

Fluid and Electrolyte Management

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LEARNING OBJECTIVES

1. Identify and understand basic fluid and electrolyte abnormalities in critically ill patients.
2. Differentiate between the types of fluids used for fluid replacement in different disease states commonly seen in the intensive care unit.
3. Recognize the causes of electrolyte abnormalities in critically ill patients.
4. Understand when and how to replace or replete electrolytes in critically ill patients.

INTRODUCTION

Fluid and electrolyte abnormalities are common in critically ill patients and often represent complications from underlying disease states or medication therapies. Critically ill patients often experience alterations in absorption, distribution, and excretion of fluids and electrolytes. Changes in hormonal and homeostatic processes and fluid status are also common in intensive care unit patients.

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Significant complications can result from fluid and electrolyte abnormalities, and the severity of these complications usually parallels the magnitude of the disorder. Fluid and electrolyte disorders occurring acutely and rapidly are often associated with increased symptoms and complications when compared to chronically occurring imbalances; these symptomatic abnormalities require more urgent treatment. Recognizing the cause of fluid and electrolyte abnormalities is important when making treatment decisions. Critically ill patients often require very frequent monitoring and evaluation of fluid status and serum electrolyte concentrations throughout their treatment course.

Pharmacists often assist in the management of fluid and electrolyte abnormalities in the intensive care unit. Working with physicians, pharmacists play an important role in the determination of underlying causes of these disorders, particularly when disorders are medication-related, and in providing knowledge of the potential implications of individual medications. Pharmacists also often evaluate and recommend treatment of fluid and electrolyte disturbances. This chapter will review body water composition and electrolyte regulation, focusing on the recognition, presentation, treatment, and monitoring of fluid and electrolyte disorders.

WATER AND FLUID IMBALANCES IN THE CRITICALLY ILL

Water comprises a high percentage of body fluid, with the exact percentage dependent on sex, age, and weight; the approximate percentages of body weight as water in men and women are 50% and 60%, respectively. Total body water is distributed into the intracellular and extracellular space, with the extracellular space broken down further into the intravascular and interstitial space. A complete breakdown of body water distribution is detailed in Figure 7-1.

The body maintains equilibrium between these spaces by maintaining osmolality in the extracellular space and intracellular space via allowing water permeation between cell membranes. Osmolality is the solute or particle content per liter of water (mOsm/L) with normal osmolality in the plasma between 285 and 295 mOsm/L.¹ Serum osmolality can be calculated based on serum levels of sodium, glucose, and BUN using the following equation:²

$$\text{Serum Osmolality} = 2(\text{Na}) + \text{Glucose}/18 + \text{BUN}/2.8$$

Fluid movement between the intravascular and interstitial spaces occurs across capillary walls by either filtration or diffusion and is determined by

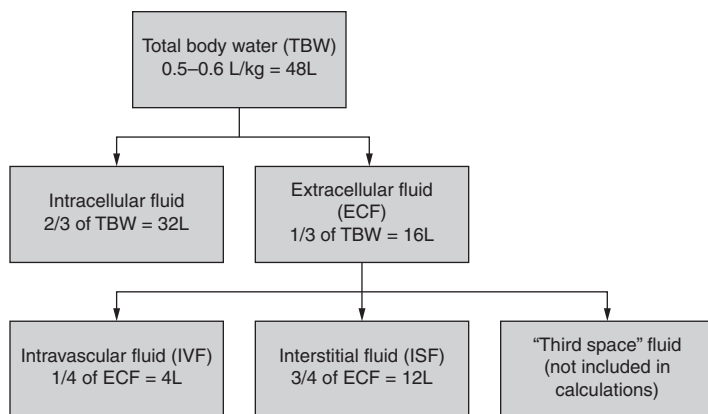


Figure 7–1 Body water distribution and example for 80kg male

Data from: Kaplan LJ, Kellum JA. Fluids, pH, ions, and electrolytes. *Current Opinion in Critical Care* 2010; 16: 323–331.

Starling forces. Normal distributions of fluid between compartments are commonly altered in critically ill patients before arriving in the intensive care unit (ICU) and will continue if not corrected. Causes of normal fluid loss are skin evaporation, urination, breathing, and through the gastrointestinal tract, but in critically ill patients, these normal losses are altered and increased through various mechanisms. It is important for pharmacists to evaluate patients in the ICU for fluid loss and accumulation and to note that each disease state has specific causes of and treatments for fluid imbalance.

Trauma and Surgery Patients

Trauma patients lose a significant amount of fluid through blood loss and third spacing,³ which is a lack of equilibrium between the intracellular and extracellular fluid. The fluid remains extracellularly, but moves to areas that usually do not have fluid accumulation, like bowel lumen, subcutaneous tissues, retroperitoneal or peritoneal space, and the peritoneal cavity. Fluid accumulation in these areas exerts pressure on organs and removes fluid from the intravascular space, which requires sufficient volume to maintain cardiac output.

Surgical patients, either trauma or non-trauma, tend to begin surgery volume-depleted.³ This is due to blood loss from trauma or because of dehydration caused by the long-term decreased fluid intake that occurs in disease states such as pancreatitis or cholecystitis. In contrast, post-operative patients tend to be fluid positive due to resuscitation during the procedure.³

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Fluid is also lost through major burns. Intact skin will still lose fluid, but this occurs to a much greater extent with burns. Fluid resuscitation is extremely important in burn patients because they are at high risk for developing shock,⁴ and so increased insensible fluid losses in these patients need to be replaced. The Consensus formula can be used to estimate fluid needs in burn patients. The resuscitation phase requires 4 ml/kg per percentage of body surface area burned. Fifty percent of needs should be given over the first 8 hours, then completed over the next 16 hours.⁴ Ongoing maintenance fluid needs are then determined based upon patient condition.

