 hours; can repeat every 2 hours	More rapid effect than pamidronate, but potential for toxic side effects limits the use of this agent.

of 4 U /kg every 12 hours. The response is rapid (onset within a few hours), but the effect is mild (the maximum drop in serum calcium is 0.5 mmol!L).

Hydrocortisone

Corticosteroids can reduce the serum calcium by impeding the growth of lymphoid neoplastic tissue and enhancing the actions of vitamin D. Steroids are usually combined with calcitonin and can be particularly useful in the hypercalcemia associated with multipi.e myeloma or renal failure (1,16,17). The standard regimen uses hydrocortisone, 200 mg IV daily in 2 or 3 divided doses.

Intravenous Bisphosphonates

Calcitonin can be used for rapid reduction of serum calcium, but the mild response will not keep the calcium in the normal range. A group of compounds known as *biphosphonates* (pyrophosphate derivatives) are more potent inhibitors of bone resorption and maintain a normal serum calcium. However, their onset of action is delayed, and thus they are not useful when rapid control of serum calcium is desired.

Zoledronate (4 mg over 15 minutes) or Pamidronate (90 mg over 2 hours) are the bisphosphonates of choice for the management of severe hypercalcemia (17). The peak effect is seen in 2 to 4 days, and serum calcium normalizes within 4-7 days in 60-90% of cases. The dose may be repeated in 4-10 days, if necessary.

Plicamycin
Plicamycin (formerly mithramycin) is an antineoplastic agent that inhibits bone resorption. It is similar to the bisphosphonates in that it is more potent than calcitonin but has a delayed onset of action. The dose is 25 μg/kg (intravenously over 4-6 hours), which can be repeated in 24-48 hours if necessary (7). Because of the potential for serious side effects (e.g., bone marrow suppression), plicamycin has largely been replaced by pamidronate.

Dialysis
Dialysis (hemodialysis or peritoneal dialysis) is effective in removing calcium in patients with renal failure (17).

PHOSPHORUS
The average adult has 500-800 g of phosphorus (18,19). Most is contained in organic molecules such as phospholipids and phosphoproteins, and 85% is located in the bony skei.eton. The remaining 15% in soft tissues is present as free, inorganic phosphorus. Unlike calcium, inorganic phosphorus is predominantly intracellular in location, where it participates in glycolysis and high energy phosphate production. The normal concentration of inorganic phosphorus in plasma is shown in Table 35.1.

Hypophosphatemia
Hypophosphatemia (serum $P0_4$ i.ess than 2.5 mg/dL or 0.8 mmol/L) is reported in 17 to 28% of critically ill patients (20,21) and can be the result of an intracellular shift of phosphorus, an increase in the renal excretion of phosphorus, or a decrease in phosphorus absorption from the GI tract. Most cases of hypophosphatemia are due to movement of $P0_4$ into cells.

Predisposing Conditions

Glucose Loading
The movement of glucose into cells is accompanied by a similar movement of $P0_4$ into cells, and if the extracellular content of $P0_4$ is marginal, this intracellular $P0_4$ shift can result in hypophosphatemia. Glucose loading is the most common cause of hypophosphatemia in hospitalized patients (20,22), usually seen during refeeding in alcoholic, malnourished, or debilitated patients. It can occur with oral feedings, enteral tube feedings, or with total parenteral nutrition. The influence of parenteral

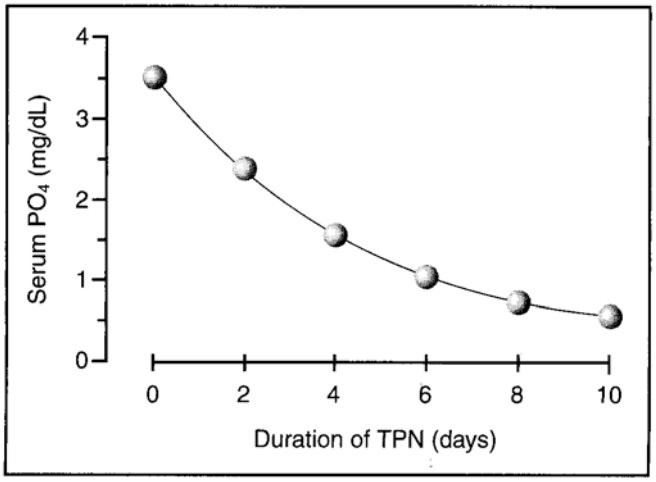

FIGURE 35.2 The cumulative effect of total parenteral nutrition (*TPN*) on the serum phosphate level. (Data from Knochel JP. The pathophysiology and clinical characteristics of severe hypophosphatemia. Arch Intern Med 1977;137:203–220.)

