Invited Review

aspen LEADING THE SCIENCE AND PRACTICE OF CLINICAL NUTRITION
American Society for Parenteral and Enteral Nutrition

Nutrition in Clinical Practice
Volume 30 Number 1
February 2015 21–33

DOI: 10.1177/0884533614565251
ncp.sagepub.com
hosted at
online.sagepub.com
SAGE

Phosphorus and Calcium: A Review for the Adult Nutrition Support Clinician

Michael D. Kraft, PharmD, BCNSP[1,2]

Abstract

Phosphorus (P) and calcium (Ca) serve vital roles in the human body and are essential components of nutrition support therapy. Regulation of P and regulation of Ca in the body are closely interrelated, and P and Ca homeostasis can be affected by several factors, including disease states, clinical condition, severity of illness, and medications. Nutrition support clinicians must understand these factors to prevent and treat P and Ca disorders in patients receiving nutrition support therapy. This review provides an overview of P and Ca for the adult nutrition support clinician, with some emphasis on the hospitalized inpatient. (*Nutr Clin Pract*. 2015;30:21-33)

Keywords

calcium; hypocalcemia; hypercalcemia; phosphorus; hypophosphatemia; hyperphosphatemia; nutritional support; parenteral nutrition; parenteral nutrition solutions

Introduction

Phosphorus (P) and calcium (Ca) are essential components of nutrition support therapy. Regulation and homeostasis of P and Ca in the body are closely interrelated, and typically they have an inverse relationship with respect to serum concentrations. Nutrition support clinicians must understand P and Ca homeostasis to provide appropriate maintenance doses, to identify factors that may predispose patients to P and Ca disorders, to take measures to prevent disorders, and to promptly identify and correct disorders when they occur. This is particularly important in patients who are acutely ill or critically ill in the inpatient setting receiving parenteral nutrition (PN) and/or enteral nutrition (EN). This article will provide an overview of P and Ca for the nutrition support clinician, with some emphasis on the adult hospitalized inpatient.

P and Ca Homeostasis

Regulation of P and Ca is influenced primarily by serum P and ionized Ca concentrations ([P], [Ca]) and the actions of parathyroid hormone (PTH), vitamin D (1,25-dihydroxyvitamin D_3), and calcitonin in the bones, kidneys, and intestines (Figure 1).[1-3] Increases in serum [P] can lead to a decrease in serum ionized [Ca], and decreases in serum ionized [Ca] stimulate release of PTH. PTH increases P and Ca resorption/release from bone, increases Ca absorption and P excretion via the kidneys, stimulates activation of vitamin D (1,25-dihydroxyvitamin D_3, or calcitriol, the most active form) in the kidneys, and appears to increase absorption of P and Ca in the intestine.[1-3] Vitamin D stimulates absorption of P and Ca from the intestine, stimulates P and Ca resorption/release from bone, and increases renal Ca resorption and increases urinary P excretion. Increases in serum ionized [Ca] and vitamin D concentrations will also suppress/decrease PTH release, which will decrease activation of vitamin D. Increases in serum ionized [Ca] will stimulate release of calcitonin, which inhibits bone resorption and decreases serum ionized [Ca]. Magnesium may impair the synthesis and/or release of PTH, which can also affect Ca homeostasis.[4]

P and Ca Considerations for Patients Receiving Nutrition Support Therapy

Phosphorus

Phosphorus is an important intracellular anion, and phosphate (PO_4) is one of the key forms of P in the body as relates to nutrition support therapy. PO_4 is the primary form of P in the serum, and P ingestion in the diet and exogenous administration of P are also in the form of PO_4. P serves many essential functions, including bone and cell membrane composition (e.g., phospholipids) as well as numerous metabolic processes. Phosphorus is a key component of 2 important molecules in the human body: adenosine triphosphate (ATP) and 2,3-diphosphoglycerate (2,3-DPG). Phosphorus (as PO_4) provides

From the [1]Department of Clinical, Social and Administrative Sciences, University of Michigan College of Pharmacy, Ann Arbor, Michigan; and [2]Department of Pharmacy Services, University of Michigan Hospitals and Health Centers, Ann Arbor, Michigan.

Financial disclosure: None declared.

This article originally appeared online on December 30, 2014.

Corresponding Author:
Michael D. Kraft, PharmD, BCNSP, Department of Pharmacy Services, University of Michigan Health System, UH/B2 D314, SPC 5008, 1500 E. Medical Center Drive, Ann Arbor, MI 48109-5008, USA.
Email: mdkraft@med.umich.edu

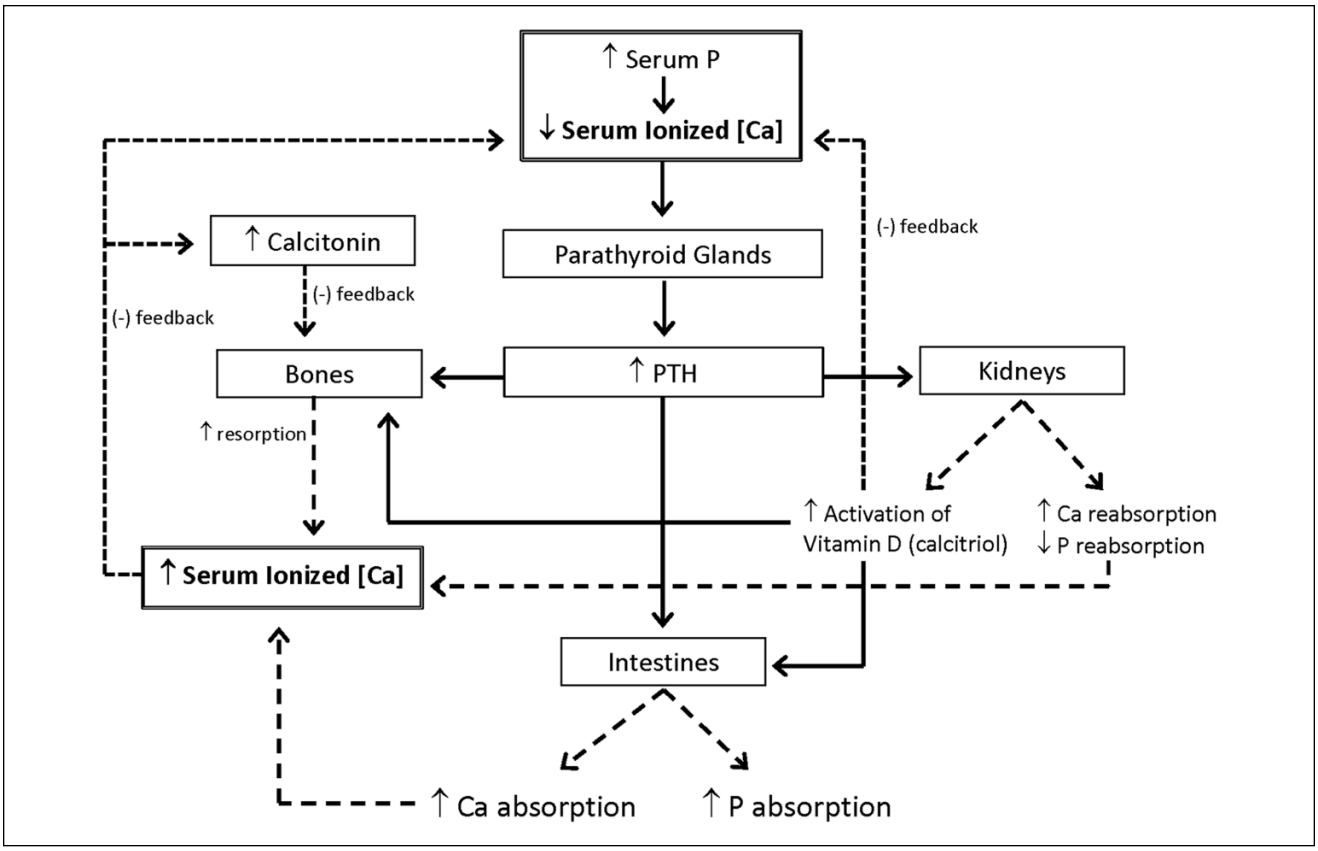

Figure 1. Calcium and phosphorus regulation in the human body.[1-3] Ca, calcium; P, phosphorus; PTH, parathyroid hormone.

energy-rich bonds in ATP, which is necessary for all physiologic and metabolic functions that require energy. 2,3-DPG is necessary for oxygen release from hemoglobin and delivery to tissues.[5-11] These functions are especially important in critically ill patients who may experience hypermetabolism and may have higher oxygen requirements. Adequate total body P is also necessary for glucose use and glycolysis, protein synthesis, neurological function, and muscle function (especially the myocardium and diaphragm).[5-11]

The normal serum P concentration ([P]) is about 2.7–4.5 mg/dL (~0.9–1.45 mmol/L); however, approximately 1% of total body P is in the extracellular fluid, with the majority of P found in the bones and soft tissues.[5-7] Therefore, serum [P] may not correlate with total body P. Although serum concentrations of electrolytes are the most readily available monitoring parameter, it is important to make a complete assessment of the patient and consider factors that may affect serum levels and total body homeostasis of P (eg, severe malnutrition leading to depletion of total body P, chronic kidney disease (CKD) leading to decreased elimination of P, medications that can affect serum [P] and P homeostasis).