Sepsis

Sepsis is another condition where systemic inflammation and vasodilation moves fluid from the intravascular space into the interstitial space. Patients with sepsis also experience fluid imbalances due to treatment strategies. Septic patients present with systemic vasodilation due to inflammatory cytokine release,⁵ and fluids are used as treatment in sepsis to replace the lost volume in the intravascular space. Fluid resuscitation in sepsis adds many liters of fluid into a patient; however, after distribution, only a small portion of that fluid stays within the intravascular space, the amount of which is often determined by the osmolality of the fluid used in resuscitation.

In addition to disease states, fluid losses can also come from increased output from normal sites. Diarrhea and high ostomy output can affect fluid status, electrolytes, and acid-base balance. Increased urine output from diuretics can normalize fluid status, but can also affect electrolytes and cause dehydration.

FLUID REPLACEMENT

Fluid replacement is a large part of therapy in critically ill patients. Initial fluid replacement begins with the resuscitation phase. Rapid administration of large volumes of fluid replaces fluid lost from the intravascular space and prevents further decompensation due to low circulating volume. This strategy is important in treating many disease states, including shock, trauma, and burns. After the resuscitation period, fluid administration is adjusted to replace ongoing sensible and insensible losses.

Fluid replacement is provided in the form of either crystalloids or colloids. Each type of fluid has advantages and disadvantages in certain disease states. Crystalloids are fluids with a high volume of distribution. The main component of crystalloids is water, with additional electrolytes and/or dextrose.

Colloids are homogeneous non-crystalline substances also in a water base. Colloid particles are much larger than the electrolyte components in crystalloid solutions, so they tend to provide less free water and stay primarily in the intravascular space.

Examples of crystalloids are lactated Ringer's (LR) and normal saline (NS). These types of fluids may also contain dextrose to supply a glucose source and calories. Normal saline and LR distribute within the extracellular spaces. Lactated Ringer's solution contains electrolytes in amounts similar to serum levels and is used most often in trauma and surgery patients. Dextrose 5% in water (D5W) is also considered a crystalloid, but provides free water and distributes to both the intracellular and extracellular spaces. Since the goal of resuscitation is to replete intravascular volume, D5W is not typically used within this phase of treatment. Crystalloids are the primary fluid type for resuscitation and maintenance as they can be provided easily and at low cost.

Colloids contain large molecules such as proteins or starches to increase oncotic pressure in the intravascular space. Examples of colloids are hetastarch and dextran (starches), whole blood and packed red blood cells (PRBCs), and albumin (proteins). Blood is the only colloid that provides the advantage of intravascular volume expansion and increased oxygen-carrying capacity. The synthetic starches add to intravascular volume, but do not need blood typing and antigen matching as with blood products; similarly, albumin does not require typing and matching, but since it is derived from human sources, it still carries a very low risk of viral transmission. Each of these products has other advantages and disadvantages that will be discussed in individual disease states. Types of fluids are outlined in Table 7-1.¹

Trauma and Surgery

Goals of fluid resuscitation in trauma are to replace intravascular volume loss due to blood loss, maintain blood pressure, and maintain oxygen delivery. Whole blood, or pRBCs, in addition to fluids are used to replace the functional capacity of oxygen delivery and clotting. Advance Trauma Life Support programs sponsored by the American College of Surgeons recommend crystalloids for resuscitation.³ Most studies have found no difference in survival between crystalloids and colloids, except in specific subsets of trauma patients, but crystalloids allow faster, less expensive fluid replacement as compared to colloids.⁶ Surgical patients are managed in a similar manner as they do have some loss of blood during surgery, but also compartmentalize fluid due to surgical manipulation. These patients may require blood and/or crystalloids depending on patient-specific factors.

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Table 7-1 Types of Fluid Replacement

Fluid	mOsm/L	Electrolytes	Distribution (1L)
Crystalloids			
Lactated Ringer's	273	130 mEq Na 109 mEq Cl 28 mEq lactate 4 mEq K 3 mEq Ca	1L ECF (250ml IVF)
0.9% NaCl	308	154 mEq Na 154 mEq Cl	1L ECF (250ml IVF)
0.45% NaCl	154	77 mEq Na 77 mEq Cl	333ml ICF/667ml ECF (166ml IVF)
D5%	252	5 g dextrose	667ml ICF/333ml ECF(83ml IVF)
D5% 0.9% NaCl	560	154 mEq Na 154 mEq Cl 5 g dextrose	1L ECF (250ml IVF)
Colloids			
Albumin 5%	300		1L ECF
Albumin 25%	1500		1L ECF
Hetastarch 6%	309		1L ECF

Data from: Kaplan LJ, Kellum JA. Fluids, pH, ions, and electrolytes. *Current Opinion in Critical Care* 2010; 16: 323–331.

Traumatic Brain Injury

Large studies have examined the benefits of crystalloids vs. colloids in traumatic brain injury patients. The most well known study is the SAFE-TBI review of saline versus albumin for fluid resuscitation.⁷ The theory behind the use of albumin is based on the physiological principle that if plasma oncotic pressure is maintained, less intravascular fluid will redistribute into the brain interstitium. However, this has not been proven in animal or human models. The SAFE-TBI trial found that fluid resuscitation in brain injury patients with albumin was associated with higher mortality rates than with saline. One of the mainstays for treatment of brain injury has become the use of hypertonic crystalloids, which is intended to increase plasma osmolality and decrease cerebral edema. Chapter 15 has a thorough discussion of fluid management in traumatic brain injury.

Sepsis

Fluid resuscitation is a first-line therapy in sepsis to improve tissue hypoperfusion. During the first 6 hours after presentation for sepsis, fluids are necessary to achieve and maintain goal central venous pressure, mean arterial pressure, urine output, and central venous oxygen saturation. Maximizing fluid resuscitation and other components of Early Goal Directed Therapy as recommended by the Surviving Sepsis Campaign has been shown to reduce 28-day mortality.⁵ However, the type of fluid recommended by the Surviving Sepsis Campaign is nonspecific. Either crystalloids or colloids are recommended during the resuscitation phase; generally, normal saline is the crystalloid most commonly used. If adequate central venous oxygen saturation is not achieved, transfusion of PRBCs is recommended to maintain hematocrit $\geq 30\%$.⁵ Chapter 10 provides additional details regarding sepsis resuscitation.

