Fluid and Electrolytes

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Introduction

Fluid and electrolyte physiology is central to the clinical management of surgical patients. The composition and regulation of body fluids has been studied for centuries, and the concept of intravenous infusion of fluids was established over a century ago [1]. David Sabiston, one of the premier surgeons of the twentieth century, reviewed Alfred Blalock's landmark work on the pathogenesis of shock, which demonstrated that fluid losses related to injury could be treated with intravascular volume repletion. This work provided the foundation for intravenous therapy in the management of hypovolemia [2]. Subsequently, the body of knowledge encompassing the complex interactions between body fluid compartments and the relationship to electrolyte physiology has increased significantly. This chapter reviews the physiologic principles underpinning fluid therapy, as well as the application of these principles to clinical fluid management. The relationship between disorders of water balance and sodium metabolism is delineated, as are the physiology and management of disorders of sodium, potassium, calcium, magnesium, and phosphorus metabolism.

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Total Body Water and the Fluid Compartments

Total body water (TBW) is defined as the total volume of water within the body. TBW is a percentage of body weight and is dependent on both the fat content and the chronological age of the individual. TBW as a percentage of body weight decreases with increasing body fat and with increasing age [3]. As a general rule, TBW is 60 % of body weight in men and 50 % of body weight in women [4].

TBW is comprised of the intracellular and the extracellular compartments. Intracellular fluid (ICF) makes up two thirds of TBW, and extracellular fluid (ECF) accounts for the remaining one third. ECF is subdivided into the intravascular and interstitial spaces. The intravascular space accounts for 25 % of the ECF and 8 % of the TBW; this space contains the plasma volume. The interstitial space comprises the remaining 75 % of the ECF and 25 % of the TBW; this space contains a free phase of fully exchangeable water and a bound phase of minimally exchangeable water. The transcellular compartment is an additional ECF designation; this compartment contains cerebrospinal fluid, synovial fluid, the water in cartilage and bone, eye fluids and lubricants of the serous membranes. This type of fluid

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is poorly exchangeable and comprises approximately 4 % of the TBW. The exchangeable components of the compartments comprising TBW are in dynamic equilibrium [5].

Effective circulating volume is the portion of the ECF that perfuses the organs. Under normal physiologic conditions, this corresponds to the intravascular volume. This relationship is altered in some disease states. For example, in congestive heart failure and in patients who have arteriovenous fistulae, the intravascular volume as well as total body salt and water are high, but effective circulating volume is low. A different type of alteration of the physiologic state occurs in bowel obstruction, pancreatitis, and the sepsis syndrome. Under these circumstances, the total ECF remains constant or increases initially, but intravascular volume is significantly decreased due to external losses or vasodysregulation. These conditions result in "third-space loss." This concept was initially recognized over 50 years ago, when experimental models of early hemorrhagic shock and elective operative tissue trauma were used to investigate changes in the body fluid compartments [6]. It was observed that ECF decreased more than the measured loss of plasma volume in these experiments. Shock and operative trauma were hypothesized to cause extracellular fluid to be sequestered in an "unexchangeable" compartment as a result of capillary leak [6, 7]. This heretofore undefined ECF compartment became known as the "loss to the third space," "deficit in functional extracellular volume," or the "nonanatomic third-space loss" [6, 8, 9]. In the ensuing decades, this concept was accepted as convention, some would argue resulting in unnecessarily aggressive resuscitation and perioperative fluid management strategies in an effort to compensate for fluid lost to the third space. The existing "third space" literature was reviewed by Brandstrup and colleagues during the past decade. They determined that the evidence in the early literature supporting the concept of the third space was based on flawed methodology [10, 11]. However, it is clear that disease processes such as bowel obstruction, pancreatitis, severe sepsis, and septic shock warrant aggressive fluid management strategies because the intravascular volume is markedly diminished in these clinical scenarios. Hypoperfusion is the end result in these cases and is best managed with restoration of circulating volume and treatment of vasodysregulation with vasoactive pressor agents.

Even though the intravascular volume is only a small percentage of the TBW, significant decreases in intravascular volume are poorly tolerated when decreased mean arterial pressure occurs. This is illustrated in the clinical consequences of the classes of hemorrhagic shock: class I (loss of <15 % blood volume), class II (loss of 15–30 % blood volume), class III (loss of 30–40 % blood volume), and class IV (loss of >40 % blood volume). Hypotension occurs in class III shock and is a relatively late manifestation of acute blood loss. Cardiac arrest ensues when >50 % of total blood volume is lost. On the other hand, the interstitial space is extremely compliant and buffers loss or excess of the intravascular space. Therefore, the volume of the interstitial space is highly variable. This relationship between the intravascular space and the interstitial space is possible because of the membranes that separate the body fluid compartments [12].

The ionic composition of the ECF and the ICF is highly defended in the normal physiologic state. The predominant cation in the ECF is sodium. Therefore, the ECF contains most of the sodium content of the body (60 mEq/kg). The ECF also contains small quantities of other cations, including potassium, calcium, and magnesium. The cations are electrochemically balanced principally by chloride and lactate anions. Bicarbonate, phosphate, sulfate, albumin, and other extracellular proteins also provide negative charge in the ECF. The predominant cation in the ICF is potassium. The ICF contains most of the potassium content of the body (42 mEq/kg). The ICF also contains smaller quantities of other cations, including magnesium and sodium. Phosphates and intracellular proteins are the primary anions of the ICF, and chloride and bicarbonate are present in lower concentrations [5].

The principles of osmosis dictate the movement of water between fluid compartments. Osmotic

equilibrium occurs when two solutions separated by a semipermeable membrane equalize the concentration of osmotically active particles on either side of that membrane as water moves along a concentration gradient. Osmolarity is measured in milliosmoles per liter, mOsm/L. Osmolality is measured in milliosmoles per kilogram H_2O, mOsm/kg H_2O. Both define the osmotic activity of particles in solution and are considered equivalent if the concentration of solutes is very low [5].