Given the numerous functions of P, especially the key role in ATP and 2,3-DPG, it is clear that P is an important component of nutrition support therapy. The Recommended Dietary Allowance for healthy adults is approximately 700 mg (~23 mmol) per day.[12] Most standard EN formulations contain approximately 700–1,200 mg (22–39 mmol) of P per liter of formula. Most unstressed, well-nourished adult patients with normal renal function receiving PN require approximately 20–40 mmol/day,[13] or approximately 10–15 mmol of P per 1,000 kcal,[8] to maintain normal serum [P]. Increasing total caloric load has been correlated with decreasing serum [P] in patients receiving PN.[8] Severe hypophosphatemia and associated sequelae have been described in patients who did not receive appropriate phosphate supplementation with nutrition support.[8,9] Patients who received PN without P supplementation developed severe hypophosphatemia and decreased erythrocyte ATP and 2,3-DPG with an associated increase in hemoglobin affinity for oxygen (suggesting decrease in oxygen delivery). In addition, hypophosphatemia led to changes in intermediates of glycolysis, suggesting a reduction in erythrocyte glycolysis.[9] There was also a significant correlation between total calories administered and the decrease in [P], as well as the amount of P administered and increase in serum [P].[8]

Severely malnourished patients will likely have higher daily P requirements when initiating nutrition support and should be supplemented accordingly to prevent hypophosphatemia associated with refeeding syndrome.[14] Critically ill and trauma

patients with normal renal function may also require higher daily maintenance doses. Patients with thermal injury,[15,16] patients with traumatic brain injury,[17,18] and those who have undergone liver resection[19] also have increased P requirements. Patients with renal insufficiency will likely need P restriction, and serum [P] should be closely monitored as they are at risk for hyperphosphatemia.

Monitor serum [P] routinely (eg, daily) in well-nourished adult inpatients receiving nutrition support therapy. Monitor serum [P] more closely when initiating nutrition support in malnourished patients (eg, every 8–12 hours for the first several days) as they have a higher risk of developing hypophosphatemia, refeeding syndrome, and subsequent complications including seizures, coma, respiratory failure, and even death.[9,14,20-23]

Calcium

Calcium serves a key role in bone structure, blood coagulation, platelet adhesion, endocrine and exocrine secretory functions, neuromuscular activity, and electrophysiology of the heart and smooth muscles. The normal range for total serum [Ca] is approximately 8.6–10.2 mg/dL (~2.15–2.55 mmol/L). About 99% of total body Ca is found in the bones, and <1% is found in the serum.[2] Approximately 40%–50% of blood Ca is bound to plasma proteins, primarily albumin.[2,24] Unbound or ionized Ca is the biologically active form of Ca and accounts for the other approximately 50% of Ca in the blood under normal conditions.[2] Ionized serum [Ca] is closely regulated by the endocrine system as described above, and this is a better indicator of the functional status of Ca metabolism than is total [Ca]. If available, measure the ionized [Ca] when monitoring Ca status in patients receiving nutrition support. The normal range for ionized serum [Ca] is approximately 1.12–1.30 mmol/L.

There is a poor correlation between ionized [Ca] and total [Ca] in some patient populations, in particular patients with acid-base disorders, patients with hypoalbuminemia, and critically ill patients.[1,2,24-28] Metabolic acidosis decreases Ca binding to plasma proteins and will increase fraction of free or ionized serum Ca; conversely, metabolic alkalosis will increase Ca binding to plasma proteins and reduce the fraction of free/ionized serum Ca.[2,29,30]

Hypoalbuminemia can cause a decrease in measured total serum [Ca], but there may be less of an impact on the free or ionized [Ca]. Therefore, clinicians may calculate a "corrected" serum [Ca] in patients with hypoalbuminemia or other conditions that may affect total vs ionized [Ca]. The most common equation used in clinical practice to "correct" serum [Ca] due to hypoalbuminemia is the modified Orrell equation.[25,31]

$$\text{Corrected serum [Ca] (mg/dL)} = \text{measured serum [Ca] (mg/dL)} + [0.8 \times (4 - \text{measured albumin (g/dL)})]$$

However, there are numerous other equations that have been used to correct serum [Ca], and as stated above, the corrected [Ca] may not correlate with ionized [Ca], especially in critically ill patients. Therefore, direct measurement of ionized [Ca] is recommended, especially in critically ill patients.[25,26,32] When ionized [Ca] is not available, it may be reasonable to calculate a corrected [Ca] in non–critically ill patients (ie, "floor" patients) using the equation above, as this is the main population in which the equation was developed.[25,31] In critically ill patients, Dickerson et al[28] found that 85% of patients with a total serum [Ca] <7 mg/dL had hypocalcemia (serum ionized [Ca] <1.12 mmol/L). When ionized [Ca] is not available in critically ill patients with a total serum [Ca] <7 mg/dL, these authors suggest immediately measuring a serum ionized [Ca] or provide conservative empiric treatment with intravenous (IV) Ca and follow-up with a serum ionized [Ca] (refer to "Hypocalcemia" section below).[28,33,34]

The recommended adequate intake for Ca for healthy adults is approximately 1,000–1,200 mg (~50–60 mEq, or ~25–30 mmol) per day, depending on gender and age.[12] Most standard EN formulations contain approximately 700–1,200 mg (~17–30 mmol) of Ca per liter of formula. Most adult patients with normal renal function will require a maintenance dose of approximately 10–15 mEq (~5–7.5 mmol) Ca per day with PN admixtures.[13] There are no specific data or algorithms to guide adjustments in maintenance Ca doses for patients receiving PN or EN. When adjusting maintenance Ca doses, it is reasonable to adjust total daily doses by approximately 20%–50% depending on the daily dose, serum [Ca], responses to dose changes, and underlying clinical conditions.

Calcium absorption from the diet and oral supplements ranges from approximately 25%–35% depending on the source, salt form, and whether or not it is taken with food, and absorption is optimal from individual doses of ≤500 mg.[12,35,36] Calcium requires acid from the stomach to facilitate dissolution and absorption; therefore, patients receiving acid-suppression therapy or patients with achlorhydria may have reduced Ca absorption.[35,37] Absorption of Ca from Ca citrate appears to be better than that of Ca carbonate, and Ca citrate is the preferred oral Ca supplement in patients receiving acid-suppression therapy or patients with achlorhydria.[36,38,39]

P and Ca Considerations in Specific Conditions

Patients receiving nutrition support therapy may have underlying conditions that can affect P and Ca homeostasis through multiple mechanisms, and these patients will require special consideration. In all cases, treatment of the underlying condition(s) would be expected to reduce the impact on P and Ca. An in-depth discussion of all of these conditions is beyond the scope of this article, but they are mentioned briefly here, and the reader should refer to other excellent resources and reviews in the citations.

Patients with CKD may have multiple derangements in P and Ca homeostasis, including hyperphosphatemia, secondary

hyperparathyroidism, vitamin D deficiency, renal osteodystrophy, soft tissue calcification, and metabolic acidosis.[40,41] Patients with CKD will require monitoring of [Ca], [P], as well as PTH and vitamin D status. They may require P restriction and adjustments in Ca and vitamin D maintenance doses, as well as adjustment of chloride-acetate ratio to minimize risk of exacerbating metabolic acidosis and associated complications (if receiving PN).

Intestinal failure (IF) has a profound effect on patients and can result from several potential disease states. A proposed consensus definition describes IF as a result of "obstruction, dysmotility, surgical resection, congenital defect, or disease-associated loss of absorption and is characterized by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balance."[42] IF can include patients with a variety of conditions that could predispose them to abnormalities in P and Ca homeostasis via several potential mechanisms, including (but not limited to) malabsorption, inflammatory bowel disease, and short bowel syndrome (SBS).[42,43] These patients can have malabsorption of fat-soluble vitamins and can often develop vitamin D deficiency.[44,45] Chronic steroid therapy (eg, for inflammatory bowel disease or other conditions) can impair bone mineralization, decrease Ca absorption, and increase renal Ca excretion. Patients with IF or SBS may require supplemental Ca to prevent oxalate kidney stone formation. These patients, especially those with IF or SBS, can also have large gastrointestinal (GI) fluid losses that can result in dehydration; in severe cases, this could lead to impaired kidney function or acute kidney injury, potentially causing further acute P and Ca derangements. Large GI losses can also lead to magnesium deficiency, which can contribute to hypocalcemia. Patients with excessive GI losses of bicarbonate can also develop metabolic acidosis, which can affect vitamin D metabolism, bone buffering systems, and P and Ca homeostasis. Patients with these conditions will require monitoring for vitamin D deficiency and may require increased maintenance doses of vitamin D and/or Ca, as well as adjustment of chloride-acetate ratio if receiving PN therapy.