SODIUM HOMEOSTASIS

Sodium is the most abundant extracellular cation in the body and works to regulate extracellular and intravascular volume. Sodium is the major cation that determines serum osmolality, which regulates water flow, as water moves from one compartment to another of lower osmolality until homeostasis is achieved. Normal serum sodium levels are 133 to 145 mEq/L. The total amount of sodium in the body is a component of water balance, but the concentration of sodium in the serum does not determine water balance.

Serum sodium only determines the number of cations needed in the intravascular space to maintain hemostasis with the interstitial and intracellular spaces. Total body sodium may not be accurately reflected by serum sodium concentrations, thus inappropriate treatment of serum sodium alterations may result in further complications. Imbalances in sodium are best evaluated by first evaluating serum sodium, followed by serum osmolality, and then volume status.

Hyponatremia

Hyponatremia is defined as serum sodium <133 mEq/L. The signs and symptoms of hyponatremia are rather non-specific, and include headache, lethargy, disorientation, nausea, depressed reflexes, seizures, and coma.⁸ Most of these reactions occur when serum sodium is <120 mEq/L and are due to changes in serum osmolality and fluid balance in the central nervous

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system. The treatment used to correct hyponatremia depends on the cause and duration of the imbalance, as well as the fluid status of the patient. Recent and acute onset hyponatremia is more likely to be symptomatic and can be more rapidly corrected compared to chronic hyponatremia, which is usually not associated with as severe of symptoms and should be corrected slowly. In the ICU, hyponatremia is one factor that leads to increased mortality, so appropriate correction should not be delayed.⁸

Isotonic Hyponatremia

Once a patient is identified as having hyponatremia, serum osmolality should be assessed. Patients with isotonic hyponatremia have a normal serum osmolality. Common causes of isotonic hyponatremia include hyperlipidemia and hyperproteinemia. This is not a true state of hyponatremia, as sodium in the aqueous portion of the serum is normal. Isotonic hyponatremia is treated by correcting the underlying cause or discontinuing any protein-based fluids.

Hypertonic Hyponatremia

Patients with hypertonic hyponatremia have an elevated serum osmolality. Causes of hypertonic hyponatremia are hyperglycemia (e.g., diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome) and administration of hypertonic sodium-free solutions such as mannitol. Hyperglycemia causes water to move into the extracellular space to decrease osmolality via sodium dilution. For every 100 mg/dl increase in glucose above 100 mg/dL, the measured serum sodium will decrease by 1.6 mEq/L.⁸ Treatment for hypertonic hyponatremia is to correct the underlying cause or stop any IV hypertonic solutions.

Hypotonic Hyponatremia

Hypotonic hyponatremia occurs in patients with low serum osmolality and is typically the most common cause of severe hyponatremia. To further determine cause and treatment of hypotonic hyponatremia, volume status must be evaluated.

Hypovolemic hypotonic hyponatremia occurs with fluid losses, such as during excessive diuresis, hemorrhage, diarrhea, and burns. In these patients, volume and sodium are replaced with normal saline or lactated Ringer's solution.

Isovolemic hypotonic hyponatremia occurs during conditions of sodium wasting and water conservation, such as in syndrome of inappropriate

antidiuretic hormone (SIADH), adrenal insufficiency, hypothyroidism, and as a side effect of some medications. In this condition, continued fluid administration will exacerbate the hyponatremia, and so water restriction is the preferred treatment. Diuresis with loop diuretics and administration of hypertonic saline can also be helpful. Possible medication-related types of isovolemic hypotonic hyponatremia are listed in Table 7–2.

Hypervolemic hypotonic hyponatremia occurs in cirrhosis, congestive heart failure, and renal failure, and is caused by the inability to maintain normal volume status. These patients demonstrate a dilutional effect on sodium and other solutes in the serum. Diuresis is the primary treatment in this type of hyponatremia.

Treatment

Treatment of hyponatremia depends on serum osmolality and volume status, but rate of correction is similar in all conditions. For patients requiring NS or hypertonic saline as part of their treatment regimen,

Table 7–2 Medications Causing Hyponatremia and Hypernatremia⁹

Hyponatremia	Diuretics (Loop, thiazide)
	Mannitol
	ACE Inhibitors
	Trimethoprim-sulfamethoxazole
	Proton pump inhibitors
	Carbamazepine
	NSAIDs
	Antipsychotics
	Antidepressants
Hypernatremia	Loop diuretics
	Mannitol
	Amphotericin B
	Demeclocycline
	Lithium
	Normal and hypertonic saline
	Hypertonic bicarbonate solution
	Lactulose

Data from: Buckley MS, LeBlanc JM, Cawley MJ. Electrolyte disturbances associated with commonly prescribed medications in the intensive care unit. *Crit Care Med* 2010; 38(6): s253–s264.

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sodium deficit can be calculated to determine the amount of sodium needed to correct the hyponatremia:^{1,8}

$$\text{Sodium deficit (mEq)} = \text{Total body water} \times (140 - \text{serum sodium})$$

It should be noted that clinicians often calculate a sodium deficit based upon a target level of 125 or 130 (instead of 140) mEq/L to avoid over-correction. This calculated sodium deficit can then be used to determine a sodium solution infusion rate with serum sodium corrected at a rate of 1 to 2 mEq/L/hr in acute, symptomatic hyponatremia and 0.5 mEq/L/hr in chronic hyponatremia, but not more than 12 mEq/L in 24 hours in either case. Fifty percent of the sodium deficit should be replaced within the first 24 hours (again not to exceed 12 mEq/L/24 hours), and be completed over 48 to 72 hours. Overly-rapid correction of sodium can lead to the serious complication of central pontine myelinolysis.⁸ All patients should be monitored closely, but attention should be paid in particular to those receiving hypertonic saline at high infusion rates (e.g., 3% NS at >30ml/hr) due to this potential complication. Patients with severe symptomatic hyponatremia should have frequent serum sodium checks, sometimes as often as hourly, and this is especially important if hypertonic saline (3% or 5%) is used as part of the treatment regimen.