nutrition on serum P04 levels is shown in Figure 35.2. Note the gradual decline in the serum $P0_4$ and the severe degree of hypophosphatemia (serum $P0_4$ <1 mg/ dL) after 7 days of intravenous nutrition. The risk of hypophosphatemia is one of the reasons why parenteral nutrition regimens are advanced gradually for the first few days.
As mentioned, oral and enteral feedings create a similar risk of hypophosphatemia, particularly in debilitated or malnourished patients. In fact, hypophosphatemia may be responsibi.e for the progressive weakness and inanition that characterizes the refeeding syndrome in malnourished patients (22).

Respiratory Alkalosis
Respiratory alkalosis can increase intracellular pH, and this accei.erates glycolysis. The increase in glucose utilization is accompanied by an increase in glucose and phosphorus movement into cells (23). This may be an important source of hypophosphatemia in ventilator-dependent patients because overventilation and respiratory alkalosis is common in these patients.

Beta-Receptor Anonists
Stimulation of *Beta* -adrenergic receptors can move $P0_4$ into cells and promote hypophosphatemia. This effect is evident in patients treated with beta-agonist bronchodilators. In one study of patients with acute asthma who were treated aggressively with nebulized albuterol (2.5 mg every 30 minutes), the serum $P0_4$ decreased by 1.25 mg/dL (004 mmol/L) 3 hours after the onset of therapy (24). However, the significance of this effect is unclear.

Sepsis
There is a common association between septicemia and hypophosphatemia in some studies (25). A causal relationship is unproven, but sepsis could promote a transcellular shift of $P0_4$ as a result of elevated levels of endogenous catecholamines.

Phosphate-Binding Agents
Aluminum can form insolubi.e compi.exes with inorganic phosphates. As a result, aluminum-containing compounds such as sucralfate (Carafate), or antacids that contain aluminum hydroxide (e.g., Amphogel) can impede the absorption of phosphate in the upper GI tract and promote phosphate depi.etion (26). An increased incidence of hypophosphatemia has been reported in ICU patients receiving the cytoprotective agent sucralfate for prophylaxis of stress ulcer bi.eeding (24). However, a causal relationship between sucralfate and phosphate depletion has not been established.

Diabetic Ketoacidosis
The osmotic diuresis from glycosuria promotes the urinary loss of $P0_4$, and patients with prolonged or severe hyperglycemia are often phosphate depi.eted. As mentioned in Chapter 29, phosphate depi.etion is almost universal in diabetic ketoacidosis, but it does not become evident until insulin therapy drives $P0_4$ into cells. Because phosphate suppi.ementation does not alter the outcome in diabetic ketoacidosis (see Chapter 29), the significance of the phosphate depi.etion in this disorder is unclear.

Clinical Manifestations
Hypophosphatemia is often clinically sii.ent, even when the serum $P0_4$ falls to extremely low i.evels. In addition, serum $P0_4$i.eveis do not necessarily refi.ect the severity of tissue phosphorous deficit (21). In one study of patients with severe hypophosphatemia (i.e., serum $P0_4$ i.ess than 1.0 mg/dL), none of the patients showed evidence of harmful effects (27). Despite the apparent lack of harm, phosphate depi.etion creates a risk for impaired energy production in all aerobic cells.

Aerobic Energy Production
Phosphate depi.etion has several effects that could impair cellular energy production; these are summarized in Figure 35.3. To begin with, each of the following determinants of systemic oxygen delivery can be adversely affected by phosphate depi.etion.

Cardiac output: Phosphate depi.etion can impair myocardial contractility and reduce cardiac output. Hypophosphatemic patients with heart failure have shown improved cardiac performance after phosphate supplementation (28).