Long-term PN therapy is associated with significant complications, some of which can affect P and Ca homeostasis.[46,47] Patients with some of the diagnoses described above (eg, IF, SBS) can often require long-term PN therapy. Metabolic bone disease (MBD), including osteopenia, osteoporosis, and osteomalacia, is common in patients receiving long-term PN therapy, and P and Ca homeostasis is an important aspect of MBD.[47] This can be especially challenging because serum [P] and [Ca] can appear normal, so further patient evaluation is required (specifically related to P and Ca: serum intact PTH and 25-hydroxyvitamin D, 24-hour urine Ca and magnesium). Several factors can contribute to abnormalities in P and Ca homeostasis and MBD in patients receiving long-term PN, including malabsorption, increased renal Ca excretion, vitamin D deficiency, metabolic acidosis, aluminum accumulation/toxicity, decreased exposure to ultraviolet light (contributing to vitamin D deficiency), and lack of physical activity/weight-bearing exercise.[46,48] High protein doses can lead to calciuria that exceeds increases in glomerular filtration rate.[49] In addition, shorter durations of total daily Ca infusion may reduce retention of the dose. Several steps should be taken to prevent MBD in patients receiving long-term PN therapy.[46] Specifically with respect to P and Ca directly, this includes providing appropriate maintenance doses (initially 15 mEq/d of Ca and Ca:P ratio of approximately 1:2, both adjusted to serum concentrations), along with an appropriate maintenance dose of vitamin D with the parenteral multivitamin preparation; encouraging weight-bearing exercises and appropriate exposure to ultraviolet light/sunlight if safe and appropriate; and treating any contributing underlying conditions.[46,47]

P/PO_4 and Ca Compatibility in PN Admixtures

Calcium and PO_4 can combine to form dibasic calcium phosphate ($CaHPO_4$) and precipitate out of solution if concentrations exceed limits of compatibility.[13] The U.S. Food and Drug Administration (FDA) published a safety alert in response to 2 deaths associated with Ca-PO_4 precipitation in PN.[50] Autopsy reports revealed diffuse microvascular pulmonary emboli containing Ca-PO_4 precipitates. Despite this safety alert, other deaths have been reported due to pulmonary emboli from a precipitate containing Ca and PO_4.[51]

Several factors can affect Ca-PO_4 solubility in PN admixtures,[13,50] including:

- Final pH
- Final amino acid concentration (which can have a significant effect on final pH of the PN admixture, and PO_4 can bind with amino acids, reducing availability to bind with Ca)
- Calcium salt (Ca gluconate is the preferred Ca salt in PN because it has a low dissociation constant and less free Ca available to bind PO_4 in solution)
- Order of mixing (Ca and PO_4 salts should not be added simultaneously or consecutively when compounding PN admixtures)
- Temperature (as temperature increases, more Ca and PO_4 dissociate and increase the risk of Ca-PO_4 precipitation)
- Time (the longer Ca and PO_4 are in solution, the higher the risk Ca-PO_4 precipitation will occur)

Pharmacists must follow safe PN practices and verify Ca-PO_4 compatibility when compounding all PN admixtures. When prescribing, compounding, and administering PN admixtures, clinicians should follow these guidelines[13,50]:

- Verify compatibility of the prescribed amounts of Ca-PO_4 in the PN prescription using established Ca-PO_4

Table 1. Potential Causes of Hypophosphatemia in Adult Patients.[5-7,52,53,60]

Decreased Intake/Absorption	Altered Distribution	Increased Renal Excretion
Malnutrition	Administration of carbohydrate loads, refeeding syndrome	Vitamin D deficiency
Vomiting/diarrhea/gastrointestinal losses	Respiratory alkalosis	Hyperparathyroidism
Malabsorption	Recovery from diabetic ketoacidosis	Continuous renal replacement therapy
Iatrogenic (inadequate phosphorus maintenance/supplementation)	Rapid cell proliferation	Volume expansion
Alcohol/alcoholism	Hungry bone syndrome	Metabolic acidosis
	Alcohol/alcoholism	Alcohol/alcoholism
	Medications	
Antacids (eg, calcium-, magnesium- and aluminum-containing antacids)	Insulin	Diuretics (eg, loop diuretics, thiazide diuretics, osmotic diuretics)
Phosphate binders (eg, calcium acetate, sevelamer, lanthanum)	Catecholamines (eg, epinephrine, norepinephrine)	Carbonic anhydrase inhibitors (eg, acetazolamide)
Sucralfate	Beta-2-agonists	Calcitonin
	Theophylline	Corticosteroids, estrogens
	Erythropoietins	Theophylline
	Colony stimulating factors	

solubility curves; in addition to the above factors, Ca-PO_4 solubility curves and compatibility are also affected by the specific amino acid formulation, the concentration of other PN components, and the use of cysteine.

- Consider the amount of PO_4 from all sources (including amino acid solutions) when determining the PO_4 concentration and Ca-PO_4 compatibility.
- Use Ca gluconate as the preferred Ca salt; avoid using Ca chloride.
- Add PO_4 salts early in the compounding sequence, and then add Ca toward the end of the compounding sequence.
- Consider the volume of the admixture at the time Ca is added when assessing Ca-PO_4 compatibility (not necessarily the final/total volume).[50]
- Periodically agitate the PN admixture, and check for precipitation during compounding.
- Use an appropriate filter when infusing the PN admixture (1.2-µm filter for a total nutrient admixture, 0.22-µm filter for a 2-in-1 PN admixture).
- Monitor the patient for any evidence of adverse effects related to embolization of a precipitate.
- Store PN admixtures at the appropriate temperature depending on the time between compounding and administering to the patient.

Treatment of P and Ca Abnormalities

Hypophosphatemia

Hypophosphatemia (serum [P] <2.7 mg/dL [~<0.9 mmol/L]) has been reported to occur in approximately 2%–3% of hospitalized patients but in as high as 28%–80% of critically ill patients (eg, trauma, sepsis, intensive care unit [ICU]), and it has been associated with severe adverse events.[52,53] Several reports describe hypophosphatemia associated with the initiation of nutrition support, including oral nutrition, EN, and PN.[8,9,20-23,54-57] Severe hypophosphatemia (eg, serum P concentration <1 mg/dL [~<0.3 mmol/L]) has been associated with impaired diaphragmatic contractility and acute respiratory failure, tissue hypoxia, decreased myocardial contractility, paresthesias, weakness, confusion, disorientation, encephalopathy, areflexic paralysis, seizures, coma, and even death.[5-11,20-23,54,55,57-59] Hypophosphatemia has also been associated with higher mortality, longer duration of hospitalization, longer duration of mechanical ventilation, and other consequences in some studies of various hospitalized adult patient populations.[53] Acutely ill and critically ill adult patients often have underlying conditions that predispose them to developing hypophosphatemia and/or receive medications that can cause hypophosphatemia. Table 1 lists some potential causes of hypophosphatemia in adult patients.[5-7,52,53,60] When administering carbohydrate loads (eg, with EN or PN), provide an adequate maintenance dose of phosphate as described above to decrease the risk of hypophosphatemia, especially in malnourished patients who are at risk for developing severe hypophosphatemia and refeeding syndrome.[8,9,14,20-23] Severely malnourished patients (with normal renal function) at risk for refeeding syndrome may initially require 25%–50% higher doses of P to prevent hypophosphatemia when initiating nutrition support.

Treatment of hypophosphatemia depends on the magnitude and whether the patient is symptomatic. In addition, understanding the underlying cause(s) of low serum [P] is important to guide treatment (eg, Is the low serum [P] due to inadequate maintenance doses, inadequate absorption, intracellular shifts, increased elimination, or a combination of these factors? Is this a true P deficiency?). Correct/remove the underlying cause

Table 2. Suggested Intravenous Treatment of Hypophosphatemia.[a,14,61-70]

Degree of Hypophosphatemia	Intravenous Phosphate Dose[a,b]
2.3–2.7 mg/dL (~0.75–0.9 mmol/L) (mild hypophosphatemia, asymptomatic)	0.08–0.16 mmol/kg
1.5–2.2 mg/dL (~0.5–0.75 mmol/L) (moderate hypophosphatemia, asymptomatic)	0.16–0.32 mmol/kg
<1.5 mg/dL (~<0.5 mmol/L) (severe symptomatic hypophosphatemia)	0.32–0.64 mmol/kg[c]

[a]Normal renal function; for patients with decreased creatinine clearance (eg, <50 mL/min), consider giving ≤50% of the initial empiric dose. Maximum recommended infusion rate = 7–7.5 mmol phosphate/h.
[b]Consider using adjusted body weight (AdjBW) in patients who are significantly obese (weight >130% of ideal body weight (IBW) or body mass index ≥30 kg/m^2): AdjBW (males) = ([wt (kg) – IBW (kg)] × 0.3) + IBW; AdjBW (females) = ([wt (kg) – IBW (kg)] × 0.25) + IBW.
[c]Doses up to 1 mmol/kg have been reported in critically ill adult trauma patients.

when feasible (eg, medication-induced hypophosphatemia). Asymptomatic mild hypophosphatemia may be treated with oral P supplementation if the GI tract is functional; however, oral P supplements can cause diarrhea, and oral absorption may be variable. Patients with symptomatic, moderate-severe hypophosphatemia and patients who cannot tolerate oral supplements should receive IV P supplementation to correct serum [P]. Estimating the appropriate dose of P is largely empiric because serum concentrations may not correlate with total body stores. A few different regimens based on patient weight and serum [P] have now been published, but these have been primarily in critically ill trauma patients and surgical ICU patients with normal renal function.[61-63] There are several other published reports of fixed-dose phosphate supplementation in patients with normal renal function.[64-70] Based on these published reports, Table 2 provides one approach to IV P dosing for treating hypophosphatemia in patients with normal renal function.[14,61-70] Although there are no specific data or algorithms to guide P repletion in patients with impaired renal function receiving nutrition support who are not being treated with continuous renal replacement therapy (CRRT), consider administering ≤ 50% of the initial empiric P dose initially. Patients being treated with CRRT may require higher initial doses (ie, closer to empiric doses used for patients with normal renal function), depending on the severity of hypophosphatemia, the amount of P being removed with CRRT, and whether P is used in the dialysate/replacement fluid.