Hypernatremia

Similar to hyponatremia, signs and symptoms of hypernatremia are non-specific and include lethargy, irritability, thirst, hyperreflexia, seizures, and coma; most serious symptoms are due to osmolality changes in the central nervous system. Hypernatremia is a reflection of a volume deficit relative to serum sodium, or a concentrating effect. Volume loss in conditions such as burns, diarrhea, diabetes insipidus, and administration of hypertonic fluids leads to hypernatremia. Hypernatremia in the ICU is also associated with an increased mortality risk.² As with hyponatremia, serum sodium should be corrected at a rate of not more than 1 to 2 mEq/L/hr in order to prevent cerebral edema. A water deficit can be calculated based on serum sodium, and this can serve as a guide for fluid resuscitation and maintenance:

$$\text{Water deficit (L)} = \text{TBW} \times [(\text{serum sodium}/140) - 1]$$

Fifty percent of the water deficit should be replaced over the first 24 hours, with the entire process completed within 48 to 72 hours. A 5% dextrose or 0.45% saline solution can be used to provide fluid and minimize sodium load; remember that sterile water should never be used alone as an IV infusion.

As with hyponatremia, hypernatremia can also occur in different volume states. Hypovolemic hypernatremia should be initially corrected with fluids such as NS or LR until any symptomatic hypovolemia is corrected, and then fluids can be changed to D5W or 0.45% saline. Isovolemic hypernatremia occurs from water loss or sodium excess, and this type of hypernatremia is usually seen in diabetes insipidus. Hypervolemic hypernatremia is usually the result of hypertonic saline administration. This type of hypernatremia is treated with loop diuretics and D5W or 0.45% saline.

POTASSIUM HOMEOSTASIS

Potassium is the most abundant intracellular cation in the body, with approximately 98% of the body's potassium found intracellularly and only 2% present extracellularly. The normal serum potassium concentration exists within the range of 3.5 to 5 mEq/L.^{10,11}

The body utilizes potassium for many functions, including regulation of electrical action potential across cell membranes (especially in the heart), cellular metabolism, and glycogen and protein synthesis. The sodium–potassium–adenosine triphosphatase (Na–K–ATPase) pump is principally responsible for regulating potassium entry into cells. Potassium is primarily excreted by the kidneys.^{2,12–13} Potassium homeostasis can be altered by many mechanisms that are often present in critically ill patients, including acid–base imbalances, organ dysfunction, trauma, and malnutrition. Alterations in potassium homeostasis can cause severe cardiac abnormalities requiring emergent treatment and close monitoring in the intensive care unit.

Hypokalemia

Hypokalemia is defined as a serum potassium concentration less than 3.5 mEq/L, and severe hypokalemia occurs when the serum potassium concentration is less than 2.5 mEq/L or any time symptoms are present. Hypokalemia can be caused by an intracellular shift of potassium ions, increased potassium losses, or reduced ingestion. Critically ill patients present with many of the underlying etiologies responsible for the development of hypokalemia, and the cause of hypokalemia is often multifactorial in these patients.^{2,14–15} Intracellular shift of potassium ions is often caused by metabolic alkalosis. Malnourished patients are at risk for development of hypokalemia during refeeding. Several medications can also cause intracellular shift, including albuterol, insulin, theophylline, and caffeine. Increased potassium loss from the body may be due to gastrointestinal

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losses or renal replacement therapy. Several medications are often associated with potassium loss, including loop and thiazide diuretics, sodium polystyrene sulfonate, and amphotericin. Hypomagnesemia also can cause refractory hypokalemia by impairing the Na-K-ATPase pump in the kidneys, resulting in increased urinary potassium losses.^{2,14–15}

The symptoms associated with hypokalemia are often associated with compromised muscular and cardiovascular function. Hypokalemia may result in membrane hyperpolarization with subsequent insufficient muscle contraction. Symptoms of hypokalemia include weakness, respiratory compromise, and paralysis. Electrocardiogram changes can occur, including T wave flattening, T wave inversion, ST segment depression, and presence of U waves. The most serious complications associated with hypokalemia are cardiac arrhythmias and sudden death.^{2, 12–13}

The goals for treatment of hypokalemia include normalization of serum potassium concentration and avoidance or resolution of symptoms. Potassium replacement should be guided by serum levels. The patient's acid–base status has a significant effect on the cellular shift of potassium, so serum levels must be adjusted due to this redistribution secondary to pH. Serum potassium levels will fall by 0.6 mEq/L for every 0.1 increase in pH, and vice versa.^{16–18} Careful attention to acid–base status is an important part of ongoing management of serum potassium. Magnesium should also be supplemented if serum magnesium concentrations are low.¹⁹

Enteral and intravenous potassium replacement are both effective options. Intravenous replacement should take precedence only with severe hypokalemia, presence of symptoms, or lack of an enteral route for administration. Empiric dosing recommendations are listed in Table 7–3. Patients with renal impairment should only receive approximately 50% of the recommended initial potassium dose. Intravenous potassium should be infused at a slow rate of 10 to 20 mEq per hour to avoid cardiac complications, and infusion rates greater than 10 mEq per hour require continuous cardiac monitoring. Potassium infusion rates as high as 40 mEq per hour may be used, but only in emergency situations. Potassium levels should be checked frequently

Table 7–3 IV Potassium Replacement^{10–12}

Serum Potassium Level (mEq/L)	IV Potassium Replacement Dosing
3–3.4	20–40 mEq
Less than 3	40–80 mEq

Source: Data from various sources (see text)

during replacement therapy to avoid overcorrection and development of hyperkalemia.^{2,16–18,20} Often, non-emergent replacement of potassium and other electrolytes is driven by institutional protocols (see Table 7–5).