Plasma osmolality (Posm) indicates total body osmolality. Sodium [Na^+] is the predominant extracellular cation, and glucose and blood urea nitrogen (BUN) concentrations are significant in certain disease states. Therefore, the following formula is used for determination of Posm:

$$\text{Posm}\left(\text{mOsm}/\text{kg}\,\text{H}_2\text{O}\right) = 2\times\text{serum}\left[\text{Na}^+\right] + \text{glucose}/18 + \text{BUN}/2.8$$

The principles of osmosis as they relate to hypothetical semipermeable membranes are generalizations. The physiologic membranes that separate the body fluid compartments are much more complex. The capillary endothelium serves as the membrane that separates the intravascular and interstitial compartments. The endothelium exhibits different characteristics in different organs and is more permeable in the lung and liver than in the periphery [13]. The capillary endothelium is very permeable, allowing for rapid equilibration between the intravascular and interstitial spaces. Therefore, the interstitial space can serve as a buffer for the more highly defended intravascular space. Of particular clinical significance, leakage of albumin depends on the endothelial characteristics of tissue. Albumin leakage is high in lung and liver [14] and low in the peripheral tissues [15]. The cell surface membrane is impermeable to protein, but permeable to water, bicarbonate, and chloride. The sodium–potassium pump (Na^+, K^+-ATPase) actively transports sodium out of cells and potassium into cells, an energy-dependent process. This enzyme-dependent cell membrane integrity is disrupted in severe shock states as a result of impaired oxygen delivery and utilization. Passive sodium entry then leads to intracellular water migration, cellular swelling, and ultimately cell death [12].

Volume Control Mechanisms

Under normal physiologic circumstances, plasma osmolality is tightly controlled, averaging 289 mOsm/kg H_2O. Thirst and antidiuretic hormone (ADH) are the two primary regulators of water balance. Osmoreceptor cells in the paraventricular and supraoptic nuclei of the hypothalamus detect small changes in cell volume and activate the neuronal centers that control thirst and ADH secretion. Therefore, osmoreceptors control the fine-tuning of volume relationships [16]. Stimulants of ADH secretion include nicotine, ether, morphine, barbiturates, and tissue injury (including operative tissue dissection and manipulation). Ethanol inhibits ADH secretion and its water resorption activity in the renal collecting ducts.

The relationship of aquaporins to ADH physiology has been the subject of significant investigation over the course of the past two decades. Peter Agre, MD, an American medical doctor and molecular biologist, won the 2003 Nobel Prize in Chemistry for the discovery of aquaporins [17, 18]. Aquaporins are integral membrane pore proteins that regulate the flow of water. These water channels are ubiquitous in nature, including in the human body. Aquaporin proteins are comprised of six transmembrane alpha-helices arranged in a right-handed bundle, with the amino and the carboxyl termini located on the cytoplasmic surface of the membrane. The specific types of aquaporins differ in their peptide sequences [19, 20].

The principal cells lining the renal collecting ducts control the fine-tuning of body water homeostasis by regulating water resorption through aquaporin-2 (AQP_2) aquaporin-3 (AQP_3) and aquaporin-4 (AQP_4). AQP_3 and AQP_4 are embedded in the basolateral plasma membrane. ADH binds to the vasopressin-2 (V_2) receptor on the basal membrane of the renal collecting duct. This triggers redistribution of AQP_2 from intracellular vesicles into the apical plasma membrane. Water enters into the cells via AQP_2 and exits through AQP_3 and AQP_4 [21].

The mechanism of action of ADH with respect to the water permeability of the renal collecting

duct has therapeutic implications. A number of nonpeptide V_2 antagonists (vaptans) are in development. The mixed V_2/V_{1a} antagonist conivaptan has been approved by the US Food and Drug Administration (FDA) for intravenous use in the treatment of euvolemic and hypervolemic hyponatremia. Conivaptan produces aquaresis (solute-free water excretion), resulting in increased serum sodium levels, free water clearance, urine flow, and plasma osmolality [22, 23].

Baroreceptors control volume via sympathetic and parasympathetic connections in a less precise manner than do osmoreceptors. Stretch receptors detect changes in pressure and changes in volume that are manifested by changes in pressure. Volume receptors are located in the intra-thoracic capacitance vessels (vena cava) and the atria. Depending on volume status, these receptors either increase or decrease sympathetic tone to the kidney, which affects renal blood flow and tubular sodium resorption. Pressure receptors of the aortic arch and carotid arteries are important in extreme changes in arterial pressure (such as occurs with hemorrhage). Intra-renal baroreceptors of the afferent arteriole cause variability in release of renin depending on pressure. Hepatic volume receptors and cerebrospinal volume receptors have also been characterized [5].

Endocrine and hormonal factors also play a role in volume control mechanisms. The renin–angiotensin–aldosterone system is the primary hormonal mediator of volume control. The natriuretic peptide system is an endocrine mechanism that regulates blood volume and electrolyte balance. There are three members of the mammalian natriuretic peptide family: atrial natriuretic peptide (ANP), brain or B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP) [24, 25].

Renal prostaglandins (PGE_2 and PGI_2) may play a role in volume control, especially in conditions such as sepsis and jaundice. Normally, inhibition of prostaglandin production has little effect on renal function. However, nonsteroidal anti-inflammatory agents (inhibitors of cyclooxygenase) can precipitate renal failure in patients with renal dysfunction due to loss of the protective effects of renal prostaglandins [26].

Endothelins are peptide vasoconstrictors involved in volume and pressure regulation [27]. Nitric oxide (NO) is a free radical produced by nitric oxide synthases and is involved in many biologic functions, including volume and pressure regulation [28]. There is interaction between the endothelin and NO systems. In general, NO and endothelin actions oppose one another.