Oral P supplementation may be considered in patients with mild, asymptomatic hypophosphatemia receiving oral nutrition or EN (Table 3). A liquid form of oral P would be preferred in patients receiving EN (eg, powder for reconstitution, crushing oral tablets and dissolving in purified water). If liquid supplements are administered via an enteral tube, EN should be held before and after administration, the powder for reconstitution would be preferred over crushing oral tablets and dissolving in water, the medication should be diluted prior to administration (purified water or saline) and should not be coadministered with any other medications or products, and the tube should be flushed with at least 15 mL of purified/sterile water before and after administration.[71] Although institutions may include an option for enteral P supplementation as part of an electrolyte correction protocol or guideline, there are limited published data describing the efficacy of this approach, especially in critically ill patients. Oral P supplementation may be limited by the volume required for dilution, diarrhea (especially with higher doses), and multiple interruptions of EN. In addition, oral P absorption may be decreased in patients with vitamin D deficiency.[5,72] Some have added P supplements directly to EN formulas (either oral or IV dosage formulations),[56,62] and this approach may be efficacious when treating asymptomatic hypophosphatemia,[56] although recent guidelines do not recommend this practice.[71] One report of 2 malnourished patients demonstrated enteral P contained in EN formulations was not adequate to prevent hypophosphatemia and ultimately required IV supplementation to correct serum [P], although there may have also been other contributing factors in these cases.[72]

Patients with persistent hypophosphatemia may require a daily P supplement. Patients who cannot receive oral supplements, critically ill patients, and/or those with moderate-severe hypophosphatemia may require IV supplementation and/or increased maintenance P doses in PN admixtures. There are no specific data to guide adjustments of P maintenance dosing in PN prescriptions, but a reasonable approach is to adjust maintenance doses of P by approximately 10%–25% as needed to avoid or reverse P deficits and to monitor serum [P] for response. Further adjustments to P maintenance dosing, P supplementation, and correction of hypophosphatemia should be guided by clinical response to doses and changes in serum [P] and clinical condition in all patients.

The IV P preparations used are available as the potassium (K) or sodium (Na) salts. Potassium phosphate (KPhos) can be used in patients with simultaneous hypokalemia; otherwise, sodium phosphate (NaPhos) is recommended. Clinicians must also take into consideration the K and Na content of all P preparations (IV and oral); 1 mmol of IV KPhos contains approximately 1.47 mEq of K, and 1 mmol of IV NaPhos contains approximately 1.33 mEq of Na.

IV P doses are typically infused over 4–6 hours (depending on the dose) to reduce the risk of Ca-PO_4 precipitation and minimize infusion-related adverse effects (eg, thrombophlebitis from KPhos). Doses can be infused up to a rate of approximately 7–7.5 mmol P per hour.[61,62,69] A few reports have demonstrated safe administration of P doses up to 15 mmol/h.[70,73] However, one study failed to demonstrate a difference in serum [P] between the slower (7.5 mmol/h) and faster (15 mmol/h)

Table 3. Select Oral Sodium/Potassium Phosphate Dosage Forms.[a]

Product	Dosage Form (Dose)	Phosphate Content	Sodium Content	Potassium Content
Phos-NaK	Powder for solution (1 packet)	250 mg (8 mmol)	160 mg (6.9 mmol)	280 mg (7.1 mmol)
K-Phos Neutral or Phospha 250 Neutral	Tablet (250 mg)	250 mg (8 mmol)	298 mg (13 mmol)	45 mg (1.1 mmol)
K-Phos No.2	Tablet (250 mg)	250 mg (8 mmol)	134 mg (5.8 mmol)	88 mg (2.3 mmol)

[a]Phosphorus 31 mg = 1 mmol; sodium 23 mg = 1 mmol (1 mEq); potassium 39 mg = 1 mmol (1 mEq).

groups at the end of infusion or 24 hours after infusion, more patients in the faster infusion groups developed hyperkalemia, and there was a trend toward increased fractional excretion of PO_4 in the faster infusion groups (suggesting the faster infusion rate may exceed the renal threshold for reabsorption).[70] Carefully evaluate risk/benefit when considering increased infusion rates of IV P (eg, severity of hypophosphatemia and symptoms, risk of hypocalcemia and Ca-PO_4 precipitation, rate of K infusion [if using KPhos], risk of hyperkalemia, and potential adverse effects). KPhos may require administration via a central vein due to irritation or phlebitis with peripheral IV administration (depending on the total dose, final K concentration, and the rate of K infusion); one study infused doses of ≥30 mmol of KPhos in 250 mL of 5% dextrose via a central venous catheter.[63] Use caution when treating hypophosphatemia with IV P in patients with elevated serum total Ca/ionized Ca levels to avoid Ca-PO_4 precipitation and hypocalcemia.

Phosphorus can shift quickly between body compartments, and serum concentrations can fluctuate.[7,64] Some publications, guidelines, and protocols describe assessing a serum [P] at the end of supplementation or within 2–6 hours after completing a dose[69,70,73]; however, data are lacking on the optimal time to recheck serum [P] after supplementation. Several published studies on the treatment of hypophosphatemia describe monitoring serum [P] within approximately 12–24 hours after supplementation or on a daily basis.[61-63,65,69] Despite this, it may be prudent to monitor serum [P] more frequently in some patients with severe hypophosphatemia until serum concentrations normalize. Administer additional P supplements until the patient is asymptomatic and the serum [P] is at least >2.0 mg/dL; the goal is to return the serum [P] to the normal range (ie, 2.7–4.5 mg/dL) and avoid symptoms. Some patients will require multiple doses over several days to completely correct hypophosphatemia, especially those with severe malnutrition/refeeding syndrome, those with P depletion, and critically ill patients.[57,61,62,65,70,74]

Finally, when using weight-based dosing, there are no definitive data or recommendations for "adjusting" weight in obese patients or what threshold should be used to adjust weight (eg, using a percentage above ideal body weight [IBW] or based on body mass index). Total body water is slightly higher in males than in females, and adipose tissue is composed of approximately 10%–30% water.[75-79] Often in practice, an adjustment of 25%–40% of the IBW is added to the IBW to determine the adjusted body weight (AdjBW) or dosing weight, and this depends on whether the adjustment is related to dosing nutrition, electrolytes, or medications (as well as the properties of the medication). To minimize the risk of overdosing, consider using an AdjBW in obese patents (weight >130% of IBW or body mass index ≥30 kg/m^2) when using weight-based dosing of electrolytes:

$$\mathbf{AdjBW\,(males) = \left(\left[wt\,(kg) - IBW\,(kg)\right] x\ 0.3\right) + IBW}$$

$$\mathbf{AdjBW\,(females) = \left(\left[wt\,(kg) - IBW\,(kg)\right] x\ 0.25\right) + IBW}$$

Hyperphosphatemia

Hyperphosphatemia is defined as a serum [P] >4.5 mg/dL (~>1.45 mmol/L). The most common cause of hyperphosphatemia, especially in hospitalized and critically ill patients, is impaired renal function.[4,5] Excessive IV and/or oral administration of P can also cause hyperphosphatemia and would be more likely in patients with renal insufficiency.[4,5,80-82] Other causes of hyperphosphatemia can include immobility, hemolysis, rhabdomyolysis, and tumor lysis.[4] Severe hyperphosphatemia, acute kidney injury, and dehydration have been reported following oral and rectal administration of P-containing laxatives (for treatment of constipation or as a bowel preparation), particularly in patients with compromised renal function.[80-84] Several over-the-counter products were voluntarily discontinued in 2008,[83] although an oral solution and an enema are again available (over-the-counter products). A prescription product is also available but carries a boxed warning and a Risk Evaluation and Mitigation Strategy as required by the U.S. FDA.[83] Other potential causes of hyperphosphatemia include hypoparathyroidism, vitamin D intoxication, bisphosphonates, acidosis (metabolic, respiratory), hemolysis, rhabdomyolysis, and tumor lysis syndrome.[4,5]

Hyperphosphatemia can lead to hypocalcemia due to Ca-PO_4 precipitation, which can further lead to clinical manifestations of hypocalcemia such as tetany.[4,5] Furthermore, Ca-PO_4 crystals can also deposit into soft tissues and cause further organ damage, especially in the lungs, myocardium, and blood vessels.[4,5,40,85,86] The risk of Ca-PO_4 precipitation appears to increase when the serum Ca × P is >55–60 mg^2/dL^2, and this product should be maintained <55 mg^2/dL^2.[40,85,87] However, more recent guidelines suggest the Ca × P product

Table 4. Pharmacologic Treatment of Hyperphosphatemia.[40,41,88,89]