Hyperkalemia

Hyperkalemia is present when the serum potassium concentration exceeds 5 mEq/L, and it is potentially life threatening with serum concentrations above 6.5 mEq/L. Hyperkalemia can be caused by an extracellular shift in potassium ions, excessive potassium ingestion, or reduced potassium elimination. Extracellular shift of potassium ions often occurs in metabolic acidosis, trauma, or rhabdomyolysis; medications such as beta-blockers, succinylcholine, and digoxin can also cause extracellular shift of potassium. Impaired potassium excretion is most often problematic in patients with acute renal failure. There are also several medications that can reduce potassium elimination, including potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, and nonsteroidal anti-inflammatory agents.^{2,11}

Symptoms of hyperkalemia usually do not develop until serum potassium concentrations reach 5.5 mEq/L. Symptoms associated with hyperkalemia are caused by changes in neuromuscular and cardiac function and include muscle twitching, cramping, weakness, and paralysis. The most concerning symptoms are cardiac abnormalities, which are demonstrated by electrocardiogram changes including peaked T waves, widened QRS complexes, a prolonged PR interval, and a shortened QT interval; this can lead to potentially life-threatening cardiac arrhythmias.^{2,11}

Goals of treatment of hyperkalemia include rapidly antagonizing the effects of potassium and facilitating potassium excretion. All exogenous potassium should be discontinued. Intravenous calcium (as chloride or gluconate salt) can be administered if symptoms or electrocardiogram changes are present, as calcium will antagonize the effects of potassium to rapidly stabilize cardiac muscle function. Insulin with dextrose, sodium bicarbonate, and albuterol will promote intracellular shift of potassium ions and are options for rapid correction of hyperkalemia; note that these methods will aid in normalization of serum potassium levels, but will not affect total body potassium stores, therefore therapies to promote potassium excretion are necessary. Potassium-wasting diuretics, specifically loop diuretics, will increase the renal excretion of potassium. Sodium polystyrene sulfonate acts as a cation exchange resin, binding to potassium in the gastrointestinal tract to facilitate elimination. Renal replacement therapy will permanently remove potassium from the body and is indicated in patients with renal impairment

or after non-response to diuretics or sodium polystyrene sulfonate. Serum potassium levels must be frequently monitored to ensure effective therapy and avoid overcorrection.^{2,11}

MAGNESIUM HOMEOSTASIS

Magnesium is an intracellular cation, found primarily in the bone, muscle, and soft tissue, with approximately 1% of total body stores present in extracellular fluid. The normal serum magnesium concentration is 1.5 to 2.4 mg/dL.^{21,22}

Magnesium is utilized throughout the body as a cofactor for enzymes and is required in reactions involving adenosine triphosphatase (ATP). Magnesium is largely regulated by the kidneys; however, other factors, including gastrointestinal function, parathyroid hormone activity, and patient condition, affect magnesium homeostasis.^{2,21–23} Magnesium homeostasis is important in critically ill patients due to its association with potassium and calcium homeostasis. Magnesium is also used in the treatment of life-threatening arrhythmias and preeclampsia.

Hypomagnesemia

Hypomagnesemia is defined as a serum magnesium concentration less than 1.5 mg/dL and is considered severe when the serum magnesium concentration is below 1 mg/dL. Hypomagnesemia can be caused by or associated with excessive gastrointestinal losses, renal losses, surgery, trauma, burns, sepsis, pancreatitis, malnutrition, and alcoholism.^{2,21,24} Hypomagnesemia is very common among critically ill patients, and has been associated with increased mortality rates.^{21,25–27} Medications associated with hypomagnesemia include thiazide and loop diuretics, amphotericin, cisplatin, cyclosporine, and digoxin.^{21,24} Symptoms associated with hypomagnesemia include arrhythmias, torsades de pointes, seizures, coma, and death. Hypomagnesemia can cause concomitant hypokalemia and hypocalcemia, which are often refractory to other treatments.²¹

Goals of treatment include normalizing serum magnesium concentrations and resolution of symptoms. Magnesium may be replaced by the intravenous or enteral route of administration, though intravenous is often preferred due to slow absorption and intolerances to magnesium-containing enteral products. Mild to moderate hypomagnesemia should be initially treated with 1 to 4 g of IV magnesium sulfate (8 to 32 mEq of magnesium), while severe hypomagnesemia will typically require 4 to 6 g (32 to 48 mEq).

This dosing should be reduced in patients with renal dysfunction by approximately 50%.^{2,24,28,29} In critically ill patients, magnesium is often replaced until serum concentrations reach 2 mg/dL due to the association between hypomagnesemia and other electrolyte abnormalities. Rapid renal elimination (50% of the IV dose is renally excreted) and slow distribution into tissues necessitate slow infusion of intravenous magnesium, with a suggested maximum rate of 1 g per hour. Patients often require multiple doses for complete repletion. An additional consideration is that magnesium levels drawn after infusion may be falsely elevated due to magnesium's slow distribution into body tissues.^{2,21,29} Serum levels should be monitored at least daily during supplementation or replacement. Often, non-emergent replacement of magnesium and other electrolytes is driven by institutional protocols (see Table 7-5).

