Electrolyte disturbances associated with commonly prescribed medications in the intensive care unit

Mitchell S. Buckley, PharmD; Jaclyn M. LeBlanc, PharmD; Michael J. Cawley, PharmD

Electrolyte imbalances are common in critically ill patients. Although multiple disease states typically encountered in the intensive care unit may be responsible for the development of electrolyte disorders, medications may contribute to these disturbances as well. Medications can interfere with the absorption of electrolytes, alter hormonal responses affecting homeostasis, as well as directly impact organ function responsible for maintaining electrolyte balance. The focus on this review is to identify commonly prescribed medications in the intensive care unit and potential electrolyte disturbances that may occur as a result of their use. This review will also discuss the postulated mechanisms associated with these drug-induced disorders. The specific drug-induced electrolyte disorders discussed in this review involve abnormalities in sodium, potassium, calcium, phosphate, and magnesium. Clinicians encountering electrolyte disturbances should be vigilant in monitoring the patient's medications as a potential etiology. Insight into these drug-induced disorders should allow the clinician to provide optimal medical management for the critically ill patient, thus improving overall healthcare outcomes. (Crit Care Med 2010; 38[Suppl.]:S253–S264)

KEY WORDS: hyponatremia; hypernatremia; hypokalemia; hyperkalemia; hypocalcemia; hypercalcemia; hypophosphatemia; hyperphosphatemia; hypomagnesemia; hypermagnesemia; critical illness; water-electrolyte imbalance

Electrolytes play an essential role in numerous physiologic functions in the body (1). Many metabolic processes and normal organ functions are dependent on precise intracellular as well as extracellular electrolyte concentrations (1). This balance is maintained through a complex system of multiple mechanisms, involving many different hormones and organs that influence electrolyte distribution (1, 2). Consequently, several factors can equally affect electrolyte homeostasis, including acid-base imbalance, fluid status, organ dysfunction, neurohormonal disorders, and disease states (1, 2).

Electrolytes abnormalities are common in the intensive care unit (ICU). Disturbances within the regulatory mechanisms can have significant consequences, especially in the critically ill patient (1, 2). Many clinical manifestations, including respiratory failure, edema, muscle weakness, altered mental status, and arrhythmias, may be attributed to electrolyte disturbances (1, 2).

Several medications have been implicated in the development of electrolyte disturbances (1, 2). Unfortunately, many common medications used in these patients can disrupt electrolyte serum concentrations (3, 4). Also, overdose ingestion (e.g., aspirin) or accumulation of long-term therapy (e.g., lithium, theophylline), resulting in drug toxicity, can contribute to impaired electrolyte homeostasis in patients admitted to the ICU (3, 4). The purpose of this review is to identify common drug-induced electrolyte disturbances in the ICU and discuss the potential mechanisms involved. Despite the associated risk of electrolyte abnormalities with intravenous fluids and parenteral hyperalimentation, a detailed review of these therapies leading to electrolytes imbalances as well as their respective treatment and prevention strategies is beyond the scope of this paper.

Sodium

Background and physiologic function

The major extracellular cation in the body is sodium, which is normally kept at a serum concentration of 135–145 mmol/L (5). It accounts for >85% of fluid osmolality and is responsible for maintaining tonicity, hence controlling water movement across cell membranes and regulating extracellular fluid volume (5, 6). It is primarily excreted via the kidney. The recommended daily intake of sodium is 1200–1700 mg each day, depending on gender and age.

Homeostasis

Sodium and water homeostasis are integrally related. As sodium regulates extracellular fluid volume, water regulates intracellular fluid volume; both volumes make up total body water (5). Renal excretion of sodium is controlled via aldosterone, which causes sodium resorption through the proximal tubule and atrial natriuretic factor (5, 7).

Water balance is regulated primarily through vasopressin, which is controlled by hypothalamic osmoreceptors (5). When a decrease in circulating volume is sensed, vasopressin is released by the posterior pituitary, causing water to be resorbed across the renal collecting ducts (8, 9). This low volume also stimulates a thirst mechanism (8).

Drug-induced hyponatremia

Hyponatremia is usually defined as a serum sodium of <135 mmol/L. This reflects an excess of water causing a dilu-

From the Department of Pharmacy (MSB), Banner Good Samaritan Medical Center, Phoenix, AZ; Department of Pharmacy (JML), Saint John Regional Hospital, Saint John, NB, Canada; Philadelphia College of Pharmacy (MJC), University of the Sciences in Philadelphia, Philadelphia, PA.

The authors have not disclosed any potential conflicts of interest.

For information regarding this article, E-mail: mitchell.buckley@bannerhealth.com

DOI: 10.1097/CCM.0b013e3181dda0be

tional effect in the plasma, or a sodium loss greater than water loss in the body (1, 9). Therefore, the plasma concentration may not reflect total body sodium, and the osmolality of the plasma should be assessed, which may be increased (hyperosmolar), decreased (hypoosmolar), or normal (isoosmolar) (1).

When hyponatremia develops, there is a shift of water into the cells, resulting in tissue edema, increased intracranial pressure, and neurologic symptoms (9). Symptoms are usually progressive as the sodium declines, ranging from nausea and malaise with serum values of 125–130 mmol/L to more aggressive neurologic signs (seizures, coma) with <115 mmol/L (9). This is a reflection of the changes in osmolarity and fluid shifts within the central nervous system (1). The symptom severity also depends on the rate that the serum sodium concentration decreases; the slower the rate, the more time the brain cells have to self-regulate, resulting in less severe symptoms (9).

Hoorn et al (10) studied hospitalized patients with hyponatremia and found that patients in the critical care area had the highest occurrence of hyponatremia (38%). Characteristics of patients with ICU-acquired hyponatremia include neurologic/trauma or surgical admissions, longer ICU stay, hyper- or hypothermia, and hyperkalemia (11). The reported occurrence rate of ICU hyponatremia has varied, with one study (11) reporting a low of 11.0% and another study (12) reporting a high of 24.5%. Acquired hyponatremia in critically ill patients during their ICU stay has been associated with increased ICU and overall hospital mortality compared with patients with normal serum sodium levels (18% and 28% vs. 9% and 16%, respectively, $p < .001$) (11). These patients also had a longer length of stay in the ICU as well as overall hospitalization (11). Various medications have been reported to cause hyponatremia in ICU patients. Common drugs and their mechanisms are shown in Table 1.

Table 1. Medication-induced causes of sodium disturbances

Sodium Disorder	Mechanism	Medication
Hyponatremia	Impairs urinary diluting capacity	Thiazide diuretics, loop diuretics (22, 23)
	Volume expansion secondary to increased osmolality	Mannitol (13, 127)
	Stimulate thirst via conversion of angiotensin I or II	ACE inhibitors (128)
	Renal salt wasting	Trimethoprim-sulfamethoxazole (24–26)
	Syndrome of inappropriate antidiuretic hormone secretion	Proton pump inhibitors (specifically, omeprazole and esomeprazole), nicotine, chlorpropramide, tolbutamide, clofibrate, cyclophosphamide, morphine, barbituates, vincristine, acetaminophen, carbamazepine, ACE inhibitors, NSAIDs, antipsychotics, desmopressin, oxytocin, and antidepressants (SSRIs, TCAs) (4, 18–21, 128–137).
	Secondary to inhibition of prostaglandins and potentiation of vasopressin's effect on the tubule	NSAIDs (138, 139)
Hypernatremia	Hypotonic fluid caused renally	Loop diuretics (6)
	Volume depletion	Mannitol (13, 127)
	Nephrogenic diabetes insipidus	Amphotericin B, demeclocycline, dexamethasone, dopamine, ifofamide, lithium, ofloxacin, orlistat, foscarnet (35, 140–142)
	Exogenous sodium load	Hypertonic 3% saline or normal (0.9%) saline, antibiotics containing sodium (40)
	Hypertonic sodium gain by renal	Hypertonic sodium bicarbonate infusion, sodium water loss chloride hypertonic infusion (6, 109)
	Gastrointestinal loss	Osmotic cathartic agents (lactulose, sorbitol) (6)

ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

Hyperosmolality

Theoretically, agents like mannitol may cause a hyperosmotic hyponatremia by instigating a fluid shift and subsequent dilution of the plasma sodium (13). In one case report (14), a patient receiving mannitol over a period of 3 days for increased intraocular pressure had a decrease in sodium to 112 mmol/L, and subsequently developed confusion, dyspnea, and anuria.

Hypoosmolality euvolemic

The syndrome of inappropriate antidiuretic hormone is the most common cause of euvolemic hyponatremia, and manifests as water retention due to arginine vasopressin release as well as urinary sodium excretion (7, 15). One drug of particular interest is carbamazepine (16, 17). In non-ICU patients, the hyponatremic effect of this medication was correlated with the medication dose, serum concentration, and low sodium concentration before initiation of therapy. This seemed to occur more frequently in patients concurrently on other medications that could cause hyponatremia. Rarer causes of hyponatremia in ICU patients may include proton pump inhibitors and desmopressin (18–21).