Medication	Dosage Forms	Initial Recommended Dose[a]	Maximum Recommended Dose[a]
Calcium acetate	Tablet: 667 mg Gelcap: 667 mg	1,334 mg 3 times daily with meals	4 tablets with meals; avoid hypercalcemia
Calcium carbonate	Tablet, capsule, liquid, and powder; various strengths	1–2 g 3 times daily with meals	7 g/d; avoid hypercalcemia
Magnesium hydroxide	Tablet: 300 mg, 600 mg Liquid: 400 mg/5 mL, 800 mg/5 mL	1–2 tablets 3 times daily with meals or 5–15 mL 3 times daily with meals	2–4 tablets 4 times daily with meals or 15 mL 4 times daily with meals and at bedtime
Aluminum hydroxide	Tablet: 300 mg, 600 mg Suspension: 320 mg/5 mL	1–2 tablets, or 15–30 mL or 3–4 times daily, with meals and at bedtime	1,800 mg (3–6 tablets) every 4 hours or 30 mL every 4 hours
Sevelamer hydrochloride Sevelamer carbonate	Tablet: 400 mg, 800 mg Packet (powder for oral suspension): 0.8 g, 2.4 g	800–1,600 mg 3 times daily with meals	4,000 mg 3 times daily with meals
Lanthanum carbonate	Chewable tablet: 500 mg, 750 mg, 1000 mg	500 mg 3 times daily with meals	4,500 mg daily in divided doses

[a]May require higher doses in rare situations or in some patients with chronic renal insufficiency and severe hyperphosphatemia; the dose should be titrated to achieve the goal serum phosphorus (P) level in these situations. Calcium 40 mg = 1 mmol (2 mEq).

may have limited utility in clinical practice, and individual serum levels should be evaluated to guide a treatment plan.[40]

Treatment of hyperphosphatemia requires a complete assessment of the patient, including laboratory values, signs/symptoms, and clinical condition. Although serum [P] may not indicate total body P, this is the most readily available monitoring parameter. Identify and correct the underlying cause when possible. Adjust/restrict the daily P intake (eg, reduce daily doses in the PN prescription; consider using a renal EN formula) in patients with impaired renal function and hyperphosphatemia. Patients receiving various forms of renal replacement therapy, including CRRT, peritoneal dialysis, or intermittent hemodialysis, will have differing requirements because of the variation in P removal with each of these therapies. Oral P binders, available as Ca, aluminum, and magnesium salts, as the non-ionic P binder sevelamer, and the newer ionic agent lanthanum carbonate that was recently approved by the U.S. FDA, are effective in lowering serum [P], but most data are in patients with CKD.[88,89] Table 4 lists potential pharmacologic treatments of hyperphosphatemia.[40,41,88,89]

Use ion-containing P binders cautiously, especially those containing magnesium and aluminum. Aluminum can cause constipation, magnesium can cause diarrhea, and both can accumulate in patients with impaired renal function and lead to toxicity. Lanthanum carbonate has been associated with nausea, vomiting, abdominal pain, diarrhea, and constipation.[89] Calcium salts and non-ionic P binders are preferred in patients with CKD or when long-term therapy is required; lanthanum carbonate was recently approved by the U.S. FDA and may also be an option.[40,41,88,89] Calcium-containing P binders should be avoided in patients with hypercalcemia or evidence of calcification. Continued use of P binders may paradoxically result in hypophosphatemia.

Because of the delayed onset of therapies for hyperphosphatemia, frequent monitoring of serum [P] is likely not needed in most patients. Routine monitoring of serum [P] (eg, every 24–48 hours) is probably appropriate for most adult hospitalized patients; patients who are critically ill, patients with severe symptoms, and/or those receiving CRRT may require more frequent monitoring. The goals of therapy should include returning the serum [P] to normal (eg, 2.7–4.5 mg/dL [~0.9–1.45 mmol/L]), avoiding or resolving symptoms of hyperphosphatemia, and possibly maintaining the serum Ca-P product <55 mg^2/dL^2.[40,85,86]

Hypocalcemia

Hypocalcemia (total serum [Ca] <8.6 mg/dL [~2.15 mmol/L], ionized [Ca] <1.1 mmol/L) has been reported in approximately 15%–88% of hospitalized adult patients,[90] and one study observed hypocalcemia in approximately 21% of critically ill trauma patients.[25] Hypocalcemia is often associated with hypoalbuminemia in hospitalized patients, but other causes can include sepsis, pancreatitis, renal insufficiency, hypoparathyroidism, administration of blood preserved with citrate, hypomagnesaemia, and hyperphosphatemia.[2,24] Magnesium deficiency may impair PTH release and/or activity and contribute to hypocalcemia.[4,90-92]

The hallmark sign of severe acute hypocalcemia is tetany, but other neuromuscular, cardiovascular, and central nervous

Table 5. Suggested Empiric Dosing of Intravenous Ca.[1,2,28,32-34,90,103]

Degree of Hypocalcemia	Preferred Ca Salt[a]	Suggested IV Dose[b]
Mild-moderate, asymptomatic Serum ionized [Ca] ~1–1.12 mmol/L	Gluconate	1–2 g Ca gluconate, infused over 1–2 h (1 g Ca gluconate/h)
Severe Serum ionized [Ca] <1 mmol/L	Gluconate	3–4 g Ca gluconate, infused over 3–4 h (1 g Ca gluconate/h)
Severe, symptomatic hypocalcemia (with serum ionized [Ca] <1 mmol/L)	Gluconate or chloride	1–3 g Ca gluconate, or 500–1,000 mg Ca chloride, infused over 10 min, may repeat ~ every 60 min as needed until stabilized, then supplement as suggested above based on serum ionized [Ca] and patient symptoms/ clinical status

Ca, calcium.
[a]Calcium chloride should be administered via a central venous catheter to avoid extravasation and tissue necrosis; 1,000 mg Ca chloride = 13.6 mEq Ca; 1 g Ca gluconate = 4.56 mEq Ca.
[b]Typically, a Ca gluconate dose of 1–2 g (4.56–9.12 mEq Ca) is mixed in 100 mL of D5W or NS and infused at a maximum rate of 1 g/h for routine supplementation (nonemergent situations).

system symptoms can be present with mild-moderate hypocalcemia. Symptoms can include muscle cramps, paresthesias, seizures, prolonged QT interval, heart block, and ventricular fibrillation.[1,2] Chronic hypocalcemia can lead to dermatologic manifestations including dermatitis, eczema, brittle grooved nails, and hair loss.[1]

Treatment of hypocalcemia should include treating or removing the underlying cause when feasible. IV Ca gluconate and Ca chloride are used to treat patients with severe hypocalcemia, patients with severe symptoms due to hypocalcemia, or when rapid correction of serum [Ca] is required. Calcium chloride provides 3 times more elemental Ca than does an equivalent amount of Ca gluconate, and there have been dosing errors reported due to confusion about the Ca salt, Ca dose, and the way Ca was ordered.[93-96] It would be prudent to establish a standardized method for ordering Ca supplementation to minimize the risk of errors.[97-99] This approach should include using Ca gluconate as the preferred salt for routine Ca maintenance dosing and supplementation and restricting Ca chloride for use in urgent and emergent situations. Calcium gluconate is the preferred salt for peripheral venous administration as Ca chloride can cause tissue necrosis if it extravasates into surrounding tissues.[100,101]

When prescribing Ca maintenance doses or supplemental doses, the order should contain the dose of Ca, the Ca salt, and the dose either in grams, milligrams, or milliequivalents; avoid dosing using the terms *amp, ampoule*, and *milliliter*.[97] Calcium should not be infused in the same IV line as solutions containing P due to risk of Ca-PO_4 precipitation.

Treatment of asymptomatic hypocalcemia due to hypoalbuminemia is not indicated. Given the discussion regarding "correcting" serum [Ca] in patients with hypoalbuminemia, it is preferred to monitor ionized [Ca], especially in critically ill patients.[25,26,28] There is also debate over the benefit or need to correct asymptomatic hypocalcemia; however, given the essential physiologic functions of Ca and the potentially detrimental effects of severe hypocalcemia, many clinicians decide to treat hypocalcemia to avoid severe hypocalcemia and potentially negative consequences, especially in critically ill patients.[34,102] Table 5 describes suggested empiric intermittent IV Ca replacement doses based on the severity of hypocalcemia in adult patients.[1,2,28,32-34,90,103] Fixed doses, rather than weight-based doses, are recommended for empiric therapy based on recent data in critically ill patients that did not demonstrate a significant correlation between Ca dose normalized for weight and serum ionized [Ca] response.[33,34] As discussed above, when ionized [Ca] is not available in critically ill patients with a total serum [Ca] <7 mg/dL and without symptoms of hypocalcemia, consider immediately measuring a serum ionized [Ca] or provide conservative empiric treatment with IV Ca (eg, 1–2 g Ca gluconate, see Table 5) and follow up with a serum ionized [Ca].[28,33,34]

Infuse intermittent doses at a maximum rate of 1 g Ca gluconate/h (~4.56 mEq elemental Ca/h), as this may improve Ca retention and may be a safer approach.[32-34] Subsequent doses should be based on the patient's response to therapy and clinical condition. In critically ill patients, it may take approximately 10 hours for serum [Ca] to stabilize after a dose (eg, 4 g Ca gluconate infused over 4 hours), possibly sooner for lower doses,[32] so it is reasonable to recheck serum/ionized [Ca] approximately 10–12 hours after a supplement (if the patient is not symptomatic due to hypocalcemia). IV Ca doses can be repeated as needed until serum/ionized [Ca] is normalized, and it may take several doses to completely correct [Ca] in some patients.[32-34]

Severe, symptomatic hypocalcemia must be corrected promptly with IV Ca^{++} administration (Table 5).[1,2,28,32-34,90,103] To control severe symptoms (eg, tetany, seizures, cardiac manifestations), treat with an initial dose of Ca chloride 500–1,000 mg (6.8–13.6 mEq Ca, if the patient has central IV access) or Ca gluconate 1–3 g (4.56–13.7 mEq Ca) over 10 minutes.[2,90,103] In some cases, doses may need to be repeated as often as approximately every 60 minutes, and in rare cases, more aggressive dosing has been suggested (eg, beta-blocker overdose, cardiac arrest).[2,90,103] However, discussion of emergency

Table 6. Properties of Various Common Calcium Supplements.