Baseline Water and Electrolyte Requirements

Sensible water losses can be measured and include urine (800–1,500 mL/24 h), stool (0–250 mL/24 h) and sweat (minimal). Sweat is a hypotonic mixture of electrolytes and water and does not contribute significantly to daily water loss except in very arid and hot climates. Insensible water losses are unmeasurable and include loss from the skin and lungs. This accounts for 600–900 mL/24 h (8–12 mL/kg/day). Insensible water loss increases 10 % for each degree of body temperature >37.2 °C. Therefore, fever is a significant contributor to insensible water loss. The normal daily sodium requirement is 1–2 mEq/kg/24 h; the potassium requirement is 0.25–0.50 mEq/kg/24 h [5].

Parenteral Solutions

Intravenous fluids are used for maintenance and resuscitation of surgical patients. The two broad categories of parenteral solutions are crystalloids and colloids. The appropriate choice of crystalloid or colloid solution depends on maintenance fluid requirements, fluid deficits, and ongoing fluid losses.

Lactated Ringer's (LR) solution is a commercially available crystalloid and has a composition similar to plasma. It is usually utilized as a resuscitative fluid to replace loss of fluid with a similar composition to plasma and is ideal when the patient's serum electrolyte concentrations are normal. LR has a relatively low sodium content (130 mEq/L), which makes this solution slightly hypotonic. Hyponatremia may result with exces-

sive or prolonged use or in patients who have impaired renal function and diminished ability to excrete free water. This may become problematic in patients who have traumatic brain injuries and other conditions that mandate a higher Posm. The lactate in LR occurs as sodium-lactate, which dissociates at physiologic pH. The lactate anions are metabolized to bicarbonate and, therefore, do not contribute to acidosis under normal conditions [29].

Normal saline solution (NSS) is another resuscitative crystalloid fluid and contains 154 mEq of both sodium and chloride. NSS is useful for treatment of hyponatremic hypochloremic metabolic alkalosis. However, the excessive and equal quantities of sodium and chloride can lead to significant electrolyte and acid–base disturbances, such as hyperchloremic metabolic acidosis (HCMA), which can aggravate any preexisting acidosis.

If a true isotonic fluid is required, but clinical circumstances mandate limitation of chloride, half-NSS (1/2 NSS) mixed with 75 mEq $NaHCO_3$/L can be utilized (1/2NSS +75 mEq $NaHCO_3$). The sodium content is essentially equivalent to NSS, but the chloride load is halved.

Hypertonic saline (HTS) solutions are utilized to replace sodium deficits in symptomatic hyponatremia. Most commonly used are 3 % NaCl and 1.5 % NaCl. The former should be administered via central venous access; the latter may be administered via peripheral veins. HTS has also been suggested for early resuscitation of hypovolemia in trauma and burn patients. Intravascular volume is increased more quickly and the total resuscitation volume may be decreased compared to standard crystalloid resuscitation. However, caution should be used because of the potential for induction of significant acid–base and electrolyte abnormalities [30].

Naturally occurring plasma volume expanders include albumin preparations (4, 5, 20, and 25 %) and fresh frozen plasma. Only 5 and 25 % albumin are available in the United States. Albumin preparations are usually prepared in NSS; therefore, large volume administration can result in HCMA. Additionally, the albumin molecule is of such a molecular weight that it readily passes through capillary pores that open in conditions that create a capillary leak [14, 15]. The SAFE trial demonstrated that albumin administration is as "safe as saline" and that hypoalbuminemia is associated with not only decreased colloid oncotic pressure but also perturbed pharmacologic agent carriage, detoxification, and immune responsivity [31].

Synthetic colloids may be utilized as resuscitative fluids, especially in surgical patients. Hydroxyethyl starch (HES) preparations are the most common. They are categorized by their average molecular weight, degree of substitution (DS) (molar substitution: # hydroxyethyl groups per 100 glucose groups) and concentration. Starches include hetastarch (DS = 0.7), pentastarch (DS = 0.5), and tetrastarch (DS = 0.4). Six percent solutions are the most commonly used in the United States. The vehicles for the starches differ. Hespan is a 6 % solution of hetastarch in a NSS vehicle, while Hextend is the identical starch in a solution with a composition similar to LR. Some interventional trials have noted an association with acute kidney injury or acute renal failure with the use of starch preparations [32]. Resuscitation with starch solutions alone provides little to no free water. Therefore, starch administration must occur in conjunction with maintenance fluid administration to mitigate against hyperoncotic renal injury [33].

Maintenance Fluid Therapy

Maintenance fluid therapy replaces fluids normally lost during the course of a day. Conversely, resuscitative fluid therapy replaces preexisting deficits or additional ongoing losses. Maintenance and resuscitative fluid therapy may occur simultaneously, but two different solutions are used to achieve differing goals.

Weight-based formulas are used to calculate maintenance water requirements, accounting for both sensible and insensible losses. One of the most commonly used is the "4–2–1 Rule":
First 10 kg body weight: 4 cc/kg/h
Second 10 kg body weight: 2 cc/kg/h
Each additional 10 kg body weight: 1 cc/kg/h

Using this formula, the hourly volume requirement for a 70 kg patient is 110 cc/h.

In patients who have clinically severe obesity, adjusted body weight (ABW) should be used when calculating a maintenance fluid rate:

$$\text{ABW} = \text{ideal body weight}\left(\text{IBW}\right) + 1/3\left(\text{actual} - \text{IBW}\right)$$

Maintenance fluid is hypotonic and contains 5 % dextrose as an aid in gluconeogenesis. The prototypical fluid is $D_5$1/2NSS + 20 mEq KCl/L in the adult. This provides the appropriate quantity of sodium and potassium based on the daily requirements outlined earlier. However, patients with renal impairment or anuria should not have potassium included in their maintenance fluid.

Resuscitative Fluid Therapy

The goal of resuscitative fluid therapy is to replace preexisting deficits and ongoing fluid losses. Crystalloid is the most common broad category of resuscitative fluid. An isotonic (or nearly isotonic) salt solution without added dextrose is utilized. LR is the most common resuscitative fluid used in surgical patients [34, 35].