Hypoosmolality hypovolemic

Thiazide diuretics have been shown to be a common cause of community-acquired hyponatremia (22). Their effect on the cortical collecting duct causes an impairment of the urinary diluting capacity (23). In a study of severe diuretic-induced hyponatremia (Na <115 mmol/L), thiazides were implicated in 93% of cases, with loop diuretics accounting for 6% (23). Rarer causes of drug-induced hyponatremia include trimethoprim-sulfamethoxazole, which is more common in patients receiving higher doses, such as in the treatment of *Pneumocystis carinii* pneumonia, or with renal dysfunction (24–26).

Drug-induced hypernatremia

Hypernatremia is usually defined as a serum sodium >145 mmol/L (1). This can result from pure water loss (e.g., diabetes insipidus, significant insensible losses), hypotonic sodium loss (e.g., gastrointestinal losses), hypotonic sodium and potassium loss (e.g., osmotic diuresis), or hypertonic sodium gain (e.g., 3% saline infusion) (6). Initially, symptoms tend to be nonspecific, pro-

gressing to severe neurologic symptoms, such as altered mental status, irritability, and coma. Patients usually do not exhibit severe symptoms until the sodium concentration increases to >158–160 mmol/L (6).

The occurrence rate of hypernatremia is seen in approximately 5% to 9% of ICU patients, but it has been reported as high as 26% (11, 27–30). Factors affecting fluid status, including hypokalemia, hypoalbuminemia, and renal dysfunction, are independent predictors of ICU-acquired hypernatremia (11, 31). Critically ill patients with hypernatremia have been associated with increased duration of mechanical ventilation, longer ICU and hospital stay, and higher risk of renal dysfunction (11, 29–34). Patients with hospital-acquired hypernatremia were found to have significantly higher mortality rates (22% to 48%) than patients with hypernatremia at the time of hospital admission (27, 28, 30, 31). Medications that cause hypernatremia are also listed in Table 1.

Hypovolemic

Hypovolemic hypernatremia can develop with medications, causing volume contraction. Osmotic diuresis with mannitol and loop diuretics has been implicated as manifesting this adverse reaction. A recent study (30) examining the prevalence and mortality in hypernatremic ICU patients found that these patients received significantly more furosemide (84.6% vs. 24.8%, $p < .001$).

Euvolemic

Nephrogenic diabetes insipidus manifests as large volumes of dilute urine brought about by the ineffective antidiuretic action of vasopressin on the kidney (35). Many medications have been implicated as a potential cause of nephrogenic diabetes insipidus, producing a euvolemic hypernatremia. Of interest, although nephrogenic diabetes insipidus occurring with amphotericin B has been reported to resolve upon changing therapy to the liposomal form of the medication, there is one case report with high-dose liposomal amphotericin B causing nephrogenic diabetes insipidus as well (36–38). Few medications have been reported to cause central diabetes insipidus. Phenytoin is one example, inhibiting antidiuretic hormone secretion and increasing urine volume, putting patients at risk for hypernatremia (39).

Hypervolemic

Excessive administration of sodium can cause hypernatremia in ICU patients. Most clinicians would consider hypertonic (3%) saline a classic example, which has been shown to cause hypernatremia in patients with traumatic brain injury (40). The sodium load associated with sodium bicarbonate is also a risk factor for the development of hypernatremia (31).

Potassium homeostasis

Mechanisms responsible for maintaining potassium homeostasis include transcellular shifting of potassium from the extracellular space into cells as well as increased renal and fecal elimination. The key components to transcellular shift include insulin, β-adrenergic catecholamines, and aldosterone (with support from angiotensin II) (41). All three components stimulate sodium/potassium adenosine triphosphate (Na/K ATPase) pumps resulting in cellular uptake of potassium (42–44). Aldosterone stimulates potassium secretion into the renal collecting duct, promoting excretion by the kidney (45). The balance of potassium homeostasis is based on a feedback mechanism for insulin and aldosterone; thus, an increase or decrease of potassium concentration within the extracellular fluid stimulates the release of both hormones (46). Renal and fecal elimination are primarily attributed to a pharmacologic etiology, which includes direct effects on sodium resorption. The result of sodium resorption creates an electrochemical gradient for potassium secretion (47). Drug-induced etiologies of hypokalemia include transcellular shifting of potassium from the extracellular compartment into cells, increased renal excretion, and abnormal loss of potassium from stool.

Drug-induced hypokalemia

Hypokalemia is one of the most common electrolyte abnormalities identified within the hospital environment with a prevalence of >20% when defined as a serum potassium of <3.6 mmol/L (48). Data are inconsistent in defining numerical values for mild-to-moderate hypokalemia, but most experts agree that a serum potassium of <2.5mEq/L is recognized as severe (49). Hypokalemia is well documented in hospitalized patients but very limited data are available in critically ill patients. Incidences within trauma patients have ranged from 50% to 60% occurring within 1 hr after injury with complete resolution occurring within 24 hrs with limited potassium replacement (50). About 40% of surgical patients experience hypokalemia with the onset occurring approximately 2.3 days after ICU admission (51). Signs and symptoms of hypokalemia include nausea, vomiting, muscle weakness, cramping, and rhabdomyolysis with a serum potassium of <2.5 mmol/L (52, 53). The most severe physiologic sequelae associated with hypokalemia is cardiac arrhythmias including ventricular tachycardia and ventricular fibrillation (49). Etiologies of hypokalemia within the ICU include limited dietary potassium intake, renal and stool volume loss, metabolic alkalosis, renal tubular acidosis, uncontrolled diabetes mellitus, hyperaldosteronism, mineralocorticoid excess, magnesium depletion, and pharmacologic agents.

Clinicians investigating etiologies of hypokalemia in the ICU patient must first review the patient's medication record for common agents associated with this phenomenon. Pharmacologic agents and associated mechanisms are summarized in Table 2. Sympathomimetic agents, including nebulized albuterol in high doses (10 mg and 20 mg) administered in patients with end-stage renal disease, decreased serum potassium levels by approximately 0.6–1 mmol/L (54, 55). Therapeutic doses of albuterol have also decreased serum potassium more modestly from 0.2 mmol/L to 0.4 mmol/L (56, 57). The hypokalemia phenomenon is proposed to be predominately mediated by the β_2 receptor, but data have also identified the β_1 receptor that also may play a role (58). Patients receiving higher doses of the intravenous dobutamine (30–40 μg/kg/min) demonstrated lowering of serum potassium as much as 0.56 mmol/L (59). Diuretics, including thiazide agents, are usually reserved as add-on therapy to a loop diuretic to enhance diuresis. Both agents promote a synergistic effect on potassium excretion and, thus, are associated with causing mild-to-severe hypokalemia, despite potassium supplementation (60). The degree of hypokalemia is directly related to the dose of the thiazide or loop diuretic and duration of treatment (60, 61). Am-

Table 2. Medication-induced causes of potassium disturbances

Potassium Disorder	Mechanisms	Medications
Hypokalemia	Stimulate Na+/K+ ATPase pump	Sympathomimetics (epinephrine, terbutaline, fenoterol, albuterol), insulin, methylxanthines (theophylline, aminophylline), dobutamine (58, 59, 143–147)
	Inhibit sodium resorption in loop of Henle and distal renal tubule	Loop and thiazide diuretics (61)
	Elevate the osmolality of the glomerular filtrate	Osmotic diuretics (72)
	Inhibiting hydrogen ion secretion by the renal distal tubule	Carbonic anhydrase inhibitors (148)
	Enhance resorption of sodium at the renal distal tubule	Adrenocortical steroids (mineralcorticoids/glucocorticoids) (3, 149)
	Sodium resorption and solute diuretic in the depletion of magnesium	Natural penicillin, penicillinase-resistant penicillin, aminopenicillins and extended renal collecting duct spectrum penicillins (150–156)
		Aminoglycosides (gentamicin, tobramycin, amikacin), amphotericin B (41)
	Inhibit secretion of hydrogen ions by renal collecting duct	Amphotericin B (60, 157, 158)
	Exchange sodium for potassium within lumen of intestine	Cation-exchange resin (sodium polysterene sulfonate) (159)
Hyperkalemia	Excess potassium administration	Citrate, penicillin G, enteral and parenteral nutrition formulations (160, 161)
	Competitive inhibitor of aldosterone/ reduce sodium absorption in renal distal tubule	Spironolactone/amiloride, triamterene, trimethoprim (79, 101, 162)
	Inhibiting Na+/K+ ATPase pump	Metoprolol, propranolol, labetalol, digoxin (98, 163, 164)
	Interferes with conversion of angiotensin I into angiotensin II/induces state of hypoaldosteronism	ACE/ARB (77, 85, 87)
	Decreasing number and affinity of angiotensin II receptors reducing aldosterone synthesis	Heparin, LMWH (91)
	Ion channel depolarization	Succinylcholine (165–167)

ATPase, adenosine triphosphatase; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; LMWH, low-molecular weight heparin.

photericin B is a polyene macrolide antifungal with a prevalence of hypokalemia documented as high as 47% (62–64). Based on this theory of developing hypokalemia, amiloride has been used to alleviate amphotericin B potassium wasting by increasing serum potassium levels 0.5 mmol/L within 5 days of administration (65). Sodium polysterene sulfonate is a cation-exchange resin that can be administered orally or as a retention enema. Because this agent is associated with causing constipation, it is sometimes administered with sorbitol as a cathartic to enhance diarrhea and potassium excretion. Although sorbitol can be used, it is not recommended due to cases of colonic necrosis that have developed because of its use (66). At doses of 15–60 g in the adult patient, each gram of the exchange resin has the potential to bind approximately 0.65 mmol of potassium (67). When administered orally, the agent has a slow onset of action (2 hrs) with a maximum effect that may not occur for >6 hrs (68). Other data have demonstrated that resins are useful for treatment of hyperkalemia but lowering of the serum potassium did not occur for 1–5 days (69). Based on its slow onset of effect, cation-exchange resins are not effective in the treatment of acute hyperkalemia, and they do not significantly enhance potassium excretion beyond the effect of diarrhea induced by osmotic or secretory cathartics (70, 71).