Calcium Salt	Dosage Form(s)/Route(s) of Administration	Strength/ Concentration	Elemental Calcium	Elemental Calcium (mEq/g)
Calcium chloride	IV	10%	27%	13.6
Calcium gluconate	Oral tablet IV	Oral: 500 mg IV: 10%	9%	4.56
Calcium acetate	Oral tablet Oral solution	667 mg, 667 mg/5mL	25%	12.7
Calcium carbonate	Oral tablet Oral suspension	500 mg, 600 mg, 750 mg, 1,000 mg, 1,250 mg	40%	20
Calcium citrate	Oral tablet Oral capsule	150 mg, 250 mg, 950 mg, 1,040 mg	21%	10.5

IV, intravenous.

situations is beyond the scope of this article. Calcium chloride should always be infused via a central vein to avoid extravasation and tissue necrosis.[100,101]

Oral Ca supplements may be considered in patients with mild-moderate hypocalcemia who are receiving EN or can tolerate oral medications, but this approach may not be feasible or adequate in critically ill patients. Table 6 describes the available Ca supplements, their elemental Ca content, and the available forms for specific administration routes. Some patients may require evaluation of PTH and vitamin D status (eg, patients with CKD or chronic hypocalcemia).

Patients may require adjustment of daily Ca maintenance doses in PN formulations or daily supplemental doses of oral Ca if receiving EN, depending on the patient's clinical condition and the underlying cause of hypocalcemia. If present, correct concomitant hypomagnesaemia using magnesium supplements. When not actively treating severe hypocalcemia, monitor serum/ionized [Ca] every 24–48 hours initially in adult inpatients receiving nutrition support therapy.

Hypercalcemia

Hypercalcemia (total serum [Ca] >10.2 mg/dL [~2.55 mmol/L], ionized [Ca] >1.3 mmol/L) can be characterized as mild-moderate hypercalcemia (total serum [Ca] = 10.3–12.9 mg/dL [~2.6–3.2 mmol/L], ionized [Ca] ~1.3–1.6 mmol/L) or severe hypercalcemia (total serum [Ca^{++}] ≥13 mg/dL [~≥3.25 mmol/L], ionized [Ca] ≥1.6 mmol/L). The most common causes of hypercalcemia include malignancy and primary hyperparathyroidism.[2,90,104] Other causes include vitamin A toxicity, vitamin D toxicity, milk-alkali syndrome, adrenal insufficiency, immobilization, Paget's disease, rhabdomyolysis, and medications (eg, thiazide diuretics, lithium).[2,90,104,105] Chronic hypercalcemia may cause Ca-PO_4 precipitation, metastatic calcification, and renal failure.[105] Patients with severe hypercalcemia can present with anorexia, fatigue, confusion, or cardiac manifestations including bradycardia or arrhythmias with electrocardiograph changes.[90,106,107] Severe hypercalcemia/hypercalcemic crisis requires immediate treatment because it can lead to acute kidney injury, ventricular arrhythmias, obtundation, coma, and death.[2,90,104]

Treatment of hypercalcemia should include treating/removing the underlying cause when possible. Patients receiving PN may require temporary reduction or removal of Ca from their PN prescription, depending on the underlying cause and severity of hypercalcemia. Mild hypercalcemia does not require immediate treatment and typically responds to hydration and ambulation. Treatment of severe hypercalcemia/hypercalcemic crisis should begin immediately with IV hydration ± calcitonin and possibly addition of an IV loop diuretic (eg, furosemide) after the patient has received adequate fluid resuscitation.[104,105,107,108] Hemodialysis with low-Ca or Ca-free dialysate may be necessary in life-threatening hypercalcemia, in patients with impaired renal function, and in patients with heart failure and/or volume overload.[2,90,107,108]

Administer hydration with isotonic IV fluid (initially more aggressive, eg, IV normal saline at a rate of ~200–300 mL/h) to reverse the volume contraction caused by hypercalcemia and facilitate Ca elimination.[2,90,107] After adequately rehydrating the patient, IV loop diuretics may be considered to enhance renal Ca elimination and avoid fluid overload from saline hydration; however, rigorous data evaluating the efficacy of loop diuretics in this setting are lacking, and some do not recommend this therapy.[90,107] If loop diuretics are used, ensure the patient has first received adequate fluid resuscitation, and monitor closely to avoid further volume depletion.[107]

Calcitonin inhibits bone resorption and increases renal Ca elimination, and it can be used in addition to IV hydration for treatment of acute hypercalcemia/hypercalcemic crisis. An initial dose of 4 units/kg given via the subcutaneous or intramuscular route every 12 hours will begin to reduce serum [Ca] within a few hours.[107,109] The dose can be increased up to 6–8 units/kg every 6 hours if the response is not adequate, but efficacy of calcitonin appears to be limited to a few days due to the development of tolerance.[107,109]

Bisphosphonates (eg, pamidronate, zoledronic acid, etidronate) are potent inhibitors of bone resorption, are often used in the treatment of hypercalcemia of malignancy,[107] and have

been used in patients with chronic critical illness who have accelerated bone breakdown and associated MBD.[110] Pamidronate is given as a single IV dose of 60–90 mg infused over 2–24 hours. In patients with chronic critical illness who have accelerated bone breakdown, they may receive pamidronate 30 mg IV daily × 3 days (along with calcitriol).[110] Zoledronic acid is given as a single IV dose of 4–8 mg infused over 15 minutes. Etidronate may be effective when given at a dose of 7.5 mg/kg/d IV over 2 hours for 3–7 days. Bisphosphonates may be given at the initiation of treatment, but they have a prolonged time to onset and longer duration of action. Serum [Ca] typically starts to decline within 1–2 days of the first dose, and the effect may persist for several weeks.[107]

Bisphosphonates are commonly used for the treatment of hypercalcemia of malignancy outside of the acute setting. Other medications including glucocorticoids, calcitonin, mithramycin, and gallium nitrate have also been used.[2,104,107,108]

Monitor serum/ionized [Ca] more frequently during active treatment of severe hypercalcemia (eg, every 4–8 hours) and every 24–48 hours once hypocalcemia has been corrected.

Summary

Phosphorus and Ca are vital components of nutrition support therapy. There are many important physiologic, pharmaceutical, and clinical factors that can affect P and Ca homeostasis. In addition, there are important safety considerations for P and Ca, both when prescribing and compounding nutrition support therapy admixtures and when treating P and Ca abnormalities in patients. Clinicians must understand these factors to optimize nutrition support therapy and avoid or minimize P and Ca derangements.