The capillary endothelium is permeable to the components of an isotonic salt solution. Therefore, crystalloid distributes between the intravascular and interstitial spaces in proportion to the starting volumes of these spaces. Since the intravascular space comprises 25 % of the ECF and the interstitial space comprises 75 % of the ECF, the resultant ratio is 1:3. For each liter of crystalloid infused intravenously, 250 cc remains in the intravascular space and 750 cc diffuses into the interstitial space [12]. Additionally, crystalloid has pro-inflammatory effects [36, 37]. Strategies to limit these inflammatory effects have been investigated [38]. Limited intravascular volume expansion and the pro-inflammatory effects of crystalloid are the cornerstone of the crystalloid versus colloid debate from a historical perspective.

Leakage of albumin into the interstitial space is proportional to the net leakage of albumin in the body. This is variable, averaging a 25–35 % leakage rate under normal physiologic conditions [15]. This would be true of other iso-oncotic solutions as well. For each liter of 5 % albumin infused intravenously, approximately 750 cc remains in the intravascular space and 250 cc diffuses into the interstitial space. This proportion is opposite that of infusion of crystalloid isotonic salt solutions. The ratio of intravascular filling between colloid and crystalloid solutions is, therefore, 3:1 [12]. However, this model is overly simplified. Even under physiologic conditions, there is a high degree of variability in the leakage rate of albumin, depending on the unique characteristics of various capillary beds. Abnormalities in microvascular permeability are the norm in the surgical patient, particularly in the critically ill. Under pathologic conditions, up to half of exogenously administered albumin may diffuse into the interstitial space [5].

The use of exogenously administered albumin in critically ill patients was analyzed in a Cochrane report published in 1998. In the three categories of patients studied (those with hypovolemia, burns or hypoalbuminemia), the risk of death in the albumin-treated groups was higher than in the comparison groups [39, 40]. This review was criticized for various reasons, including the inclusion characteristics and small volume effects limitations. Subsequently, the SAFE (*S*aline versus *A*lbumin *F*luid *E*valuation) trial indicated no difference between albumin and saline in a double-blind randomized study of approximately 7,000 critically ill patients. These patients did not require massive plasma volume administration. Albumin was noted to be as safe as saline in this population [31]. Albumin appears safe in most groups but may not provide a survival advantage. In patients with traumatic brain injury, there may be a durable increased risk of death with exogenous albumin [39, 40].

The synthetic plasma expanders are alternatives to albumin. These include the broad category of HES, delineated above. A paradigm shift in the use of these solutions is again occurring. In 2012, several papers were published comparing the use of HES to crystalloid in subsets of the critically ill population. Perner et al. demonstrated that patients with severe sepsis receiving HES 130/0.42

had an increased risk of death at day 90 and were more likely to require renal replacement therapy, compared to patients receiving Ringer's acetate [41]. Myburgh et al. demonstrated that there was no significant difference in 90-day mortality between randomly selected critically ill patients resuscitated with 6 % HES (130/0.4) or saline. However, more patients who received resuscitation with HES were treated with renal replacement therapy [42]. In patients with severe sepsis, Bayer et al. demonstrated that shock reversal was achieved equally fast with synthetic colloids or crystalloids. Use of colloids resulted in only marginally lower required volumes of resuscitation fluid. In addition, they found that both low molecular weight HES and gelatin may impair renal function [43].

Another Cochrane review of colloids versus crystalloids for fluid resuscitation in critically ill patients was published in 2013. From assessment of randomized controlled trials, the authors con - cluded that there is no evidence to indicate that resuscitation with colloids reduces the risk of death, compared to resuscitation with crystalloids, in patients with trauma, burns, or following surgery. The use of HES might increase mortality. Since colloids are not associated with improved survival and are more expensive than crystalloids, continued use in clinical practice may not be justified [44]. When extrapolating these studies to clinical practice, each clinical scenario must be considered carefully, keeping in mind the patient populations assessed in the reviewed literature, the specific types of fluids studied and the limitations of the studies.

The Relationship Between Disorders of Water Balance and Sodium Balance

Sodium is the primary extracellular cation and principal determinant of plasma osmolality. The concentration of sodium and TBW shares an inverse relationship. As TBW increases, the serum sodium concentration decreases and vice versa. The sodium level thereby is a marker of TBW. Abnormal sodium concentration reflects abnormal TBW content [45].

Disorders of sodium levels are a common occurrence in clinical practice. Such disturbances are usually secondary to changes in water balance and not sodium levels. Sodium concentration is a reflection of body fluid tonicity and not a reflection of total body sodium content [46]. Often clinicians misinterpret changes in sodium levels as changes in total body sodium content. There are scenarios in which sodium content is abnormal, but this occurs less often than instances in which TBW is abnormal.

Disorders of Sodium Metabolism

Sodium abnormalities are a common occurrence in the surgical patient. Sodium abnormalities occur due to a host of reasons, some iatrogenic and some physiological.

Hyponatremia is defined as a sodium level of less than 135 mEq/L. It is the most common electrolyte abnormality in the hospitalized patient, occurring in as many as 20–25 % of hospitalized patients and in 30 % of patients in the intensive care unit (ICU). Approximately 4.4 % of surgical ward patients develop the abnormality within one week of surgery [47]. Hyponatremia is a risk factor for mortality, with 10–15 % mortality in chronic hyponatremia and 50 % in acute circumstances. Hyponatremia has been demonstrated to be a predictor of inpatient mortality in several patient populations [48–50]. Mortality likely represents the severity of the underlying disease and not accrual mortality from the electrolyte abnormality itself [51]. Hyponatremia in critically ill patients is more likely secondary to elevated secretion of ADH without an osmotic stimulus [52–54]. Critically ill patients are also more likely to have multi-organ failure that is associated with impaired water handling [55]. The inflammatory cascade via interleukin-6 may also play a role in ADH secretion and hyponatremia [56].

Hyponatremia is usually asymptomatic. In severe cases, cerebral edema may occur as fluid tonicity falls, thereby causing inflow of water into cells. Severe hyponatremia may present clinically as nausea, vomiting, lethargy, confusion, seizures, cerebral herniation, coma, and death [57].