Drug-induced hyperkalemia

Hyperkalemia is a common occurrence in hospitalized patients with frequencies that range from 1.3% (serum potassium of >6 mEq/L) to 10% (serum potassium of >5.3 mEq/L) (72). Drug-induced hyperkalemia has been identified as a primary cause or contributing factor in 35% to 75% of hospitalized patients (73–75). The prevalence of hyperkalemia in critically ill patients is unknown, but patients at highest risk include a diagnosis of moderate-to-severe chronic renal insufficiency, hypoaldosteronism, and diseases associated with impaired response to the potassium secretory effects of aldosterone (76). Hyperkalemia is primarily precipitated by excessive potassium intake, impaired renal excretion of potassium, or abnormal or altered cellular uptake of potassium. The major physiologic sequelae of hyperkalemia include weakness, ascending paralysis, and respiratory failure (60). Early electrocardiographic changes include elevated T wave, as the serum potassium increases prolonged PR interval, widened QRS complex, and merging S and T waves. Left untreated, electrocardiographic changes include sine-wave pattern, idioventricular rhythms, and asystolic cardiac arrest (49). Pharmacologic agents and associated mechanisms are summarized in Table 2.

Potassium supplementation is the most obvious etiology of hyperkalemia, which has been identified as a cause of hyperkalemia in 15% to 40% of hospitalized patients (77). Administration of 100–200 mEq of potassium may increase serum potassium levels by approximately 1 mEq/L (78). Although potassium supplementation alone rarely causes hyperkalemia, it is often the underlying acute change in potassium excretion that leads to an elevated potassium level. Potassium-sparing diuretics, including spironolactone, triamterene, and amiloride, inhibit potassium secretion. Fatal hyperkalemia has been reported with all three agents in 10% to 20% of patients prescribed these medications (41, 79, 80). Nonselective β blockers have been associated with contributing to hyperkalemia in 4% to 17% of hospitalized patients (77). The level of potassium increase is small and has been reported to be as low as 0.3 mEq/L (3). Angiotensin-converting enzyme (ACE) is a peptide that has been

associated with the development of hyperkalemia in 9% to 38% of hospitalized patients (81–83). Risk of ACE inhibitor hyperkalemia seems to be related to a number of factors, including diagnosis of diabetes, hypoaldosteronism, heart failure, cirrhosis, drug interactions, and the degree of renal insufficiency (81, 84–86). Hyperkalemia can develop, despite normal kidney function (77, 85). Life-threatening hyperkalemia has also been identified with concomitant spironolactone. Patients with renal insufficiency, diabetes, heart failure, and dehydration are at greater risk of developing hyperkalemia with adjunctive therapy (86). Angiotensin receptor blockers induce a state of hypoaldosteronism similar to that with ACE inhibitors. Several trials have shown no difference in the incidence of hyperkalemia (serum potassium of ≥5.5 mEq/L) between an angiotensin receptor blocker (1.5%) compared with an ACE inhibitor (1.3%) (87). Until more data are available, both ACEs and angiotensin receptor blockers should be considered equally important as an etiology of hyperkalemia in high-risk patient populations. Heparin and heparinoid compounds, including unfractionated and low-molecular weight heparin-induced hyperkalemia, are well documented (88–90). Greater than normal potassium levels occur in about 7% of patients, and this has occurred with unfractionated doses as low as 5000 units twice daily (91). Elevations in serum potassium have ranged from 0.2 mEq/L to 1.7 mEq/L with an onset 1 to 3 days after drug exposure (91, 92). Succinylcholine has been reported to cause severe hyperkalemia in patients with burns, trauma, and severe infection (93, 94). Succinylcholine causes an increase in serum potassium up to 1 mEq/L, which peaks in 2–5 mins and then quickly returns to baseline in normal healthy patients (94, 95). Although this rise is transient, significant adverse drug events, including cardiac arrest, have been reported with a prevalence of 0% to 40% (96, 97). Digoxin does not contribute to hyperkalemia with traditional dosing. However, toxic overdoses can lead to life-threatening hyperkalemia, because cellular potassium transport is impaired in a dose-dependent manner (98). Trimethoprim (TMP) acts synergistically with sulfonamides, blocking sequential biochemical steps in the production of folic acid. Several reports (25, 99–101) have associated TMP with hyperkalemia. The prevalence of hyperkalemia (>5 mEq/L) has been reported as high as 50% in human immunodeficiency virus patients treated with high-dose TMP, whereas nonhuman immunodeficiency virus patients treated with a standard dose of TMP (360 mg daily) carried a lower incidence (21%) (101, 102). TMP has been associated with increasing serum potassium levels of 0.6–1.1 mmol/L (102, 103). Risk factors for development of hyperkalemia are attributed to the drug's pharmacologic structure, which is similar to the potassium-sparing diuretic amiloride and degree of renal dysfunction (serum creatinine of >1.2 mg/dL) (25, 101).

Calcium

Background and physiologic function

Calcium is one of the most abundant electrolytes within the human body (104). The three fractions of circulating calcium present in the blood are: 1) protein-bound (40% to 50%); 2) nonionized chelated complexes with anions, including citrate, phosphate, and sulfate (10% to 15%); and (3) the ionized form (40% to 45%) (104, 105). The ionized form is the physiologically active, regulated fraction (105, 106). The majority of extracellular calcium (99%) is stored in the bone, which reflects <0.2% of serum calcium concentrations (106).

Calcium functions as an important component for multiple organ systems and intracellular processes. The excitation-contraction coupling in skeletal, myocardial, and smooth muscle is dependent on calcium. It also plays a pivotal role in neurohormonal activity, coagulation responses, and maintenance of bone structure, as well as cell membrane integrity (2, 105). However, excessive intracellular free calcium may be associated with metabolic derangements, possibly leading to cellular death (105).

Homeostasis

Serum calcium is primarily regulated within a narrow therapeutic range by the parathyroid hormone (PTH) and vitamin D, although several other substances (e.g., calcitonin, magnesium, epinephrine, phosphate, H+, interleukins) have a minor effect t (5, 105, 107). Low ionized calcium serum levels are detected by calcium-sensing receptors on the parathyroid cells, which stimulate the secretion of PTH from the parathyroid gland. Parathyroid hormone maintains serum calcium concentrations through three mechanisms: 1) osteoclast-induced liberation of calcium from the bone; 2) pronounced renal resorption of calcium in the convoluted tubule along with increased phosphorus excretion; and 3) enhancing calcium intestinal absorption in conjunction with vitamin D (105). Vitamin D is obtained exogenously through our diet or synthesized endogenously in the skin from ultraviolet light (105). Subsequently, the liver hydroxylates vitamin D to 25-hydroxyvitamin D (calcidiol) (105). Further hydroxylation occurs within the kidney to form 1,25 dihydroxyvitamin D_3 (calcitriol) (105). Calcitriol increases calcium through intestinal absorption as well as bone and renal resorption (105). Parathyroid hormone enhances the conversion of calcidiol to calcitriol. Consequently, increased calcitriol concentrations act as a negative feedback signal to decrease PTH secretion (105).