References

1. Olinger ML. Disorders of calcium and magnesium metabolism. *Emerg Med Clin North Am*. 1989;7:795-822.
2. Bushinsky DA, Monk RD. Calcium. *Lancet*. 1998;352(9124):306-311.
3. Khanal RC, Nemere I. Regulation of intestinal calcium transport. *Ann Rev Nutr*. 2008;28:179-96.
4. Weisinger JR, Bellorin-Font E. Magnesium and phosphorous. *Lancet*. 1998;352(9125):391-396.
5. Peppers MP, Geheb M, Desai T. Hypophosphatemia and hyperphosphatemia. *Crit Care Clin*. 1991;7:201-214.
6. Knochel JP. The pathophysiology and clinical characteristics of severe hypophosphatemia. *Arch Intern Med*. 1977; 37:203-220.
7. Stoff JS. Phosphate homeostasis and hypophosphatemia. *Am J Med*. 1982;72:489-495.
8. Sheldon GF, Grzyb S. Phosphate depletion and repletion: relation to parenteral nutrition and oxygen transport. *Ann Surg*. 1975;182:683-689.
9. Travis SF, Sugerman HJ, Ruberg RL, et al. Alterations of red-cell glycolytic intermediates and oxygen transport as a consequence of hypophosphatemia in patients receiving intravenous hyperalimentation. *N Engl J Med*. 1971;283:763-768.
10. Newman JH, Neff TA, Ziporin P. Acute respiratory failure associated with hypophosphatemia. *N Engl J Med*. 1977;296:1101-1103.
11. Aubier M, Murciano D, Lecocguic Y, et al. Effect of hypophosphatemia on diaphragmatic contractility in patients with acute respiratory failure. *N Engl J Med*. 1985;313:420-424.
12. National Academy of Sciences, Institute of Medicine. Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. Available from: http://www.iom.edu/reports/1997/dietary-reference-intakes-for-calcium-phosphorus-magnesium-vitamin-d-and-fluoride.aspx. Published August 13, 1997. Accessed September 7, 2014.
13. Mirtallo J, Canada T, Johnson D, et al. Safe practices for parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 2004;28(suppl):S39-S70.
14. Kraft MD, Btaiche IF, Sacks GS. Review of the refeeding syndrome. *Nutr Clin Pract*. 2005;20:625-633.
15. Loven L, Larsson L, Nordstrom H, Lennquist S. Serum phosphate and 2,3-diphosphoglycerate in severely burned patients after phosphate supplementation. *J Trauma*. 1986;26:348-352.
16. Yang HT, Yim H, Cho YS, et al. Change of serum phosphate level and clinical outcome of hypophosphatemia in massive burn patient. *J Trauma Acute Care Surg*. 2012;73:1298-1302.
17. Gadisseux P, Sica DA, Ward JD, Becker DP. Severe hypophosphatemia after head injury. *Neurosurgery*. 1985;17:35-40.
18. Polderman KH, Bloemers FW, Peerdeman SM, Girbes ARJ. Hypomagnesemia and hypophosphatemia at admission in patients with severe head injury. *Crit Care Med*. 2000;28:2022-2025.
19. Buell JF, Berger AC, Plotkin JS, Kuo PC, Johnson LB. The clinical implications of hypophosphatemia following major hepatic resection or cryosurgery. *Arch Surg*. 1998;133:757-761.
20. Silvis SE, Paragas PD. Paresthesias, weakness, seizures, and hypophosphatemia in patients receiving hyperalimentation. *Gastroenterology*. 1972;62:513-520.
21. Sand DW, Pastore RA. Paresthesias and hypophosphatemia occurring with parenteral alimentation. *Digest Dis*. 1973;18:709-713.
22. Weinsier RL, Krumdieck CL. Death resulting from overzealous total parenteral nutrition: the refeeding syndrome revisited. *Am J Clin Nutr*. 1981;34:393-399.
23. Youssef HAE. Hypophosphatemic respiratory failure complicating total parenteral nutrition—an iatrogenic potentially lethal hazard. *Anesthesiology*. 1982;57:246.
24. Zaloga GP. Hypocalcemic crisis. *Crit Care Clin*. 1991;7:191-200.
25. Dickerson RN, Alexander KH, Minard G, Croce MA, Brown RO. Accuracy of methods to estimate ionized and "corrected" serum calcium concentrations in critically ill multiple trauma patients receiving specialized nutrition support. *JPEN J Parenter Enteral Nutr*. 2004;28:133-141.
26. Byrnes MC, Huynh K, Helmer SD, Stevens C, Dort JM, Smith RS. A comparison of corrected serum calcium levels to ionized calcium levels among critically ill surgical patients. *Am J Surg*. 2005;189:310-314.
27. Vincent JL, Bredas P, Jankowski S, et al. Correction of hypocalcaemia in the critically ill: what is the haemodynamic benefit? *Intensive Care Med*. 1995;21:838-841.
28. Dickerson RN, Henry NY, Miller PL, Minard G, Brown RO. Low serum total calcium concentration as a marker of low serum ionized calcium concentration in critically ill patients receiving specialized nutrition support. *Nutr Clin Pract*. 2007;22:323-328.
29. Moore EW. Ionized calcium in normal serum, ultrafiltrates, and whole blood determined by ion-exchange electrodes. *J Clin Invest*. 1970;49:318-334.
30. Wang S, McDonnell EH, Sedor FA, Toffaletti JG. pH effects on measurements of ionized calcium and ionized magnesium in blood. *Arch Pathol Lab Med*. 2002;126:947-950.
31. Orrell DH. Albumin as an aid to the interpretation of serum calcium. *Clin Chimica Acta*. 1971;35:483-489.
32. Dickerson RN, Morgan LM, Croce MA, Minard G, Brown RO. Dose-dependent characteristics of intravenous calcium therapy for hypocalcemic critically ill patients receiving specialized nutritional support. *Nutrition*. 2007;23:9-15.
33. Dickerson RN, Morgan LG, Cauthen AD, et al. Treatment of acute hypocalcemia in critically ill multiple-trauma patients. *JPEN J Parenter Enteral Nutr*. 2005;29:436-441.

34. Dickerson RN, Morgan LM, Croce MA, Minard G, Brown RO. Treatment of moderate to severe acute hypocalcemia in critically ill trauma patients. *JPEN J Parenter Enteral Nutr*. 2007;31:228-233.
35. Guéguen L, Pointillart A. The bioavailability of dietary calcium. *J Am Coll Nutr*. 2000;19:119S-136S.
36. Harvey JA, Zobitz MM, Pak CYC. Dose dependency of calcium absorption: a comparison of calcium carbonate and calcium citrate. *J Bone Miner Res*. 1988;3:253-258.
37. Ito T, Jensen RT. Association of long-term proton pump inhibitor therapy with bone fractures and effects on absorption of calcium, vitamin B_{12}, iron, and magnesium. *Curr Gastroenterol Rep*. 2010;12:448-457.
38. Heller HJ, Greer LG, Haynes SD, Poindexter JR, Pak CYC. Pharmacokinetic and pharmacodynamics comparison of two calcium supplements in postmenopausal women. *J Clin Pharmacol*. 2000;40: 1237-1244.
39. Recker RR. Calcium absorption and achlorhydria. *N Engl J Med*. 1985;313:70-73.
40. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis*. 2003;42(suppl 3):S1-S202.
41. Moe SM, Drüeke TB, Block GA, et al. KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int*. 2009;76(suppl 113):S1-S130.
42. O'Keefe SJD, Buchman AL, Fishbein TM, Jeejeebhoy KN, Jeppesen PB, Shaffer J. Short bowel syndrome and intestinal failure: consensus definitions and overview. *Clin Gastroenterol Hepatol*. 2006;4:6-10.
43. Matarese LE. Nutrition and fluid optimization for patients with short bowel syndrome. *JPEN J Parenter Enteral Nutr*. 2013;37:161-170.
44. Braga CBM, Vannucchi H, Freire CMM, et al. Serum vitamins in adult patients with short bowel syndrome receiving intermittent parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 2011;35:493-498.
45. DeLuca HF. Vitamin D and the parenteral nutrition patient. *Gastroenterology*. 2009;137:S79-S91.
46. Seidner DL. Parenteral nutrition-associated metabolic bone disease. *JPEN J Parenter Enteral Nutr*. 2002;26:S37-S42.
47. Kirby DF, Corrigan ML, Speerhas RA, Emery DM. Home parenteral nutrition tutorial. *JPEN J Parenter Enteral Nutr*. 2012;36:632-644.
48. Kruger PC, Parsons PJ, Galusha AL, Morrissette M, Recker RR, Howard LJ. Excessive aluminum accumulation in the bones of patients on long-term parenteral nutrition: postmortem analysis by electrothermal atomic absorption spectrometry. *JPEN J Parenter Enteral Nutr*. 2014;38: 728-735.
49. Bengoa JM, Sitrin MD, Wood RJ, Rosenberg IH. Amino acid-induced hypercalciuria in patients on total parenteral nutrition. *Am J Clin Nutr*. 1983;38:264-269.
50. Lumpkin MM. Safety alert: hazards of precipitation associated with parenteral nutrition. *Am J Hosp Pharm*. 1994;51:1427-1428.
51. Hill SE, Heldman LS, Goo EDH, Whippo PE, Perkinson JC. Fatal microvascular pulmonary emboli from precipitation of a total nutrient admixture solution. *JPEN J Parenter Enteral Nutr*. 1996;20:81-87.
52. Gaasbeek A, Meinders AE. Hypophosphatemia: an update on its etiology and treatment. *Am J Med*. 2005;118:1094-1101.
53. Brunelli SM, Goldfarb S. Hypophosphatemia: clinical consequences and management. *J Am Soc Nephrol*. 2007;18:1999-2003.
54. Furlan AJ, Hanson M, Cooperman A, Farmer RG. Acute areflexic paralysis: association with hyperalimentation and hypophosphatemia. *Arch Neurol*. 1975;32:706-707.
55. Baughman FA Jr, Papp JP. Wernicke's encephalopathy with intravenous hyperalimentation: remarks on similarities between Wernicke's encephalopathy and the phosphate depletion syndrome. *Mt Sinai J Med*. 1976;43:48-52.
56. Hayek ME, Eisenberg PG. Severe hypophosphatemia following the institution of enteral feedings. *Arch Surg*. 1989;124:1325-1328.
57. Patel U, Sriram K. Acute respiratory failure due to refeeding syndrome and hypophosphatemia induced by hypocaloric enteral nutrition. *Nutrition*. 2009;25:364-367.
58. Vanneste J, Hage J. Acute severe hypophosphatemia mimicking Wernicke's encephalopathy. *Lancet*. 1986;1(8471):44.
59. Mattioli S, Miglioli M, Montagna P, Lerro MF, Pilotti V, Gozzetti G. Wernicke's encephalopathy during total parenteral nutrition: observation in one case. *JPEN J Parenter Enteral Nutr*. 1988;12:626-627.
60. Liamis G, Milionis HJ, Elisaf M. Medication induced hypophosphatemia: a review. *Q J Med*. 2010;103:449-459.
61. Clark CL, Sacks GS, Dickerson RN, et al. Treatment of hypophosphatemia in patients receiving specialized nutrition support using a graduated dosing scheme: results from a prospective clinical trial. *Crit Care Med*. 1995;23:1504-1510.
62. Brown KA, Dickerson RN, Morgan LM, et al. A new graduated dosing regimen for phosphorus replacement in patients receiving nutrition support. *JPEN J Parenter Enteral Nutr*. 2006;30:209-214.
63. Taylor BE, Huey WY, Buchman TG, Boyle WA, Coopersmith CM. Treatment of hypophosphatemia using a protocol based on patient weight and serum phosphorus level in a surgical intensive care unit. *J Am Coll Surg*. 2004;198:198-204.
64. Lentz RD, Brown DM, Kjellstrand CM. Treatment of severe hypophosphatemia. *Ann Intern Med*. 1978;89:941-944.
65. Vannatta JB, Whang R, Papper S. Efficacy of intravenous phosphorous therapy in the severely hypophosphatemic patient. *Arch Intern Med*. 1981;141:885-887.
66. Andress DL, Vannatta JB, Whang R. Treatment of refractory hypophosphatemia. *South Med J*. 1982;75:766-767.
67. Vannatta JB, Andress DL, Whang R, et al. High-dose intravenous phosphorus therapy for severe complicated hypophosphatemia. *South Med J*. 1983;76:1424-1426.
68. Kingston M, Al-Siba'i MB. Treatment of severe hypophosphatemia. *Crit Care Med*. 1985;13:16-18.
69. Rosen GH, Boullata JI, O'Rangers EA, et al. Intravenous phosphate repletion regimen for critically ill patients with moderate hypophosphatemia. *Crit Care Med*. 1995;23:1204-1210.
70. Charron T, Bernard F, Skrobik Y, et al. Intravenous phosphate in the intensive care unit: more aggressive repletion regimens for moderate and severe hypophosphatemia. *Intensive Care Med*. 2003;29:1273-1278.
71. Bankhead R, Boullata J, Brantley S, et al. A.S.P.E.N. enteral nutrition practice recommendations. *JPEN J Parenter Enteral Nutr*. 2009;33: 122-167.
72. Maier-Dobersberger T, Lochs H. Enteral supplementation of phosphate does not prevent hypophosphatemia during refeeding of cachectic patients. *JPEN J Parenter Enteral Nutr*. 1994;18:182-184.
73. French C, Bellomo R. A rapid intravenous phosphate replacement protocol for critically ill patients. *Crit Care Resusc*. 2004;6:175-179.
74. Terlevich A, Hearing SD, Woltersdorf WW, et al. Refeeding syndrome: effective and safe treatment with phosphates polyfusor. *Aliment Pharmacol Ther*. 2003;17:1325-1329.
75. Hankin ME, Munz K, Steinbeck AW. Total body water content in normal and grossly obese women. *Med J Aust*. 1976;2:533-537.
76. Watson PE, Watson ID, Batt RD. Total body water volumes for adult males and females estimated from simple anthropometric measurements. *Am J Clin Nutr*. 1980;33:27-39.
77. Schoeller DA, van Santen E, Peterson DW, et al. Total body water measurement in humans with ^{18}O and ^{2}H labeled water. *Am J Clin Nutr*. 1980;33:2686-2693.
78. Webster JD, Hesp R, Garrow JS. The composition of excess weight in obese women estimated by body density, total body water and total body potassium. *Hum Nutr Clin Nutr*. 1984;38C:299-306.
79. Foster GD, Wadden TA, Mullen JL, et al. Resting energy expenditure, body composition, and excess weight in the obese. *Metabolism*. 1988;37:467-472.