Table 2.1 Causes of hyponatremia

– Hypovolemic hyponatremia
Gastrointestinal losses
Cerebral salt wasting
Diuretics
Third space loss
Gastrointestinal losses
– Euvolemic hyponatremia
SIADH
Malignancy related
Psychiatric polydipsia
Glucocorticoid deficiency
Hypothyroidism
– Hypervolemic hyponatremia
Congestive heart failure
Liver failure
Nephrotic syndrome
Renal failure

Hyponatremia can be classified according to volume status as hypovolemic hyponatremia, euvolemic hyponatremia, and hypervolemic hyponatremia (Table 2.1). Treatment strategies should be guided based upon etiology of the hyponatremia and volume status [46].

Hypovolemic hyponatremia results from a deficit of total body sodium and water with the sodium deficit greater than the water deficit. The decrease in ECF increases ADH secretion to help preserve ECF volume. In hypervolemic hyponatremia, there is an excess of total body sodium and water, though the water gain is greater than the sodium gain. The hyponatremia is a result of the volume overload. It is possible for total body sodium stores to be depleted, resulting in hyponatremia. In such circumstances, the sodium and chloride levels are both low.

The decision to treat depends on the presence or absence of symptoms and the rapidity of onset of the hyponatremia. Acute hyponatremia develops within a 48-h time frame, whereas chronic hyponatremia develops over greater than 48 h. Symptomatic hyponatremia should be treated. The sodium deficit can be calculated by the following formula:

$$\text{Sodium deficit} = 0.5 \times \text{lean body weight} \times \left(120 - \text{measured}\left[\text{Na}^{+}\right]\right)$$

Hyponatremia corrected at too rapid a rate may result in osmotic pontine demyelination (also known as central pontine demyelination or central demyelination syndrome). The development of this syndrome is a risk when there are sudden changes in concentration (12–15 mEq/L per 24h) or a rapid rate of change (>1–2 mEq/L/h). Clinically, the syndrome presents as generalized encephalopathy followed by behavioral changes, cranial nerve palsies, and quadriplegia 2–3 days after the sodium level is corrected. High risk patient populations include those with chronic hyponatremia that is rapidly corrected, such as alcoholics, the malnourished, geriatric patients, and those with thermal injury [57–67].

Sodium can be administered as 3 % NaCl. The hyponatremia should be corrected at a rate similar to the rate of developing the imbalance. Acute hyponatremia should be corrected more quickly than chronic hyponatremia. Dilutional hyponatremia is more common than total body sodium deficit. Therefore, administration of 3 % NaCl can be combined with forced diuresis and volume restriction to remove the excess water load. Recently, vasopressin receptor antagonists (vaptans) have been developed in the treatment of hypervolemic and euvolemic hyponatremia. Vaptans are not approved for the treatment of hypovolemic hyponatremia [68].

Most hyponatremic patients are not symptomatic and do not require treatment with hypertonic saline. Most hyponatremic patients are euvolemic, and the most common diagnosis is syndrome of inappropriate antidiuretic hormone (SIADH). SIADH is a diagnosis of exclusion with specific criteria, including a plasma osmolality <270 mOsm/kg H_2O; urine osmolality >100 mOsm/kg H_2O; euvolemia; elevated urine sodium concentration; absence of adrenal, thyroid, pituitary or renal insufficiency and absence of diuretic use [46].

Hypernatremia is a state of serum sodium greater than 145 mEq/L. It occurs in approximately 2 % of hospitalized patients and 15 % of patients in the intensive care unit. Mortality rates approach 70 % [51]. Hypernatremia results from either free water deficit or excess total body sodium and can occur in the setting of hypovolemia, euvolemia, or hypervolemia. Therapy can

be correctly guided by assessing volume status and urine sodium to determine the etiology of hypernatremia.

Hypernatremia increases extracellular tonicity and thereby results in cellular dehydration. Symptoms are referable to the central nervous system and include confusion, weakness and lethargy progressing to seizures, coma and death. Hypernatremia must be corrected carefully to avoid cerebral edema. In general, just as is the case with hyponatremia, hypernatremia should be corrected as quickly as the onset. The mainstay treatment for hypernatremia is the replacement of the free water deficit. The deficit is calculated as follows:

$$\text{Free water deficit} = \left[0.6 \times \text{total body weight}\right] \times \left[\left(\text{measured}\left[\text{Na}^{+}\right]/140\right) - 1\right]$$

Half the calculated deficit should be replaced in the first 12–24 h so as not to correct at a rate faster than 2 mEq/L/h. The remaining deficit should be replaced over the next 48 h.

Disorders of Potassium Metabolism

The normal extracellular concentration of potassium range is 3.5–5.0 mEq/L. It is the principal cation in the intracellular fluid, ranging from 140 to 160 mEq/L. This difference in concentration is essential in providing a transmembrane potential required to maintain the excitability of nerve and muscle tissues. Potassium deficiency in dietary intake has been implicated in the development of hypertension, cardiovascular disease, and glucose intolerance [69].

Hypokalemia refers to a serum potassium level of less than 3.6mEq/L. Causes of hypokalemia include losses through the gastrointestinal (GI) tract via diarrhea, vomiting or high nasogastric tube (NGT) output through intentional decompression. Hypokalemia may result from intracellular shifting of potassium in a variety of conditions (Table 2.2). Pseudohypokalemia may occur in specimens collected from leukemia patients with profound leukocytosis. Under these circumstances, white blood cells absorb potassium in vitro [70]. Common iatrogenic etiologies include losses via renal excretion caused by potassium wasting diuretic use.