Drug-induced hypocalcemia

Hypocalcemia is common among critically ill patients (105). Low total serum calcium concentrations have been reported to be as high as 90% in ICU patients (105). The prevalence of hypocalcemia as measured ionized calcium develops in about 15% to 20% of the critically ill but may vary among different ICU patient populations (108). The true prevalence is further complicated by the inaccuracies of calculating ionized hypocalcemia from total serum calcium levels and albumin concentrations (104). Overall, hypocalcemia occurs as a result of four primary pathways: 1) PTH insufficiency; 2) vitamin D deficiency; 3) calcium chelation; or 4) bone resorption dysfunction (105). An extensive list of insults leading to hypocalcemia has been identified in critically ill patients, including but not limited to trauma, renal failure, hyperphospatemia, and sepsis (104). Furthermore, medications responsible for this electrolyte disorder affect at least one of the previously mentioned pathways resulting in hypocalcemia. These medications and their associated mechanisms are summarized in Table 3. Medications responsible for this electrolyte disorder affect at least one of the previously mentioned pathways. Several medications can inhibit PTH or calcitriol's effects on the bone, resulting in decreased calcium mobilization (105). Pre-

Table 3. Medication-induced causes of calcium disturbances

Calcium Disorder	Mechanism	Medications
Hypocalcemia	Decreased bone resorption	Fluoride poisoning, chemotherapeutic agents (cisplatin, carboplatin, 5-fluorouracil with leucovorin, dactinomycin, cyclophosphamide, ifosfamide, doxorubicin with cytarabine), bisphosphonates, calcitonin, amphotericin B, cimetidine, ethanol (5)
	Calcium chelation or vitamin D deficiency	Foscarnet, citrate, phosphate ingestion (oral, enema, intravenous), edetate (contrast dye precipitation and propofol), albumin, lipid emulsion solutions with TPN, heparin (4, 5, 104, 109), Phenytoin, phenobarbital, ketoconazole, rifampicin, isoniazid, primidone (5)
	Decreased PTH secretion/ action	Aspirin, estrogen, magensium sulfate, cochicine, propylthiouracil, calcitonin, loop diurectis (4)
	Hypomagnesiumia	Aminoglycosides (amikacin, gentamicin, tobramycin, neomycin) (3)
	Increased urinary calcium excretion	Loop diuretics (107)
Hypercalcemia	Increased bone resorption	Vitamin D (4)
	Increased calcium absorption	Vitamin D, vitamin A (4)
	Decreased urinary calcium excretion	Loop diuretics (4)
	Miscellaneous	Estrogen, tamoxifen, thiazide diuretics, lithium (4, 114)

TPN, total parenteral nutrition; PTH, parthyroid hormone.

cipitation of calcium can develop with increased exogenous sources of phosphate (e.g., phosphate-containing enema). Chelation may also occur with commonly used agents in the ICU, such as propofol and contrast dye, which both contain edentate (104, 109). This substance may be responsible for calcium binding, although the clinical significance of this compound developing hypocalcemia remains debatable (109). Albumin has been associated with hypocalcemia in a transient phenomenon (108). Heparin can promote hydrolysis of triglycerides to monoglycerides and free fatty acids, which complex with calcium (110). Vitamin D deficiency secondary to medications is another major cause for hypocalcemia. Drugs, such as the anticonvulsants, may induce liver enzyme activity to increase metabolism of vitamin D into inactive metabolites (3). Also, aminoglycosides can contribute to increased renal excretion of magnesium (3). Thus, hypocalcemia may be attributed to inhibited PTH secretion as a result of hypomagnesemia (3).

Drug-induced hypercalcemia

Although hypercalcemia is a common complication in cancer patients, it occurs in about 15% of critically ill patients as well (46). The kidneys in conjunction with the parathyroid gland maintain calcium homeostasis after significant increases in extracellular calcium concentrations (111). The rate and magnitude of extracellular calcium influx exceeds the kidney's capability to eliminate it from the body (111), with renal impairment leading to increased calcium concentrations (111). Nephrocalcinosis resulting from calcium precipitation advances renal dysfunction and may progress to irreversible damage (111). Ultimately, renal dysfunction and hypercalcemia propagate the other condition. Several etiologies of hypercalcemia have been recognized, although malignancy and hyperparathyroidism encompass the majority of cases (106). However, commonly used medications have been associated with hypercalcemia (Table 3). The drug-induced pathophysiology leading to hypercalcemia is not as well documented as hypocalcemia. However, this adverse drug event may be attributed to disturbing the calcium homeostasis pathways involving PTH and vitamin D. Vitamin D toxicity, resulting from high doses (10,000–40,000 units/day) over an extended period of time, increases calcium absorption from the intestine and kidney as well as bone resorption (4, 111). As vitamin D is a lipid-soluble substance, excessive stores in the liver and adipose tissue can be slowly released into the serum up to several months after discontinuation (111). Thiazide diuretics increase serum calcium by 0.5–1 mg/dL (112). The mechanism responsible for thiazide-induced hypercalcemia is not well understood. Potential theories explaining this finding include stimulation of PTH secretion, or a direct action of the diuretic on enhancing the peripheral effects of PTH (113). The impact of lithium, estrogen, and tamoxifen on calcium homeostasis is not well understood (4). However, lithium may competitively inhibit calcium transport through cellular membranes, thus increasing extracellular concentrations (114).

Phosphate

Background and physiologic function

Phosphorus is the most abundant intracellular anion in the body (115). The bone accounts for 85% of total body distribution, whereas the soft tissue, muscle, and blood store the remaining amounts (115, 116). Serum phosphorus poorly reflects total body stores since intracellular concentrations are about 100 times greater than extracellular concentrations (115, 116). Two thirds of serum phosphorus exists as an organic form with the remaining in its inorganic state (115). Furthermore, the inorganic form is present as unbound phosphate (85%) comprising of $HPO42^{-}$, $H2PO4^{-}$, and $PO43^{-}$ ions; protein-bound (10%), as well as complexes (5%) formed with calcium, magnesium, and sodium (115).

Phosphorus is an important component in multiple physiologic processes impacting many different organ systems. It is a vital element in nucleic acids, nucleoproteins, and cellular membranes (116). Intracellular messenger pathways, urinary and serum pH buffer systems, immunity, as well as coagulation processes are influenced by phosphorus (116). Most importantly, phosphorus is the source of adenosine triphosphate production, which drives muscle contractility, neuronal transmission, and electrolyte transport (116).

Homeostasis

Phosphorus homeostasis is primarily regulated by the kidney where up to 90%

of phosphorus is filtered, although the gastrointestinal tract and bone are also involved to a lesser degree (116, 117). Declining serum phosphorus levels stimulate renal 1-α hydroxylase converting calcidiol to calcitriol, resulting in increased intestinal absorption, decreased renal excretion, and stimulated bone resorption (106). As phosphorus levels rise, PTH increases renal excretion (106). Although this complex process has been overly simplified, it should be noted several other factors (e.g., calcium, calcitonin, growth hormone, acid-base balance) are involved (106, 115–117).

Table 4. Medication-induced causes of phosphate disturbances

Phosphate Disorder	Mechanism	Medications
Hypophosphatemia	Malabsorption	Antacids (aluminum- or magnesium-containing), sucralfate, phosphate binders (calcium-containing products) (116, 118)
	Transcellular shift	Aspirin (overdose), albuterol, catecholamines (epinephrine, dopamine), insulin (exogenous), sodium bicarbonate (115, 116, 118)
	Urinary excretion	Acetaminophen (overdose), chemotherapeutic agents (ifosfamide, cisplatin, cyclophosphamide, doxorubicin), diuretics (thiazides, loop, osmotic, carbonic anhydrase inhibitors), glucocorticoids, theophylline (overdose) (118)
Hyperphosphatemia	Excess phosphate administration	Phosphate-containing enema/laxative, phosphate (exogenous intravenous or oral sources) (116)

Drug-induced hypophosphatemia

The prevalence of moderate hypophosphatemia (0.32–0.65 mmol/L) is relatively low (<5%) in hospitalized patients; the frequency of severe hypophosphatemia (<0.32 mmol/L) is even lower (<0.05%) (115). However, hypophosphatemia can be observed in about 28% of critically ill patients, more notably in the trauma population (115). Clinical features of severe hypophosphatemia can include respiratory failure, such as difficulties in weaning mechanical ventilation as well as cardiac, neurologic, hematologic, and muscular abnormalities (115). Potential drug-induced causes of hypophosphatemia should be considered among other sources commonly encountered in the ICU, such as sepsis, malabsorption, alkalosis, hypothermia, and hemodialysis (115, 116).

The etiology for most medications causing hypophosphatemia in the ICU can be explained by one of the following mechanisms: 1) malabsorption or decreased intake of phosphorus; 2) transcellular shifts of extracellular phosphorus into the intracellular space; or 3) loss of phosphorus through urinary excretion (115). These medications and their associated mechanisms are summarized in Table 4. Aluminum in antacids, as well as sucralfate, binds to phosphorus and forms a nonabsorbable salt within the gastrointestinal tract (118). Although hypophosphatemia has been reported after just a couple weeks of antacid therapy, sucralfate's effect on significantly lowering serum concentrations is debatable (118). The influence of catecholamine and albuterol on intracellular shifting of serum phosphorus may be mediated through β-adrenergic actions (118). Diuretics have been associated with hypophosphatemia through increased renal excretion. However, the degree in which these agents lower serum levels is related to its potency on inhibiting carbonic anhydrase to increase bicarbonate excretion (i.e., urine pH) (118). The majority of phosphorus is absorbed in the proximal tubule through a process determined by urinary pH (118). The phosphorus form, H_2PO4^-, is the most prevalent at higher urinary pH levels, which is not as easily resorbed as other forms (116). Acetazolamide is the most potent phosphorus-lowering agent, whereas loop and thiazide diuretics have minimal effects based on carbonic anhydrase-inhibiting potential (118). The significance of mannitol-lowering phosphorus serum concentrations remains unknown. This may be attributed to its effect on falsely lowering test results, thus hindering the reliability and validity of phosphate assay methods (118). Whereas most medications have a direct effect on phosphorus absorption, excretion or transcellular shift, aspirin toxicity lowers serum levels indirectly through the development of respiratory alkalosis (116).