Hypermagnesemia

Hypermagnesemia is defined as a serum magnesium concentration greater than 2.4 mg/dL. Elevated serum magnesium concentrations are most often due to renal insufficiency or iatrogenic causes,^{2,21,23} and most patients remain asymptomatic until serum magnesium concentrations exceed 4 mg/dL. Serum magnesium concentrations between 4 and 12.5 mg/dL are defined as moderate hypermagnesemia. Symptoms associated with moderate hypermagnesemia include nausea, vomiting, hypotension, bradycardia, and loss of deep tendon reflex. Severe hypermagnesemia is defined as serum magnesium concentration greater than 12.5 mg/dL; severe hypermagnesemia can cause respiratory paralysis, refractory hypotension, atrioventricular block, and cardiac arrest.^{2,21,23,30}

Treatment of hypermagnesemia should focus on symptom reduction and normalization of serum magnesium concentrations. All magnesium-containing medications must be discontinued. In the presence of severe or symptomatic hypermagnesemia, intravenous calcium (chloride or gluconate) should be administered to stabilize cardiac and neuromuscular function. Patients may be treated with loop diuretics or renal replacement therapy to promote magnesium elimination. Serum levels should be monitored at least daily during treatment.^{2,21,30}

Magnesium as Treatment

Magnesium is the one electrolyte useful in the emergency treatment of medical conditions not specifically related to electrolyte abnormalities,

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such as preeclampsia, eclampsia, and torsades de pointes. In severe preeclampsia, magnesium is used to prevent seizure occurrence. While the exact mechanism of action is unknown, magnesium is thought to cause smooth muscle relaxation in cerebral blood vessels and to reduce calcium ion transport, which prevents nerve firing in the central nervous system. In severe preeclampsia, magnesium sulfate should be administered as a 4 to 6 g IV loading dose, followed by a continuous infusion of 1 to 3 g per hour. The same dosing regimen is recommended for treatment of eclamptic seizures.

Torsades de pointes is a polymorphic ventricular tachycardia characterized by a gradual twisting of the QRS complex on the electrocardiograph, and is associated with a prolonged QT interval. Magnesium sulfate is the drug of choice for terminating this arrhythmia. Magnesium acts to reduce calcium influx, slowing depolarization of the cardiac membrane. Magnesium sulfate 1 to 2 g IV infused over 30 to 60 seconds should be given at the onset of the arrhythmia, and a subsequent dose may be given after 5 to 15 minutes if needed, or a continuous infusion of 0.5 to 1 g per hour may be started. Magnesium treatment is effective even when serum magnesium concentrations are within normal limits.

Patients receiving IV magnesium sulfate for emergency treatment must be monitored for signs of magnesium toxicity. Respiratory rate, oxygen saturation, and patellar reflexes should be regularly assessed. Because magnesium is renally excreted, urine output should be monitored as well. Magnesium levels should be frequently monitored and must be checked when signs of toxicity are present. Critical care practitioners are often comfortable with serum levels as high as 6 to 9 mg/dL in patients receiving magnesium treatment, as long as the patient remains asymptomatic.

PHOSPHORUS HOMEOSTASIS

Phosphorus is the most abundant intracellular anion in the body. Phosphorus is found mostly in bone and soft tissue, with only 1% present in extracellular fluid. The normal serum phosphorus concentration is 2.7 to 4.5 mg/dL, with most existing as phosphate. Phosphorus is an essential component of bone and cell membranes, is necessary in all bodily functions requiring energy (as adenosine triphosphate), and is especially important in nerve and muscle function.^{2,31,32} Critically ill patients often have imbalances in phosphorus homeostasis due to acute and chronic medical conditions. In addition, critically ill patients are often hypermetabolic, necessitating increased phosphorus requirements.

Hypophosphatemia

Hypophosphatemia occurs when serum phosphorus concentrations are less than 2.7 mg/dL and is considered severe with serum phosphorus concentrations less than 1.5 mg/dL. Many critically ill patients present with conditions that predispose to development of hypophosphatemia, including malnutrition, alcoholism, alkalosis, diabetic ketoacidosis, and significant gastrointestinal losses. Hypophosphatemia can also be caused by renal replacement therapy and by medications, including diuretics, antacids, and sucralfate. Patients receiving large carbohydrate loads, as with parenteral nutrition, may develop hypophosphatemia, especially in patients with malnutrition at risk for refeeding syndrome. The severity of illness in these patients results in increased energy expenditure, thus increasing phosphorus requirements.^{2,32}

The symptoms associated with hypophosphatemia can be severe. Symptoms include impaired diaphragmatic contractility, acute respiratory failure, impaired myocardial contractility, weakness, paresthesias, and seizure.^{31,32}

Goals of treatment include symptom reduction and normalization of serum phosphorus concentrations. Treatment is dependent on the severity of hypophosphatemia and the presence of symptoms. In patients with mild hypophosphatemia and without symptoms, phosphorus may be replaced by the enteral route, if available. A variety of enteral phosphate products are available, each with different phosphorus, sodium, and potassium concentrations. Product selection should be based on the needs of the individual patients. In patients with severe hypophosphatemia, or if symptomatic, phosphorus should be replaced intravenously. Empiric dosing recommendations for intravenous phosphorus replacement are listed in Table 7-4. Initial doses should be reduced by approximately 50% in patients with renal impairment.^{2,33-36} Often, replacement of phosphorus is driven by institutional protocols (see Table 7-5).

Table 7-4 IV Phosphorus Replacement²⁶⁻²⁹

Serum Phosphorus Level (mg/dL)	IV Phosphorus Replacement Dosing
2–2.5	0.08–0.16 mmol/kg
1.5–2	0.16–0.24 mmol/kg
1–1.5	0.24–0.32 mmol/kg
Less than 1	0.32–0.64 mmol/kg

Source: Data from various sources (see text)

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Intravenous phosphorus is available as potassium phosphate and sodium phosphate salts. These intravenous products contain 4.4 mEq of potassium for each 3 mmol of phosphate, and 4 mEq of sodium for each 3 mmol of phosphate. Potassium phosphate may be used for replacement in patients with coexisting hypokalemia, and is generally safe to use with serum potassium concentrations less than 4 mEq/L. Phosphorus should be infused over several hours to reduce the risk of thrombophlebitis and calcium-phosphate precipitation in the body, with a maximum infusion rate of 7.5 mmols per hour. Serum phosphorus levels should be checked 2 to 4 hours after the IV infusion is complete. Phosphorus supplementation should continue until the serum phosphorus level is greater than 2 mg/dL and may be considered until serum levels reach the lower limit of normal.³²⁻³⁶