Table 2.2 Causes of hypokalemia

– Insufficient intake
– Increased losses
GI losses
Diarrhea
Vomiting
NGT decompression
Ileostomy
Laxatives
Renal losses
– Drug induced losses
Mannitol
Diuretics
Aminoglycosides
Amphotericin
– Hyperaldosteronism
– Skin losses
Sweat
Burns
– Transcellular shifts
Overfeeding syndrome
Drug induced
Insulin administration
Beta adrenergic agonists
– Miscellaneous
Hypomagnesemia
Mountain sickness

Mild hypokalemia is usually asymptomatic. In severe cases, it may present as muscle cramps and weakness and in extreme cases progresses to muscle breakdown and necrosis. An ascending muscle paralysis may result in respiratory failure and arrest [71]. Cardiac signs include EKG changes appearing as ST depression, flattened T waves, U waves and QT interval prolongation and ventricular arrhythmias [72]. Disturbances in cardiac conduction resulting in death can be seen in patients with underlying cardiac disease and digitalis use [73].

Severe hypokalemia should be repleted intravenously or orally depending on the clinical scenario. In cases of hypokalemia due to transcellular shifts, treating the underlying condition is necessary, versus replacement in the case of true depletion. Sustained hypokalemia results

from true depletion compared to transient hypokalemia from transcellular shifts. Serum potassium falls approximately 0.3 mEq/L for every 100 mEq/L decrease in total body potassium [74]. A serum potassium level below 3.0 mEq/L should be corrected using intravenous replacement in a monitored setting due to the risk of arrhythmias. If hypomagnesemia is present, it should be corrected first, as such a state promotes excretion of potassium. Hypokalemia accompanies hypomagnesemia about 60 % of the time due to reduced Na^+, K-ATPase activity, in which magnesium acts as a dependent enzyme [75, 76]. When serum potassium is below 3.0 mEq/L, an additional 8–10 g of magnesium may also be required. Once the serum potassium level falls below 3.0 mEq/L, the amount of replacement required increases in a nonlinear fashion, and a minimum of 100 mEq is required to restore normal levels.

Hyperkalemia refers to a serum potassium level greater than 5.0 mEq/L. Pseudohyperkalemia results from marked leukocytosis, thrombocytosis or hemolysis of collected specimens, resulting in release of intracellular potassium. Pseudohyperkalemia can also be seen in blood samples of patients who have hereditary spherocytosis and hereditary stomatocytosis. A temperature dependent breakdown and leakage of potassium from these abnormal cells occurs. There are many possible causes of true hyperkalemia (Table 2.3).

Mild hyperkalemia is usually asymptomatic, but predominantly affects the muscular and cardiac systems. Muscular symptoms include parasthesias, extremity weakness, and flaccidity. Ascending muscle weakness may involve the trunk and respiratory muscles. Hyperkalemia can lead to cardiac conduction abnormalities. EKG findings include peaked T waves, widening of the QRS complex, AV conduction abnormalities, ventricular fibrillation, and eventual asystole [72].

Hyperkalemia results from: (1) an inability to secrete potassium due to renal dysfunction, (2) a shift of potassium out of cells, and (3) excessive administration of potassium. Renal failure is the most common cause of inability to excrete potassium. Traditional teaching has held that there is an inverse relationship between serum potassium levels and pH [77]. However, this has been disproven, and the relationship is complex and not completely understood.

Table 2.3 Causes of hyperkalemia

–	Excessive intake (rare with normal renal function)
–	Pseudohyperkalemia
	Hemolysis
	Leukocytosis
	Thrombocytosis
–	Impaired excretion
	Renal failure
–	Outward shift of potassium from cells
	Cell destruction
	Tumor lysis
	Intravascular hemolysis
	Tissue destruction
	Rhabdomyolysis
	Burns
–	Drugs
	Succinylcholine
	Digoxin

Symptomatic hyperkalemia as demonstrated by EKG changes or asymptomatic patients with a serum potassium level greater than 6.5 mEq/L should be treated emergently. Strategies include [71]:

1. Cardiac stabilization with calcium chloride.
2. Shifting potassium intracellularly with administration of insulin.
3. Increasing potassium excretion by volume expansion followed by the administration of potassium wasting diuretics.
4. Increasing excretion through the GI tract with sodium polystyrene sulfonate.
5. Extra-corpeal removal via dialysis.

In most cases, dialysis is reserved for patients who have renal failure. In rare circumstances, patients with healthy kidneys will have their excretory capacity overwhelmed and require temporary emergent dialysis as a life-saving intervention.

Disorders of Calcium Metabolism

Calcium is a divalent cation that plays an important role in several biological processes. Extracellularly, it is the main substrate for the skeletal system and is bound to phosphate as

hydroxyapatite. The average adult has 1–2 kg of total body calcium localized in bone as hydroxyapatite. In its intracellular form, calcium plays an important role as a signaling molecule for several pathways, including cardiac, skeletal and smooth muscle contraction, and neurotransmitter release. The concentration of extracellular and intracellular calcium is tightly regulated. The extracellular concentration of calcium is 10,000 times greater than intracellular concentrations. Release of calcium from its vast stores in the skeletal system is regulated by parathyroid hormone (PTH).

Serum calcium levels normally range from 9.4 to 10 mg/dL. The incidence of hypocalcemia ranges from 70 to 90 % when total serum calcium is measured versus 15–50 % when ionized calcium is measured [78]. This is due to the high incidence of hypoalbuminemia in critically ill and postoperative patients. Calcium is bound to albumin in serum, though the ionized form is the biologically active form.

Hypocalcemia refers to a serum calcium level of less than 8.5 mg/dL or an ionized level of less than 1.0 mmol/L. There are many reasons for hypocalcemia in the postoperative and critically ill patient population. The etiology is usually multifactorial. Ionized hypocalcemia is common in patients with sepsis, pancreatitis, severe trauma or postoperatively after plasma volume expansion with hypocalcemic solutions and is associated with increased mortality [78, 79]. Cytokine levels in critically ill patients, especially tumor necrosis factor, interleukin-6 and prolactin, serve as a measure of systemic inflammation and correlate with the degree of hypocalcemia [80, 81].