Drug-induced hyperphosphatemia

Hyperphosphatemia occurs as a result of increased exogenous or endogenous sources of phosphorus exceeding the kidney's elimination capacity (119). This electrolyte abnormality is typically rare in otherwise healthy individuals (119). However, patients with severely compromised renal function, particularly the critically ill, are at highest risk (119). The list of medications causing hyperphosphatemia is not extensive and mostly limited to phosphate-containing products (Table 4).

Magnesium

Background and physiologic function

Although magnesium is the second most common intracellular cation following potassium, serum magnesium concentrations poorly reflect overall body content (120). Total body stores are concentrated primarily in the bone (53%) with other storage locations found in the muscle (27%), soft tissue (19%), erythrocytes (0.5%), and serum (0.3%) (120). Serum magnesium exists as its ionized form (65%), bound with proteins (27%) and complexes (8%) with other substrates (e.g., phosphorus, citrate) (121).

Magnesium plays a pivotal role in multiple organ systems and physiologic processes. Over 300 enzymatic reactions involve magnesium as a cofactor (2, 121). More specifically, Na/K/Ca-adenosine triphosphate activation is directly impacted (120–122). Consequently, magnesium contributes to the regulation of intracellular ions responsible for cellular metabolism and conduction (122). Immunologic functions, neuromuscular processes, and cardiovascular effects are also influenced by magnesium (120–122).

Homeostasis

Unfortunately, comprehension of regulatory mechanisms involved in maintaining magnesium homeostasis is incomplete (120). Three organs (bone, gastrointestinal tract, and kidneys) have been identified as regulating serum magnesium concentrations (120). PTH, as well as insulin, vitamin D, vasopressin, and calcitonin, are also believed to influence serum magnesium levels, although

their significance remains debatable (112, 121, 123).

The kidneys are the principal organ for governing magnesium homeostasis (121). About 75% of serum magnesium is filtered through the kidneys in otherwise healthy adults, of which most is resorbed (122). The ascending loop of Henle resorbs >50% of renally filtered magnesium with the proximal convoluted tubules consuming back another 15% to 25% of magnesium; the remaining amount is excreted (5%) (122).

Table 5. Medication-induced causes of magnesium disturbances

Magnesium Disorder	Mechanism	Medications
Hypomagnesemia	Increased renal excretion	Aminoglycosides (gentamicin, tobramycin, amikacin, neomycin), amphotericin B, cisplatin, cyclosporine, colony-stimulating factors, digoxin, diuretics (loops, thiazides, osmotic and carbonic anhydrase inhibitors), foscarnet, methotrexate, pentamidine, polymycin B, ticarcillin (4, 121, 168)
Hypermagnesemia	Transcellular shifts	Catecholamines (exogenous), insulin (exogenous) (169)
	Decreased renal excretion	Lithium intoxication (4)
	Excess magnesium administration	Magnesium-containing enema/laxative/antacids, magnesium (exogenous) administration (intravenous or oral) (126)

Drug-induced hypomagnesemia

Hypomagnesemia is relatively common in the ICU and has been reported to be prevalent in up to 50% of critically ill patients (2). Although most patients rarely experience signs and symptoms of hypomagnesemia with serum magnesium concentrations of >1.5 mg/dL, clinical manifestations may become apparent when serum levels are <1.2 mg/dL (2, 120). However, it is important to recognize that patients may have a total body deficit of magnesium, despite normal serum levels (122).

Hypomagnesemia can result in deleterious outcomes, especially in the ICU. Muscle weakness associated with hypomagnesemia can make it difficult for mechanical ventilation weaning (120). Cardiac conduction abnormalities secondary to magnesium depletion and possibly coexisting hypokalemia can result in PR as well as QT interval prolongation (121). Consequently, cardiac arrhythmias including torsades de pointes can ensue (120, 121). Most importantly, hypomagnesemia has been correlated with increased morbidity and mortality in ICU patients, although these findings remain conflicted (121, 122).

The complexity of critically ill patients can pose a challenge in determining the etiology. Many chronic disease states, as well as acute insults, can contribute to magnesium deficits mostly through excessive gastrointestinal losses (e.g., malabsorption, decreased intake), renal wasting, and endocrine disturbances (120). Drug-induced causes primarily affect the kidney's magnesium resorption capacity, although a few medications can impact transcellular shifts (Table 5). Although for several medications the specific mechanism for hypomagnesemia remains unclear, it has been theorized that nephrotoxic drugs (e.g., aminoglycosides, cisplatin, cyclosporine, amphotericin B) can induce magnesium renal loss as a direct result of drug-induced injury (121, 124). Furthermore, it should be noted that higher aminoglycoside cumulative dosages are proportionally related to the degree of hypomagnesemia (124). Diuretics increase urinary losses of magnesium (121). However, the significance of these losses is dependent on the site of action for the specific diuretic (121). The loop diuretics have a pronounced effect on the development of magnesium losses (121). This is attributed to their primary site of action on the loop of Henle, the major region for renal resorption of magnesium, whereas the thiazides influence the distal tubule within the kidney (120, 121). Minimal amounts of magnesium (<5%) are resorbed at this section of the nephron, so thiazide-induced losses are often insignificant (120). However, other reports (121, 125) stated thiazides can have significant effects on lowering serum magnesium levels. The development of hypomagnesemia has been implicated with digoxin (4, 124). The precise mechanism of how digoxin exerts its effects on magnesium remains unknown. However, it has been hypothesized that increased magnesium urinary excretion may be caused by digoxin's impairment of the Na/K ATPase pump, therefore inhibiting magnesium's glomerular filtration and transcellular movement (4, 124).

Drug-induced hypermagnesemia

Elevated magnesium serum concentrations are not as common as hypomagnesemia (106). Patients with compromised renal function are typically at greater risk (106). The clinical manifestations of hypermagnesemia typically present when levels exceed 4 mEq/L (112). Excessive magnesium can result in cardiovascular and neuromuscular abnormalities (112).

Few medications contribute to the development of hypermagnesemia (4, 106, 112). Overzealous magnesium administration (oral or intravenous) as well as the use of magnesium-containing products (e.g., enemas, laxatives, and antacids) may lead to increased serum levels (106). However, oral magnesium administration resulting in hypermagnesemia is rather infrequent, as gastrointestinal absorption is inversely related to serum magnesium levels (i.e., increased oral absorption when serum magnesium concentrations are low and vice versa) (126). Lithium use and toxicity have been implicated in elevated magnesium serum levels (106). Although the mechanism remains unknown, it is believed lithium disturbs the kidneys' ability to eliminate magnesium (4, 106).

Conclusion

Electrolyte abnormalities are common in critically ill patients. These disturbances may be attributed to several possible sources, which may often be multifactorial. However, clinicians should have an appreciation of medications as a potential cause of electrolyte disorders. These drug-induced causes in the ICU may be a result of medications altering the physiology of these critically ill patients, or they may manifest from medication toxicity. Increased awareness of drug-induced

causes in the ICU is imperative in correcting the electrolyte abnormalities.