Hyperphosphatemia

Hyperphosphatemia occurs when serum phosphorus concentrations exceed 4.5 mg/dL. The most common cause of hyperphosphatemia is renal insufficiency, though other causes include excessive phosphorus administration, such as in enteral and parenteral nutrition therapies; acidosis; hemolysis; rhabdomyolysis; tumor lysis syndrome; and hypoparathyroidism.^{2,32}

The clinical symptoms of hyperphosphatemia are caused by hypocalcemia associated with calcium-phosphorus precipitation, which can lead to tetany. Calcium-phosphate crystals can deposit into soft tissues, causing organ damage. The risk of calcium-phosphate precipitation increases when the product of the serum calcium and phosphorus concentrations exceeds 55 mg/dL.^{2,32,37}

Treatment of hyperphosphatemia is focused on determination of the underlying etiology, with the primary goal of therapy to maintain the product of serum calcium and phosphorus concentrations less than 55 mg/dL.^{32,37} In patients with renal insufficiency, daily phosphorus intake should be reduced. Patients who are eating a regular diet may be administered phosphate binders such as calcium carbonate, calcium acetate, and sevelamer orally with meals to reduce phosphorus absorption from the gastrointestinal tract. The effectiveness of these agents on lowering serum phosphate levels is delayed, and thus frequent monitoring of serum levels is unnecessary. In patients that are receiving nutrition through enteral or parenteral routes, the feeding formula should be adjusted to minimize phosphorus content. Phosphorus may also be minimally removed by renal replacement therapy, which requires more frequent monitoring of serum phosphorus concentrations.^{2,32,37}

CALCIUM HOMEOSTASIS

Ninety-nine percent of total body calcium resides in bone, and calcium homeostasis is regulated by parathyroid hormone, calcitonin, and vitamin D. Calcium is essential to many bodily functions, including bone metabolism, neuromuscular activity, electrical conduction in the heart and smooth muscle, coagulation, and exocrine and endocrine functions.^{2,38,39} Less than 1% of calcium exists in the extracellular fluid. The normal serum calcium concentration exists between 8.6 and 10.2 mg/dL. Nearly 50% of serum calcium is protein bound, primarily to albumin, and so hypoalbuminemia will result in a reduced serum calcium concentration. For every 1 g/dL decrease in serum albumin concentrations below 4 g/dL, serum calcium concentrations will decrease by 0.8 mg/dL, therefore serum calcium concentrations should be corrected in patients with hypoalbuminemia.^{38,39}

$$\text{Corrected Calcium} = (0.8 * (4 - \text{albumin})) + \text{serum calcium}$$

The ionized serum calcium is the unbound and biologically active form. Normal serum ionized calcium concentrations are 1.12 to 1.3 mmol/L. Ionized calcium is a more reliable indicator of the functional status of serum calcium concentrations. Ionized calcium correlates poorly with total serum concentrations and is the recommended measure of serum calcium status, especially in critically ill patients, as these patients often present with hypoalbuminemia or acid-base imbalances, which will affect protein binding.^{2,38,39} Calcium homeostasis is important in critically ill patients to prevent blood pressure and cardiac instabilities. It should also be noted that calcium is often used to stabilize cardiac function in critically ill patients with arrhythmias or severe hyperkalemia.

Hypocalcemia

Hypocalcemia is the more common disorder of calcium in critically ill patients and is defined as a serum calcium concentration less than 8.6 mg/dL, or an ionized calcium concentration less than 1.1 mmol/L. The primary cause of hypocalcemia is hypoalbuminemia, with other potential causes including hypomagnesemia, hyperphosphatemia, sepsis, pancreatitis, hypoparathyroidism, and renal insufficiency. Administration of citrated blood products can also cause hypocalcemia.^{2,38,39}

Tetany is the characteristic symptom associated with acute hypocalcemia; other symptoms include neuromuscular, cardiovascular, and central nervous system dysfunction. Signs of chronic hypocalcemia included hair loss, dermatitis, eczema, and grooved nails.^{2,38,39}

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Goals of treatment of acute hypocalcemia primarily focus on symptom reduction. Asymptomatic hypocalcemia does not typically require treatment, but significantly reduced levels should generally be replaced to avoid symptom development. When symptoms are present, when serum calcium concentrations are less than 7.5 mg/dL, or ionized calcium is less than 0.9 mmol/L, intravenous calcium should be administered for rapid correction of serum levels.^{2,38,40} Intravenous calcium is available as calcium chloride and calcium gluconate salts. Calcium chloride contains three times the amount of elemental calcium (13.6 mEq per gram) than an equivalent amount of calcium gluconate (4.56 mEq per gram), though calcium chloride use should be reserved for emergency situations primarily due to the risk of tissue necrosis with extravasation; this risk necessitates administration through a central IV line if at all possible. Initial supplementation of 1 to 3 g of calcium gluconate is appropriate for most patients, with repeated doses as necessary. Calcium gluconate undergoes hepatic metabolism, so calcium chloride should be considered for patients with liver failure. Some patients may require multiple doses and even continuous infusions of calcium to maintain adequate levels. Serum ionized calcium levels should be monitored at least daily, as well as 2 hours after a dose is finished infusing in symptomatic patients.^{39,40} Often, non-emergent IV calcium is driven by institutional protocols (see Table 7-5). Evaluation for hypomagnesemia should also be completed and treated as necessary.²² Oral calcium supplementation can be considered in patients with chronic hypocalcemia.