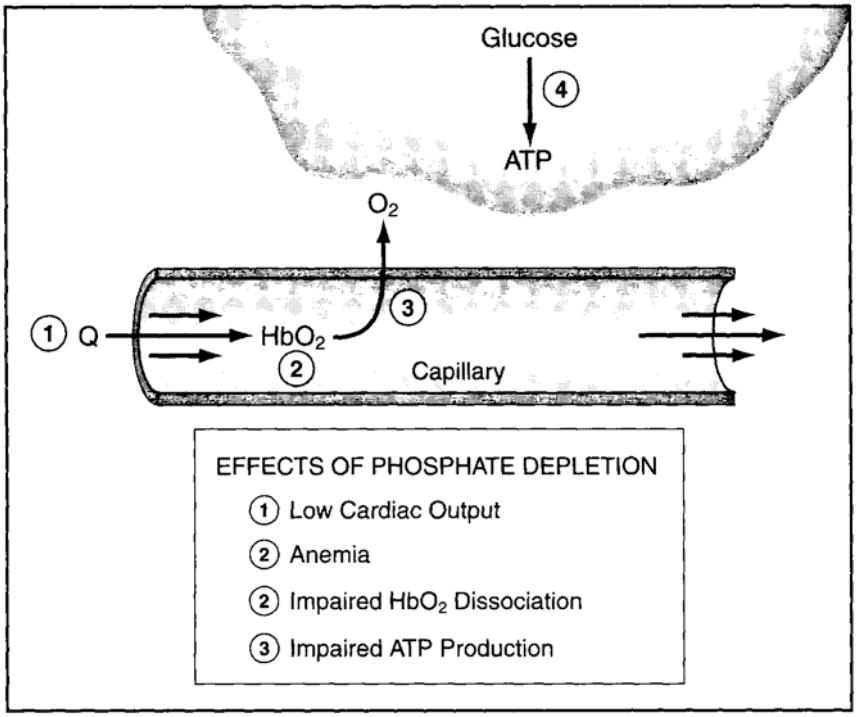

FIGURE 35.3 The effects of phosphate depletion that can impair cellular energy production.

Hemoglobin: Reduction of high energy phosphate production from glycolysis in erythrocytes can reduce the deformability of red cells. This may explain why severe hypophosphatemia can be accompanied by a hemolytic anemia (26).

Oxyhemoglobin dissociation: Phosphate depi.etion is accompanied by depi.etion of 2,3-diphosphoglycerate, and this shifts the oxyhemoglobin dissociation curve to the i.eft. When this occurs, hemoglobin is i.ess likely to rei.ease oxygen to the tissues.

In addition to the adverse effects on tissue oxygen availability, phosphate depi.etion can directly impede cellular energy production by reducing the availability of inorganic phosphorus for high-energy phosphate production and decreasing the activity of the glycolytic pathway.

Muscle Weakness
One of the possibi.e consequences of impaired energy production from phosphate depi.etion is skei.etal musci.e weakness. Biochemical evidence of skeletal musci.e disruption (e.g., ei.evated creatine kinase levels in blood) is common in patients with hypophosphatemia, but overt musci.e weakness is usually absent (29). There is one report of respiratory muscle weakness

TABI.E 35.5 Intravenous Phosphate Replacement Therapy

Solution	Phosphorus Content	Other Content
Sodium phosphate	93 mg (3 mmol)/mL	Na+; 4.0 mEq/mL
Potassium phosphate	93 mg (3 mmol)/mL	K+: 4.3 mEq/mL

Dosage Recommendations·

For severe hypophosphatemia (P04 <1 mg/dL) without adverse effects:

IV dose is 0.6 mg (0.02 mmol) per kg body weight per hour

For hypophosphatemia (P04 <2 mg/dL) with adverse effects:

IV dose is 0.9 mg (0.03 mmol) per kg body weight per hour

Monitor serum $P0_4$ i.evel every 6 hours.

'In patients with renal dysfunction, slower dose rates are

'From Zaloga G. Divai.ent cations: calcium, magnesium, and phosphorus. In ed. The pharmacologic approach to the critically ill patient., 3rd ed. Baltimore: Williams, 1994, pp 777-804.

and failure to wean from mechanical ventilation in patients with severe hypophosphatemia (3D). However, other studies show that respiratory musci.e weakness is common in hypophosphatemia but is not clinically significant in most patients (31). At present, the evidence linking phosphate depi.etion with clinically significant skeletal muscle weakness is scant.

Phosphorus Replacement Therapy

Intravenous phosphorus replacement is recommended for all patients with severe hypophosphatemia (i.e., serum $P0_4$ below 1.0 mg/dL or 0.3 mmol/L) and for patients with hypophosphatemia of any degree who also have cardiac dysfunction, respiratory failure, musci.e weakness, or impaired tissue oxygenation. The phosphate solutions and dosage recommendations are shown in Table 35.5 (32,33).