REFERENCES

1. Kraft MD, Btaiche IF, Sacks GS, et al: Treatment of electrolyte disorders in adult patients in the intensive care unit. *Am J Health Syst Pharm* 2005; 62:1663–1682
2. Besunder JB, Smith PG: Toxic effects of electrolyte and trace mineral administration in the intensive care unit. *Crit Care Clin* 1991; 7:659–693
3. Brass EP, Thompson WL: Drug-induced electrolyte abnormalities. *Drugs* 1982; 24: 207–228
4. Nanji AA: Drug-induced electrolyte disorders. *Drug Intell Clin Pharm* 1983; 17: 175–185
5. Weiss-Guillet EM, Takala J, Jakob SM: Diagnosis and management of electrolyte emergencies. *Best Pract Res Clin Endocrinol Metab* 2003; 17:623–651
6. Adrogue HJ, Madias NE: Hypernatremia. *N Engl J Med* 2000; 342:1493–1499
7. Verbalis JG: Disorders of body water homeostasis. *Best Pract Res Clin Endocrinol Metab* 2003; 17:471–503
8. Palmer B:. Hyponatremia in the intensive care unit. *Semin Nephrol* 2009; 29:257–270
9. Reynolds RM, Padfield PL, Seckl JR: Disorders of sodium balance. *BMJ* 2006; 332: 702–705
10. Hoorn EJ, Lindemans J, Zietse R: Development of severe hyponatraemia in hospitalized patients: Treatment-related risk factors and inadequate management. *Nephrol Dial Transplant* 2006; 21:70–76
11. Stelfox HT, Ahmed SB, Khandwala F, et al: The epidemiology of intensive care unit-acquired hyponatraemia and hypernatraemia in medical-surgical intensive care units. *Crit Care* 2008; 12:R162
12. DeVita MV, Gardenswartz MH, Konecky A, et al: Incidence and etiology of hyponatremia in an intensive care unit. *Clin Nephrol* 1990; 34:163–166
13. Oster JR, Singer I: Hyponatremia, hyposmolality, and hypotonicity: Tables and fables. *Arch Intern Med* 1999; 159:333–336
14. Yun JJ, Cheong I: Mannitol-induced hyperosmolal hyponatraemia. *Intern Med J* 2008; 38:73
15. Patel GP, Balk RA: Recognition and treatment of hyponatremia in acutely ill hospitalized patients. *Clin Ther* 2007; 29: 211–229
16. Sordillo P, Sagransky DM, Mercado RM, et al: Carbamazepine-induced syndrome of inappropriate antidiuretic hormone secretion. Reversal by concomitant phenytoin therapy. *Arch Intern Med* 1978; 138: 299–301
17. Henry DA, Lawson DH, Reavey P, et al: Hyponatraemia during carbamazepine treatment. *Br Med J* 1977; 1:83–84
18. Odeh M, Oliven A: Coma and seizures due to severe hyponatremia and water intoxication in an adult with intranasal desmopressin therapy for nocturnal enuresis. *J Clin Pharmacol* 2001; 41:582–584
19. Bernstein SA, Williford SL: Intranasal desmopressin-associated hyponatremia: A case report and literature review. *J Fam Pract* 1997; 44:203–208
20. Brewster UC, Perazella MA: Proton pump inhibitors and the kidney: Critical review. *Clin Nephrol* 2007; 68:65–72
21. Delfanian K, Zawada ET Jr: DDAVP-associated hyponatremia. *S D J Med* 2001; 54:255–256
22. Liamis G, Christidis D, Alexandridis G, et al: Uric acid homeostasis in the evaluation of diuretic-induced hyponatremia. *J Investig Med* 2007; 55:36–44
23. Sonnenblick M, Friedlander Y, Rosin AJ: Diuretic-induced severe hyponatremia. Review and analysis of 129 reported patients. *Chest* 1993; 103:601–606
24. Noto H, Kaneko Y, Takano T, et al: Severe hyponatremia and hyperkalemia induced by trimethoprim-sulfamethoxazole in patients with Pneumocystis carinii pneumonia. *Intern Med* 1995; 34:96–99
25. Mori H, Kuroda Y, Imamura S, et al: Hyponatremia and/or hyperkalemia in patients treated with the standard dose of trimethoprim-sulfamethoxazole. *Intern Med* 2003; 42:665–669
26. Kaufman AM, Hellman G, Abramson RG: Renal salt wasting and metabolic acidosis with trimethoprim-sulfamethoxazole therapy. *Mt Sinai J Med* 1983; 50:238–239
27. Polderman KH, Schreuder WO, Strack van Schijndel RJ, et al: Hypernatremia in the intensive care unit: An indicator of quality of care? *Crit Care Med* 1999; 27:1105–1108
28. Aiyagari V, Deibert E, Diringer MN: Hypernatremia in the neurologic intensive care unit: How high is too high? *J Crit Care* 2006; 21:163–172
29. Lindner G, Funk GC, Schwarz C, et al: Hypernatremia in the critically ill is an independent risk factor for mortality. *Am J Kidney Dis* 2007; 50:952–957
30. O'Donoghue SD, Dulhunty JM, Bandeshe HK, et al: Acquired hypernatraemia is an independent predictor of mortality in critically ill patients. *Anaesthesia* 2009; 64: 514–520
31. Hoorn EJ, Betjes MG, Weigel J, et al: Hypernatraemia in critically ill patients: Too little water and too much salt. *Nephrol Dial Transplant* 2008; 23:1562–1568
32. Gondim Fde A, Aiyagari V, Shackleford A, et al: Osmolality not predictive of mannitol-induced acute renal insufficiency. *J Neurosurg* 2005; 103:444–447
33. Dziedzic T, Szczudlik A, Klimkowicz A, et al: Is mannitol safe for patients with intracerebral hemorrhages? Renal considerations. *Clin Neurol Neurosurg* 2003; 105: 87–89
34. Perez-Perez AJ, Pazos B, Sobrado J, et al: Acute renal failure following massive mannitol infusion. *Am J Nephrol* 2002; 22: 573–575
35. Garofeanu CG, Weir M, Rosas-Arellano MP, et al: Causes of reversible nephrogenic diabetes insipidus: A systematic review. *Am J Kidney Dis* 2005; 45:626–637
36. Smith OP, Gale R, Hamon M, et al: Amphotericin B-induced nephrogenic diabetes insipidus: Resolution with its liposomal counterpart. *Bone Marrow Transplant* 1994; 13: 107–108
37. Spath-Schwalbe E, Koschuth A, Dietzmann A, et al: Successful use of liposomal amphotericin b in a case of amphotericin B-induced nephrogenic diabetes insipidus. *Clin Infect Dis* 1999; 28:680–681
38. Canada TW, Weavind LM, Augustin KM: Possible liposomal amphotericin B-induced nephrogenic diabetes insipidus. *Ann Pharmacother* 2003; 37:70–73
39. Fichman MP, Kleeman CR, Bethune JE: Inhibition of antidiuretic hormone secretion by diphenylhydantoin. *Arch Neurol* 1970; 22:45–53
40. Froelich M, Ni Q, Wess C, et al: Continuous hypertonic saline therapy and the occurrence of complications in neurocritically ill patients. *Crit Care Med* 2009; 37:1433–1441
41. Gennari F: Disorders of potassium metabolism. *In:* Therapy of Renal Diseases and Related Disorders. Third Edition. Suki W, Massry S (Eds). Boston, Kluwer Academic, 1997, pp 53–84
42. Macknight AD: Epithelial transport of potassium. *Kidney Int* 1977; 11:391–414
43. Bia MJ, DeFronzo RA: Extrarenal potassium homeostasis. *Am J Physiol* 1981; 240: F257–F268
44. Defronzo R: Regulation of extrarenal potassium homeostasis by insulin and catecholamines. *In:* Current Topics in Membranes and Transport. Giebisch G (Ed). San Diego, Academic Press, 1987, pp 299–329
45. Field MJ, Giebisch GJ: Hormonal control of renal potassium excretion. *Kidney Int* 1985; 27:379–387
46. Martinez FJ, Lash RW: Endocrinologic and metabolic complications in the intensive care unit. *Clin Chest Med* 1999; 20: 401–421, ix
47. Chiou CY, Kifor I, Moore TJ, et al: The effect of losartan on potassium-stimulated aldosterone secretion in vitro. *Endocrinology* 1994; 134:2371–2375
48. Paice BJ, Paterson KR, Onyanga-Omara F, et al: Record linkage study of hypokalaemia in hospitalized patients. *Postgrad Med J* 1986; 62:187–191
49. Anonymous: Life-threatening electrolyte abnormalities. *Circulation* 2005; 112:IV-121–IV-125
50. Vanek VW, Seballos RM, Chong D, et al: Serum potassium concentrations in trauma patients. *South Med J* 1994; 87:41–46
51. Gercek A, Umuroglu T, Inci F, et al: The etiology and incidence of hypokalemia in intensive care unit. *Marmara Med J* 2003; 16:32–35