Mild hypocalcemia is usually asymptomatic. However, severe derangements result in significant physiological consequences. Diminished cardiac contractility can result in refractory hypotension. Arrhythmias include ventricular tachycardia. Prolonged QT interval and marked QRS and ST segment changes may mimic acute myocardial infarction and heart block. Calcium plays an important role in the coagulation process, including the conversion of fibrin to fibrinogen and enhancement of other coagulation factors. Maintaining an ionized calcium level above 0.9 mmol/L has a beneficial cardiovascular and coagulation effect in the resuscitation of patients in massive hemorrhage [82]. Citrate components present in blood products may also exacerbate the hypocalcemia by precipitation. Therefore, calcium levels should be monitored during massive transfusion.

Neurologically, hypocalcemia may present as parasthesias and seizures. Neuromuscular symptoms include spasms and tetany. An acute decline in the serum calcium level can result in laryngospasm and death. Chronic hypocalcemia may present with less pronounced symptoms that include neuromuscular irritability. At the bedside, hypocalcemia can be detected by testing for Chvostek's sign or Trousseau's sign. Chvostek's sign is facial nerve irritability that is elicited by gently tapping the facial nerve. Chvostek's sign is present in approximately 10–25 % of normal adults and may be absent in chronic hypocalcemia. Trousseau's sign is carpopedal spasm that is elicited by decreasing blood flow to the hand with a blood pressure cuff inflated to 20 mm Hg for 3 min. It is absent in one third of hypocalcemic patients. Psychiatric symptoms of hypocalcemia include dementia, psychosis, and depression [83, 84].

Symptomatic hypocalcemia and severe hypocalcemia (0.8 mmol/L) should be treated with intravenous calcium administration [85–87]. Intravenous calcium can be administered as calcium gluconate or calcium chloride. Calcium chloride has the advantage of being immediately available in equal amounts of calcium and chloride. Calcium gluconate must undergo hepatic degluconation to be available in the ionized form. Calcium chloride contains more calcium in terms of milliequivalents than calcium gluconate. Calcium infusions can also be used in the therapy of cardiac drug toxicity involving beta blockers and calcium channel blockers [86, 87].

Hypercalcemia is rare in the ICU setting and occurs in less than 15 % of hospitalized patients [78]. Hypercalcemia refers to a serum calcium level greater than 10.4 mg/dL. In the critically ill patient, increased bone reabsorption resulting from paraneoplastic syndromes and prolonged immobilization are common etiologies. Hyperparathyroidism and malignancy causing excessive PTHrP

are the most common causes of hypercalcemia in hospitalized patients, occurring in more than 50 % of cases [88]. Conversely, among outpatients referred to endocrinologists for hypercalcemia, more than 90 % are found to have primary hyperparathyroidism [89]. Other causes include renal failure, thyrotoxicosis, adrenal insufficiency, and drugs. In particular, thiazides may increase proximal tubule reabsorption of calcium [83, 84, 88].

Calcium levels greater than 12 mg/dL result in symptoms that particularly impact the neurologic and digestive systems and include fatigue, lethargy, confusion, coma, anorexia, abdominal pain, and constipation. Cardiac arrhythmias may also occur, including bradyarrhythmias or heart block. ST segment elevation responsive to treatment of the hypercalcemia may also occur.

Calcium levels greater than 14 mg/dL and symptomatic patients should be treated. Hypercalcemia can be treated by volume expansion with fluids followed by diuresis. In cases of excessive calcium reabsorption from bone due to underlying malignancy, a bisphosphonate or plicamycin may be used to suppress calcium reabsorption. Treatment of the underlying cause is necessary. Rarely in the acute care setting is dialysis with a low or zero calcium dialysate or parathyroidectomy necessary for the treatment of hypercalcemia refractory to medical management.

Disorders of Magnesium Metabolism

Magnesium is a divalent cation that plays an important role in the metabolism of other cations including sodium, potassium, and calcium. Magnesium is also an important cofactor in ATP energy metabolism. It is the second most common intracellular cation and fourth most common extracellular cation [89]. Normal serum concentration ranges from 1.5 to 2.3 mg/dL. The body stores magnesium mainly in the bones, muscles, and soft tissues. Total body magnesium can be low in low albumin states without affecting ionized magnesium levels. Sixty seven percent of serum magnesium is in the ionized form. Ionized magnesium is the biologically active form that can be measured using ion selective electrodes, but this technique has limitations with respect to accuracy [90, 91]. There are no known hormonal pathways in the regulation of magnesium. Magnesium homeostasis is achieved through absorption via the kidneys, digestive tract, and bone mobilization. Disorders of magnesium metabolism are seen in 15–60 % of patients in the critical care setting [92].

A serum magnesium level less than 1.5 mg/dL defines hypomagnesemia. There are several etiologies of hypomagnesemia (Table 2.4). In surgical and critically ill patients, common causes are plasma volume expansion, diuretic use, and severe sepsis. Other etiologies are excess GI losses from diarrhea, laxative use, and enteric decompression. It is often seen in association with hypocalcemia, hypokalemia, and hypophosphatemia. Hypokalemia and hypocalcemia are refractory to correction unless magnesium is replaced first [93, 94].

Hypomagnesemia is usually asymptomatic. When symptoms do occur, they are often similar to those associated with hypocalcemia, hypokalemia,

Table 2.4 Causes of hypomagnesemia

– Inadequate intake
– GI losses
Diarrhea
Vomiting
Fistula loss
Nasogastric decompression
Bowel preparation
– Renal losses
Genetic magnesium wasting syndromes
ATN
Ethanol
Drug induced
Digoxin
Diuretics (loop, thiazide, osmotic)
Cis-platinum
Cyclosporine
Tacrolimus
Cetuximab
– Intracellular shift of magnesium
Refeeding syndrome
Catecholamines
Correction of respiratory acidosis
Correction of diabetic ketoacidosis
– Blood transfusions
– Extensive burns
– Excessive sweating

and hypophosphatemia due to the close metabolic relationship of the cations. Symptoms include muscle weakness, cramps, seizures and arrhythmias, namely torsades de pointes. The treatment for torsades de pointes and symptomatic hypomagnesemia is intravenous replacement of magnesium, 1–2 g over 5 min.