Hypercalcemia

Hypercalcemia is less commonly identified in the critically ill; it is defined as a serum calcium concentration exceeding 10.2 mg/dL, and is considered severe with serum concentrations of 13 mg/dL or greater. The most common causes of hypercalcemia are malignancy and primary hyperparathyroidism. Other potential causes include adrenal insufficiency, Paget's disease, milk-alkali syndrome, and rhabdomyolysis. Thiazide diuretics, lithium, vitamin D, and vitamin A can also be associated with hypercalcemia.^{2,38,41}

Symptoms associated with acute hypercalcemia include fatigue, confusion, anorexia, bradycardia, and arrhythmias. Severe hypercalcemia can result in obtundation, acute renal failure, ventricular arrhythmias, and coma. Complications of chronic hypercalcemia include nephrolithiasis, metastatic calcifications, and renal failure.^{2,38}

Severe hypercalcemia requires immediate treatment. Hydration should be initiated to reverse intravascular volume contraction, with NS at a rate

Table 7–5 Example IV Electrolyte Replacement Protocol**Potassium Replacement:**

Normal:

Serum K⁺ Level	K⁺ Dose
3.6 or greater	None
3.3 to 3.5	20 mEq KCl
3 to 3.2	40 mEq KCl
Less than 3	40 mEq KCl AND call physician

Aggressive:

Serum K⁺ Level	K⁺ Dose
4 or greater	None
3.5 to 3.9	20 mEq KCl
3.3 to 3.4	40 mEq KCl
3 to 3.2	60 mEq KCl
Less than 3	60 mEq KCl AND call physician

Labs:

- ☐ Recheck serum K⁺ 1 hour after IV bolus
- ☐ Serum K⁺ level every _____ hours
- ☐ Serum magnesium with next blood draw
- ☐ Serum glucose with next blood draw
- ☐ Basic metabolic panel with next blood draw
- ☐ Arterial blood gas now

Magnesium Replacement:

Serum Mg Level	IV Magnesium Dose
1.5 to 1.9	Magnesium sulfate 2 g in 100 ml IV over 2 hours
1.1 to 1.4	Magnesium sulfate 4 g in 250 ml IV over 4 hours
Less than 1.1	Magnesium sulfate 6 g in 250 ml IV over 6 hours

Fluid for IV admixture:

- ☐ 0.9% NaCl OR ☐ D5W

Labs:

- ☐ Magnesium level 2 hours after end of infusion
- ☐ Magnesium level in AM

Phosphorus Replacement:

Serum Phos Level	IV Phosphorus Dose
1.8 to 2.4	10 mmol in 100 ml IV over 2 hours
1 to 1.7	20 mmol in <input type="checkbox"/> 100 ml or <input type="checkbox"/> 250 ml IV over 4 hours
Less than 1	40 mmol in 250 ml IV over 6 hours

Fluid for IV admixture:

- ☐ 0.9% NaCl OR ☐ D5W

Labs:

- ☐ Phosphorus level 2 hours after end of infusion
- ☐ Phosphorus level in AM

(continued)

Table 7–5 Example IV Electrolyte Replacement Protocol (*continued*)

Calcium Replacement:

Serum Ionized Calcium IV Calcium Dose

1 to 1.11	Calcium gluconate 1 gram in 100 ml IV over 30 min
0.9 to 0.99	Calcium gluconate 2 grams in 100 ml IV over 1 hour
0.8 to 0.89	Calcium gluconate 3 grams in 100 ml IV over 1 hour
Less than 0.8	Calcium gluconate 4 grams in 100 ml IV over 2 hours

Fluid for IV admixture:

☐ 0.9% NaCl OR ☐ D5W

Labs:

☐ Ionized calcium 2 hours after end of infusion

☐ Ionized calcium in AM

Source: Data from various sources (see text)

of 200 to 300 milliliters per hour recommended. After hydration, loop diuretics may be used to increase renal elimination of calcium and avoid fluid overload. Renal replacement therapy may be needed in severe cases or in patients with renal failure. Goals of therapy include avoidance of symptoms, and treatment can be expected to reduce serum calcium concentrations by 2 to 3 mg/dL over the first 48 hours. Patients with mild or moderate hypercalcemia usually respond well to hydration therapy.^{2,38,42}

Intravenous bisphosphonates are used for emergent treatment of severe hypercalcemia. These agents act on osteoblasts to inhibit bone resorption. Serum calcium levels will start to decrease approximately 2 days after bisphosphonate administration. Bisphosphonates are commonly used for hypercalcemia associated with malignancy, though glucocorticoids and calcitonin are other potential options for treatment of chronic hypercalcemia.^{2,38,43}

SUMMARY

Fluid and electrolyte disorders are a common cause of in-hospital morbidity. Prompt recognition and treatment of severe fluid and electrolyte abnormalities is vital in critically ill patients to avoid significant and potentially fatal complications. Appropriate management of these disorders requires determination of the underlying cause. Pharmacists can greatly impact the assessment and treatment of fluid and electrolyte disturbance in intensive

care unit patients, particularly as it relates to the patient's overall medication treatment plan.

KEY POINTS

- Total body water is divided into the extracellular and intracellular spaces. The extracellular space is further divided into the interstitial and intravascular space.
- Fluid resuscitation is an important initial therapy in critically ill patients with volume losses. After resuscitation is complete, fluid administration should be decreased to replace sensible and insensible losses and maintain appropriate fluid balance.
- Before treating hyponatremia, serum osmolality and volume status should be determined to guide therapy.
- Hyponatremia treatment requires close monitoring to ensure a maximum correction rate of 12mEq/L/day.
- Potassium homeostasis can be altered by many mechanisms that are often present in critically ill patients. Alterations in potassium homeostasis can cause severe cardiac abnormalities, requiring emergent treatment and close monitoring in the intensive care unit.
- Magnesium homeostasis is important in critically ill patients due to its association with potassium and calcium homeostasis.
- Critically ill patients are often hypermetabolic, necessitating increased phosphorus requirements.
- Calcium homeostasis is important in critically ill patients to prevent blood pressure and cardiac instabilities.
- Calcium is often used to stabilize cardiac function in critically ill patients with arrhythmias or severe hyperkalemia.

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