52. Kunau RT, Stein JH: Disorders of hypo- and hyperkalemia. *Clin Nephrol* 1977; 7:173–190
53. Freedman BI, Burkart JM: Endocrine crises. Hypokalemia. *Crit Care Clin* 1991; 7:143–153
54. Allon M, Copkney C: Albuterol and insulin for treatment of hyperkalemia in hemodialysis patients. *Kidney Int* 1990; 38:869–872
55. Allon M, Dunlay R, Copkney C: Nebulized albuterol for acute hyperkalemia in patients on hemodialysis. *Ann Intern Med* 1989; 110: 426–429
56. Bremner P, Burgess C, Beasley R, et al: Nebulized fenoterol causes greater cardiovascular and hypokalaemic effects than equivalent bronchodilator doses of salbutamol in asthmatics. *Respir Med* 1992; 86: 419–423
57. Burgess CD, Flatt A, Siebers R, et al: A comparison of the extent and duration of hypokalaemia following three nebulized beta 2-adrenoceptor agonists. *Eur J Clin Pharmacol* 1989; 36:415–417
58. Reid JL, Whyte KF, Struthers AD: Epinephrine-induced hypokalemia: The role of beta adrenoceptors. *Am J Cardiol* 1986; 57: 23F–27F
59. Coma-Canella I: Changes in plasma potassium during the dobutamine stress test. *Int J Cardiol* 1991; 33:55–59
60. Gennari FJ: Hypokalemia. *N Engl J Med* 1998; 339:451–458
61. Greger R: Why do loop diuretics cause hypokalaemia? *Nephrol Dial Transplant* 1997; 12:1799–1801
62. Patterson RM, Ackerman GL: Renal tubular acidosis due to amphotericin b nephrotoxicity. *Arch Intern Med* 1971; 127:241–244
63. Douglas JB, Healy JK: Nephrotoxic effects of amphotericin B, including renal tubular acidosis. *Am J Med* 1969; 46:154–162
64. Mohan S, Ahmed S, Alimohammadi B, et al: Proteinuria lowers the risk of amphotericin B-associated hypokalaemia. *J Antimicrob Chemother* 2007; 60:690–693
65. Bearden DT, Muncey LA: The effect of amiloride on amphotericin B-induced hypokalaemia. *J Antimicrob Chemother* 2001; 48:109–111
66. LLC S-A: Sorbitol package insert, 2009
67. Lillemoe KD, Romolo JL, Hamilton SR, et al: Intestinal necrosis due to sodium polystyrene (kayexalate) in sorbitol enemas: Clinical and experimental support for the hypothesis. *Surgery* 1987; 101:267–272
68. Scherr L, Ogden DA, Mead AW, et al: Management of hyperkalemia with a cation-exchange resin. *N Engl J Med* 1961; 264: 115–119
69. Flinn RB, Merrill JP, Welzant WR: Treatment of the oliguric patient with a new sodium-exchange resin and sorbitol; A preliminary report. *N Engl J Med* 1961; 264: 111–115
70. Kamel KS, Wei C: Controversial issues in the treatment of hyperkalaemia. *Nephrol Dial Transplant* 2003; 18:2215–2218
71. Weisberg LS: Management of severe hyperkalemia. *Crit Care Med* 2008; 36:3246–3251
72. Evans KJ, Greenberg A: Hyperkalemia: A review. *J Intensive Care Med* 2005; 20: 272–290
73. Paice B, Gray JM, McBride D, et al: Hyperkalaemia in patients in hospital. *Br Med J (Clin Res Ed)* 1983; 286:1189–1192
74. Ponce SP, Jennings AE, Madias NE, et al: Drug-induced hyperkalemia. *Medicine (Baltimore)* 1985; 64:357–370
75. Shemer J, Modan M, Ezra D, et al: Incidence of hyperkalemia in hospitalized patients. *Isr J Med Sci* 1983; 19:659–661
76. DeFronzo RA: Hyperkalemia and hyporeninemic hypoaldosteronism. *Kidney Int* 1980; 17:118–134
77. Perazella MA: Drug-induced hyperkalemia: Old culprits and new offenders. *Am J Med* 2000; 109:307–314
78. Schaefer TJ, Wolford RW: Disorders of potassium. *Emerg Med Clin North Am* 2005; 23:723–747, viii–ix
79. Greenblatt DJ, Koch-Weser J: Adverse reactions to spironolactone. A report from the Boston collaborative drug surveillance program. *JAMA* 1973; 225:40–43
80. Walker BR, Capuzzi DM, Alexander F, et al: Hyperkalemia after triamterene in diabetic patients. *Clin Pharmacol Ther* 1972; 13: 643–651
81. Rimmer JM, Horn JF, Gennari FJ: Hyperkalemia as a complication of drug therapy. *Arch Intern Med* 1987; 147:867–869
82. Ahmed EU, Mohammed BN, Matute R, et al: Etiology of hyperkalemia in hospitalized patients: An answer to Harrington's question. *J Am Soc Nephrol* 1998; 9:103A
83. Memon A, Siddiqui M, Agraharkar M, et al: Incidence and predictors of hyperkalemia in patients with chronic renal failure on angiotensin converting enzyme inhibitors. *J Am Soc Nephrol* 1999; 10:294A
84. Acker CG, Johnson JP, Palevsky PM, et al: Hyperkalemia in hospitalized patients: Causes, adequacy of treatment, and results of an attempt to improve physician compliance with published therapy guidelines. *Arch Intern Med* 1998; 158:917–924
85. Textor SC, Bravo EL, Fouad FM, et al: Hyperkalemia in azotemic patients during angiotensin-converting enzyme inhibition and aldosterone reduction with captopril. *Am J Med* 1982; 73:719–725
86. Schepkens H, Vanholder R, Billiouw JM, et al: Life-threatening hyperkalemia during combined therapy with angiotensin-converting enzyme inhibitors and spironolactone: An analysis of 25 cases. *Am J Med* 2001; 110:438–441
87. Goldberg AI, Dunlay MC, Sweet CS: Safety and tolerability of losartan potassium, an angiotensin II receptor antagonist, compared with hydrochlorothiazide, atenolol, felodipine ER, and angiotensin-converting enzyme inhibitors for the treatment of systemic hypertension. *Am J Cardiol* 1995; 75: 793–795
88. Aull L, Chao H, Coy K: Heparin-induced hyperkalemia. *DICP* 1990; 24:244–246
89. Day JR, Chaudhry AN, Hunt I, et al: Heparin-induced hyperkalemia after cardiac surgery. *Ann Thorac Surg* 2002; 74:1698–1700
90. Edes TE, Sunderrajan EV: Heparin-induced hyperkalemia. *Arch Intern Med* 1985; 145: 1070–1072
91. Oster JR, Singer I, Fishman LM: Heparin-induced aldosterone suppression and hyperkalemia. *Am J Med* 1995; 98:575–586
92. Canova CR, Fischler MP, Reinhart WH: Effect of low-molecular-weight heparin on serum potassium. *Lancet* 1997; 349: 1447–1448
93. Hunter JM: New neuromuscular blocking drugs. *N Engl J Med* 1995; 332:1691–1699
94. Yentis SM: Suxamethonium and hyperkalaemia. *Anaesth Intensive Care* 1990; 18: 92–101
95. Mazze RI, Escue HM, Houston JB: Hyperkalemia and cardiovascular collapse following administration of succinylcholine to the traumatized patient. *Anesthesiology* 1969; 31:540–547
96. Larach MG, Rosenberg H, Gronert GA, et al: Hyperkalemic cardiac arrest during anesthesia in infants and children with occult myopathies. *Clin Pediatr (Phila)* 1997; 36: 9–16
97. Hambly PR, Martin B: Anaesthesia for chronic spinal cord lesions. *Anaesthesia* 1998; 53:273–289
98. Lown B, Black H, Moore FD: Digitalis, electrolytes and the surgical patient. *Am J Cardiol* 1960; 6:309–337
99. Greenberg S, Reiser IW, Chou SY: Hyperkalemia with high-dose trimethoprim-sulfamethoxazole therapy. *Am J Kidney Dis* 1993; 22:603–606
100. Perazella MA, Mahnensmith RL: Trimethoprim-sulfamethoxazole: Hyperkalemia is an important complication regardless of dose. *Clin Nephrol* 1996; 46:187–192
101. Alappan R, Perazella MA, Buller GK: Hyperkalemia in hospitalized patients treated with trimethoprim-sulfamethoxazole. *Ann Intern Med* 1996; 124:316–320
102. Velazquez H, Perazella MA, Wright FS, et al: Renal mechanism of trimethoprim-induced hyperkalemia. *Ann Intern Med* 1993; 119: 296–301
103. Greenberg S, Reiser IW, Chou SY, et al: Trimethoprim-sulfamethoxazole induces reversible hyperkalemia. *Ann Intern Med* 1993; 119:291–295
104. Desai TK, Carlson RW, Geheb MA: Hypocalcemia and hypophosphatemia in acutely ill patients. *Crit Care Clin* 1987; 3:927–941
105. Zaloga GP: Hypocalcemia in critically ill patients. *Crit Care Med* 1992; 20:251–262
106. Moe SM: Disorders involving calcium, phosphorus, and magnesium. *Prim Care* 2008; 35:215–237, v–vi
107. Body JJ, Bouillon R: Emergencies of calcium homeostasis. *Rev Endocr Metab Disord* 2003; 4:167–175