Magnesium also has therapeutic properties in certain clinical scenarios. Magnesium competitively binds to *N*-methyl-D-aspartate receptors to depress the seizure threshold and is therefore used in the treatment of preeclampsia and eclampsia [93–96]. Magnesium also has smooth muscle relaxant properties that make it useful for treating bronchospasm in asthmatics [95, 96].

Hypermagnesemia is usually seen in the setting of renal failure, because normal kidneys can excrete large quantities of magnesium, up to 500 mEq/day [89]. Other etiologies are extensive soft tissue ischemia or necrosis in patients with trauma, sepsis, cardiopulmonary arrest, burns, or shock. Symptoms of hypermagnesemia occur at levels above 4 mg/dL and involve the muscular, neurologic, and cardiac systems. Muscular symptoms range from depressed deep tendon reflexes to muscle paralysis, including respiratory depression at levels above 8–10mg/dL. Neurologic symptoms include somnolence and lethargy. Cardiovascular symptoms include bradycardia and hypotension unresponsive to volume expansion and vasopressors. Complete heart block resulting in cardiac arrest is seen at levels approaching 20 mg/dL [89, 97]. Hypermagnesemia related hypotension can be treated with administration of calcium. Excess levels can be removed with hydration and forced diuresis with furosemide. Extreme cases of magnesium toxicity may require dialysis. Hypermagnesemia is a rare phenomenon in the ICU setting, excluding patients undergoing tocolysis with large doses of magnesium.

Disorders of Phosphorous Metabolism

The majority of the body's total reserve of phosphorous is stored in the bones as hydroxyapatite along with calcium [89]. The metabolic pathways of the two ions are closely intertwined. Phosphate plays an important role as a constituent of nucleic acids, phospholipids, complex carbohydrates, glycolytic intermediates, enzymatic phosphoproteins, and nucleotide cofactors for enzymes. Phosphate is also important for energy metabolism as a constituent of ATP. Phosphate levels are regulated by PTH, mainly via three routes: (1) bone reserves, (2) intestine, and (3) kidneys.

A serum phosphate level less than 3.0 mg/dL defines hypophosphatemia, which is classified according to degree of deficiency. Mild hypophosphatemia ranges 2.5–3.0 mg/dL, moderate 1.0–2.5 mg/dL, and severe less than 1 mg/dL. Phosphate depletion refers to low stores of total body phosphate. There are numerous causes of phosphate depletion (Table 2.5). Among hospitalized patients, the overall prevalence of severe

Table 2.5 Causes of hypophosphatemia

–	Shifts of extracellular phosphate into cells or bone
	Insulin administration
	Refeeding syndrome (initiation of carbohydrate causes an insulin spike, which increases cellular phosphate uptake)
	Respiratory alkalosis
	Catecholamines (epinephrine, albuterol, dopamine)
	Net bone formation
	Post-parathyroidectomy
	Osteoblastic metastases
–	Impaired intestinal phosphate absorption
	Malnutrition
	Aluminum containing antacids
	Chronic diarrhea
	NGT suction
	Malabsorption
–	Extreme catabolic states
	Burns
	Trauma
	Sepsis
–	Renal losses
	Excess PTH or PTHrP
	Diuretics
	Intrinsic renal disease
	Fanconi Syndrome
–	Hyperthermia/rewarming
–	Heavy metal poisoning
–	Amyloidosis

hypophosphatemia is less than 1 %, whereas mild or moderate hypophosphatemia occurs in 2–5 % of these patients [98].

Hypophosphatemia results in several clinical manifestations. Neuromuscular symptoms vary depending on the degree of phosphate depletion, ranging from progressive lethargy, muscle weakness and paresthesias to paralysis, coma, and death. Confusion, profound weakness, paralysis, seizures, and other major sequelae are usually limited to those patients who have serum phosphate concentrations lower than 0.8–1.0 mg/dL [99]. Rhabdomyolysis is observed within 2 days in more than one third of patients whose serum phosphate concentrations fall to less than 2 mg/dL [100]. Respiratory muscle weakness may prevent successful weaning from mechanical ventilation [101, 102]. Cardiac symptoms resulting from profound hypophosphatemia include left ventricular dysfunction, heart failure, and ventricular arrhythmias but may not be significant if the serum phosphate concentration is greater than 1.5 mg/dL [103]. Hematologic derangements include acute hemolytic anemia and leukocyte dysfunction. Depletion requires electrolyte replacements via enteric or intravenous routes. Severe depletion warrants intravenous replacement. Replacements should be carried out with caution in patients with renal failure and hypercalcemia due to the risk of metastatic calcifications.

Hyperphosphatemia refers to a serum phosphate level greater than 4.5 mg/dL. Elevated phosphate levels result most often from acute or chronic renal dysfunction in which the renal tubules are unable to clear the daily phosphate load despite maximal inhibition of phosphate reabsorption in the remaining functional nephrons. Cellular damage from rhabdomyolysis, tumor lysis syndrome, hemolysis, and thyrotoxicosis may also result in increased phosphate levels [104]. Iatrogenic causes include excess electrolyte correction, laxative use, and bisphosphonate therapy.

Hyperphosphatemia results in hypocalcemia through three mechanisms: (1) precipitation of calcium, (2) interfering with PTH levels, and (3) decreasing vitamin D levels [105]. Hyperphosphatemia, therefore, clinically presents as hypocalcemia. Tetany, muscle cramps, paresthesias, and seizures may occur. Calcium phosphate precipitation into soft tissues may cause organ dysfunction, particularly renal failure.

Excess phosphate may be removed by increasing urinary excretion with hydration and diuresis, acetazolamide being the most effective [106]. Dialysis may be necessary in acute cases. Patients with chronic renal failure may require oral phosphate binders to prevent hyperphosphatemia. Enteral nutrition should also be modified to decrease the phosphate load when feasible. In the acute care setting, increased dietary protein requirements may prevent phosphate load reduction.

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