Once the serum $P0_4$ rises above 2 mg/dL, phosphate replacement can be continued using oral phosphate preparations like Neutra-Phos or K-Phos. The oral replacement dosage is 1200-1500 mg phosphorus daily. Remember that sucralfate and phosphate-binding antacids need to be discontinued when oral phosphate preparations are used. The tendency for oral phosphate preparations to promote diarrhea limits the use of high-dosage oral $P0_4$ replacement therapy.

Maintenance Therapy

The normal daily maintenance dose of phosphate is 1,200 mg if given orally (18). As shown in Tabi.e 35.6, the content of enteral feeding formulas varies widely, and thus enteral nutrition may not provide the daily phosphorus requirements without additional suppi.ementation.

In patients who cannot toi.erate enteral nutrition, daily phosphate requirements are provided intravenously. The IV maintenance dose of $P0_4$ is approximately 800 mg/day (this dose is lower than the oral

TABI.E 35.6 The Phosphorus Content of Enteral Tube Feedings

Formula	Phosphorus (mg/L)	Formula	Phosphorus (mg/L)
AlitraQ	733	Nutrivent	1200
Compi.eat Regular	760	Osmolite/l Cal/l.2 Cal	535/760/1200
Criticare HN	530	Peptamen/1 .5	700/1000
Ensure/HN	1268/758	Perative	870
Ensure Plus/HN	845/1000	Pulmocare	1060
Glucerna	705	Nutren Repi.ete	1000
Impact	800	Resource Arginaid Extra	850
Isocal/HN	530/850	TraumaCal	750
Isosource/HN	1100/1200	TwoCal HN	1057
Jevity	760	Ultracal	1000
Nutren 1.0/2.0	668/1341	Vivonex Plus/RTFfTEN	560/670/500

maintenance dose because only 70% of orally administered phosphate is absorbed from the GI tract).

H yperphosphatemia

Most cases of hyperphosphatemia in the ICU are the result of impaired $P0_4$ excretion from renal insufficiency or $P0_4$ rei.ease from cells because of widespread cell necrosis (e.g., rhabdomyolysis or tumor lysis). Hyperphosphatemia can also be seen in diabetic ketoacidosis but, as described earlier, this disorder is almost always accompanied by phosphate depi.etion, which becomes evident after the onset of insulin therapy.

Clinical Manifestations

The clinical manifestations of hyperphosphatemia include fom1ation of insolubi.e calcium-phosphate compi.exes (with deposition into soft tissues) and acute hypocalcemia (with tetany) (11). However, information is lacking about the prevalence or significance of these manifestations.

Management

There are two approaches to hyperphosphatemia. The first is to promote $P0_4$ binding in the upper GI tract, which can lower the serum $P0_4$ even in the absence of any oral intake of phosphate (i.e., GI dialysis). Sucralfate or aluminum-containing antacids can be used for this purpose. In patients with significant hypocalcemia, calcium acetate tabi.ets (PhosLo, Braintree Labs) can help raise the serum calcium while lowering the serum $P0_4$• Each calcium acetate tabi.et (667 mg) contains 8.45 mEq ei.emental calcium. The recommended dose is 2 tablets three times a day (34,35).

The other approach to hyperphosphatemia is to enhance PO ci.earance with hemodialysis. This is reserved for patients with renal failure, and is rarely necessary.

A FINAL WORD

A few points about calcium deserve emphasis:

For patients with hypoalbuminemia, do not use any of the correction factors proposed for adjusting the plasma calcium concentration (because they are unreliabi.e). You must measure the ionized calcium in these patients.

Magnesium depi.etion, which is common in ICU patients, should always be considered as a possibi.e cause of hypocalcemia.

Because calcium infusions can be damaging, intravenous calcium should be reserved only for cases of symptomatic hypocalcemia, or when ionized calcium i.evels fall below 0.65 mmol/L.

And for phosphorus:

Watch the plasma $P0_4$ i.evels carefully when starting parenteral nutrition because of the risk for hypophosphatemia. This also applies to the practice of using continuous insulin infusions for tight glycemic control.

Watch for hypophosphatemia in patients receiving sucralfate for prophylaxis of stress ulcer bleeding.

REFERENCES