108. Zaloga GP: Hypocalcemic crisis. *Crit Care Clin* 1991; 7:191–200
109. Sedlacek M, Schoolwerth AC, Remillard BD: Electrolyte disturbances in the intensive care unit. *Semin Dial* 2006; 19:496–501
110. Nanji AA, Denegri JF: Hypomagnesemia associated with gentamicin therapy. *Drug Intell Clin Pharm* 1984; 18:596–598
111. Davis KD, Attie MF: Management of severe hypercalcemia. *Crit Care Clin* 1991; 7:175–190
112. Agus ZS, Wasserstein A, Goldfarb S: Disorders of calcium and magnesium homeostasis. *Am J Med* 1982; 72:473–488
113. Popovtzer MM, Subryan VL, Alfrey AC, et al: The acute effect of chlorothiazide on serum-ionized calcium. Evidence for a parathyroid hormone-dependent mechanism. *J Clin Invest* 1975; 55:1295–1302
114. Rifai MA, Moles JK, Harrington DP: Lithium-induced hypercalcemia and parathyroid dysfunction. *Psychosomatics* 2001; 42: 359–361
115. Bugg NC, Jones JA: Hypophosphataemia. Pathophysiology, effects and management on the intensive care unit. *Anaesthesia* 1998; 53:895–902
116. Peppers MP, Geheb M, Desai T: Endocrine crises. Hypophosphatemia and hyperphosphatemia. *Crit Care Clin* 1991; 7:201–214
117. Stoff JS: Phosphate homeostasis and hypophosphatemia. *Am J Med* 1982; 72: 489–495
118. Brown GR, Greenwood JK: Drug- and nutrition-induced hypophosphatemia: Mechanisms and relevance in the critically ill. *Ann Pharmacother* 1994; 28:626–632
119. Kapoor M, Chan GZ: Fluid and electrolyte abnormalities. *Crit Care Clin* 2001; 17: 503–529
120. Noronha JL, Matuschak GM: Magnesium in critical illness: Metabolism, assessment, and treatment. *Intensive Care Med* 2002; 28:667–679
121. Tong GM, Rude RK: Magnesium deficiency in critical illness. *J Intensive Care Med* 2005; 20:3–17
122. Dube L, Granry JC: The therapeutic use of magnesium in anesthesiology, intensive care and emergency medicine: A review. *Can J Anaesth* 2003; 50:732–746
123. Rude RK: Physiology of magnesium metabolism and the important role of magnesium in potassium deficiency. *Am J Cardiol* 1989; 63:31G–34G
124. Salem M, Munoz R, Chernow B: Hypomagnesemia in critical illness. A common and clinically important problem. *Crit Care Clin* 1991; 7:225–252
125. Hollifield JW: Magnesium depletion, diuretics, and arrhythmias. *Am J Med* 1987; 82: 30–37
126. Van Hook JW: Endocrine crises. Hypermagnesemia. *Crit Care Clin* 1991; 7:215–223
127. Aviram A, Pfau A, Czaczkes JW, et al: Hyperosmolality with hyponatremia, caused by inappropriate administration of mannitol. *Am J Med* 1967; 42:648–650
128. Liamis G, Milionis H, Elisaf M: A review of drug-induced hyponatremia. *Am J Kidney Dis* 2008; 52:144–153
129. Madhusoodanan S, Osnos R: Amitriptyline induced hyponatremia: A case report. *Mt Sinai J Med* 1981; 48:431–433
130. Storch AS: Acute water retention associated with continuous slow infusion of oxytocin. A case report. *Obstet Gynecol* 1971; 37: 109–111
131. Burt RL, Oliver KL, Whitener DL: Water intoxication complicating elective induction of labor at term. Report of a patient who survived. *Obstet Gynecol* 1969; 34: 212–214
132. Cutting HO: Inappropriate secretion of antidiuretic hormone secondary to vincristine therapy. *Am J Med* 1971; 51:269–271
133. Dong X, Leppik IE, White J, et al: Hyponatremia from oxcarbazepine and carbamazepine. *Neurology* 2005; 65:1976–1978
134. Izzedine H, Fardet L, Launay-Vacher V, et al: Angiotensin-converting enzyme inhibitor-induced syndrome of inappropriate secretion of antidiuretic hormone: Case report and review of the literature. *Clin Pharmacol Ther* 2002; 71:503–507
135. Jacob S, Spinler SA: Hyponatremia associated with selective serotonin-reuptake inhibitors in older adults. *Ann Pharmacother* 2006; 40:1618–1622
136. Oldham RK, Pomeroy TC: Vincristine-induced syndrome of inappropriate secretion of antidiuretic hormone. *South Med J* 1972; 65:1010–1012
137. DeFronzo RA, Braine H, Colvin M, et al: Water intoxication in man after cyclophosphamide therapy. Time course and relation to drug activation. *Ann Intern Med* 1973; 78:861–869
138. Ayus JC, Arieff AI: Noncardiogenic pulmonary edema in marathon runners. *Ann Intern Med* 2000; 133:1011
139. Rault RM: Case report: Hyponatremia associated with nonsteroidal antiinflammatory drugs. *Am J Med Sci* 1993; 305:318–320
140. Navarro JF, Quereda C, Gallego N, et al: Nephrogenic diabetes insipidus and renal tubular acidosis secondary to foscarnet therapy. *Am J Kidney Dis* 1996; 27:431–434
141. Farese RV Jr, Schambelan M, Hollander H, et al: Nephrogenic diabetes insipidus associated with foscarnet treatment of cytomegalovirus retinitis. *Ann Intern Med* 1990; 112:955–956
142. Sjovall J, Bergdahl S, Movin G, et al: Pharmacokinetics of foscarnet and distribution to cerebrospinal fluid after intravenous infusion in patients with human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1989; 33:1023–1031
143. Bradberry SM, Vale JA: Disturbances of potassium homeostasis in poisoning. *J Toxicol Clin Toxicol* 1995; 33:295–310
144. Clausen T, Everts ME: Regulation of the na,k-pump in skeletal muscle. *Kidney Int* 1989; 35:1–13
145. Deenstra M, Haalboom JR, Struyvenberg A: Decrease of plasma potassium due to inhalation of beta-2-agonists: Absence of an additional effect of intravenous theophylline. *Eur J Clin Invest* 1988; 18:162–165
146. Hurlbert BJ, Edelman JD, David K: Serum potassium levels during and after terbutaline. *Anesth Analg* 1981; 60:723–725
147. Montoliu J, Lens XM, Revert L: Potassium-lowering effect of albuterol for hyperkalemia in renal failure. *Arch Intern Med* 1987; 147:713–717
148. Frazier HS, Yager H: The clinical use of diuretics. 2. *N Engl J Med* 1973; 288: 455–457
149. Tsai WS, Wu CP, Hsu YJ, et al: Life-threatening hypokalemia in an asthmatic patient treated with high-dose hydrocortisone. *Am J Med Sci* 2004; 327:152–155
150. Cabizuca SV, Desser KB: Carbenicillin-associated hypokalemic alkalosis. *JAMA* 1976; 236:956–957
151. Gill MA, DuBe JE, Young WW: Hypokalemic, metabolic alkalosis induced by high-dose ampicillin sodium. *Am J Hosp Pharm* 1977; 34:528–531
152. Halperin ML, Kamel KS: Potassium. *Lancet* 1998; 352:135–140
153. Hoffbrand BI, Stewart JD: Carbenicillin and hypokalaemia. *Br Med J* 1970; 4:746
154. Lipner HI, Ruzany F, Dasgupta M, et al: The behavior of carbenicillin as a nonreabsorbable anion. *J Lab Clin Med* 1975; 86: 183–194
155. Nanji AA, Lindsay J: Ticarcillin associated hypokalemia. *Clin Biochem* 1982; 15: 118–119
156. Schlaeffer F: Oxacillin-associated hypokalemia. *Drug Intell Clin Pharm* 1988; 22: 695–696
157. Sawaya BP, Briggs JP, Schnermann J: Amphotericin B nephrotoxicity: The adverse consequences of altered membrane properties. *J Am Soc Nephrol* 1995; 6:154–164
158. Steinmetz PR, Lawson LR: Defect in urinary acidification induced in vitro by amphotericin B. *J Clin Invest* 1970; 49:596–601
159. Frohnert PP, Johnson WJ, Mueller GJ, et al: Resin treatment of hyperkalemia. II. Clinical experience with a cation exchange resin (calcium cycle). *J Lab Clin Med* 1968; 71: 840–846
160. Browning JJ, Channer KS: Hyperkalaemic cardiac arrhythmia caused by potassium citrate mixture. *Br Med J (Clin Res Ed)* 1981; 283:1366
161. Mercer CW, Logic JR: Cardiac arrest due to hyperkalemia following intravenous penicillin administration. *Chest* 1973; 64: 358–359
162. Gatzy JT: The effect of K+-sparing diuretics on ion transport across the excised toad bladder. *J Pharmacol Exp Ther* 1971; 176: 580–594
163. Lundborg P: The effect of adrenergic blockade on potassium concentrations in different conditions. *Acta Med Scand Suppl* 1983; 672:121–126

164. Rosa RM, Silva P, Young JB, et al: Adrenergic modulation of extrarenal potassium disposal. *N Engl J Med* 1980; 302:431–434
165. Gronert GA, Theye RA: Pathophysiology of hyperkalemia induced by succinylcholine. *Anesthesiology* 1975; 43:89–99
166. Martyn JA, White DA, Gronert GA, et al: Up-and-down regulation of skeletal muscle acetylcholine receptors. Effects on neuromuscular blockers. *Anesthesiology* 1992; 76:822–843
167. Mishina M, Takai T, Imoto K, et al: Molecular distinction between fetal and adult forms of muscle acetylcholine receptor. *Nature* 1986; 321:406–411
168. Whang R: Magnesium deficiency: Pathogenesis, prevalence, and clinical implications. *Am J Med* 1987; 82:24–29
169. Dacey MJ: Hypomagnesemic disorders. *Crit Care Clin* 2001; 17:155–173, viii