80. Escalante CP, Weiser MA, Finkel K. Hyperphosphatemia associated with phosphorus-containing laxatives in a patient with chronic renal insufficiency. *South Med J*. 1997;90:240-242.
81. Ehrenpreis ED, Wieland JM, Cabral J, et al. Symptomatic hypocalcemia, hypomagnesemia, and hyperphosphatemia secondary to Fleet's Phospho-Soda colonoscopy preparation in a patient with a jejunoileal bypass. *Dig Dis Sci*. 1997;42:858-860.
82. Ullah N, Yeh R, Ehrinpreis M. Fatal hyperphosphatemia from a phosphosoda bowel preparation. *J Clin Gastroenterol*. 2002;34:457-458.
83. American Society of Health-System Pharmacists. Drug shortages: oral sodium phosphate (over-the-counter) solution: http://www.ashp.org/menu/DrugShortages/DrugsNoLongerAvailable/Bulletin.aspx?id=549. Published June 12, 2013. Accessed September 7, 2014.
84. U.S. Food and Drug Administration. Oral sodium phosphate (OSP) products for bowel cleansing (marketed as Visicol and OsmoPrep, and oral sodium phosphate products available without a prescription). http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103354.htm. Updated January 7, 2014. Accessed September 7, 2014.
85. Block GA, Port FK. Re-evaluation of risks associated with hyperphosphatemia and hyperparathyroidism in dialysis patients: recommendations for a change in management. *Am J Kidney Dis*. 2000;35:1226-1237.
86. Goodman WG, Goldin J, Kuizon BD, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med*. 2000;342:1478-1483.
87. Velentzas C, Meindok H, Oreopoulos DG, et al. Visceral calcification and the Ca X P product. *Adv Exper Med Biol*. 1978;103:195-201.
88. Navaneethan SD, Palmer SC, Craig JC, Elder GJ, Strippoli GFM. Benefits and harms of phosphate binders in CKD: a systematic review of randomized controlled trials. *Am J Kidney Dis*. 2009;54:619-637.
89. Curran MP, Robinson DM. Lanthanum carbonate: a review of its use in lowering serum phosphate in patients with end-stage renal disease. *Drugs*. 2009;69:2329-2349.
90. French S, Subauste J, Geraci S. Calcium abnormalities in hospitalized patients. *South Med J*. 2012;105:231-237.
91. Anast CS, Winnacker JL, Forte LR, et al. Impaired release of parathyroid hormone in magnesium deficiency. *J Clin Endocrinol Metab*. 1976;42:707-717.
92. Fatemi G, Ryzen E, Flores J, et al. Effect of experimental human magnesium depletion on parathyroid hormone secretion and 1,25-dihydroxyvitamin D metabolism. *J Clin Endocrinol Metab*. 1991;73:1067-1072.
93. Smetzer J, Cohen MR, eds. *ISMP medication safety alert!* [newsletter]. Vol. 2. Huntingdon Valley, PA: ISMP; October 22, 1997.
94. Smetzer J, Cohen MR, eds. *ISMP medication safety alert!* [newsletter]. Vol. 3. Huntingdon Valley, PA: ISMP; December 2, 1998.
95. Smetzer J, Cohen MR, eds. *ISMP medication safety alert!* [newsletter]. Vol. 5. Huntingdon Valley, PA: ISMP; December 13, 2000.
96. Smetzer J, Cohen MR, eds. *ISMP medication safety alert!* [newsletter]. Vol. 7. Huntingdon Valley, PA: ISMP; April 17, 2002.
97. Smetzer J, Cohen MR, eds. *ISMP medication safety alert!* [newsletter]. Vol. 2. Huntingdon Valley, PA: ISMP; May 7, 1997.
98. Smetzer J, Cohen MR, eds. *ISMP medication safety alert!* [newsletter]. Vol. 6. Huntingdon Valley, PA: ISMP; January 10, 2001.
99. Smetzer J, Cohen MR, eds. *ISMP medication safety alert!* [newsletter]. Vol. 6. Huntingdon Valley, PA: ISMP; January 24, 2001.
100. Jucgla A, Sais G, Curco N, et al. Calcinosis cutis following liver transplantation: a complication of intravenous calcium administration. *Br J Dermatol*. 1995;132:275-278.
101. Semple P, Booth C. Calcium chloride; a reminder. *Anaesthesia*. 1996;51:93.
102. Forsythe RM, Wessel CB, Billiar TR, Angus DC, Rosengart MR. Parenteral calcium for intensive care unit patients. *Cochrane Database Syst Rev* 2008;4:CD006163.
103. Vanden Hoek TL, Morrison LJ, Shuster M, et al. Part 12: cardiac arrest in special situations: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2010;122:S829-S861.
104. Davis KD, Attie MF. Management of severe hypercalcemia. *Crit Care Clin*. 1991;7:175-190.
105. Mundy GR, Guise TA. Hypercalcemia of malignancy. *Am J Med*. 1997;103:134-145.
106. Agus ZS, Wasserstein A, Goldfarb S. Disorders of calcium and magnesium homeostasis. *Am J Med*. 1982;72:473-488.
107. Davidson TG. Conventional treatment of hypercalcemia of malignancy. *Am J Health-Syst Pharm*. 2001;58(suppl 3):S8-S15.
108. Deftos LJ. Hypercalcemia: mechanisms, differential diagnosis, and remedies. *Postgrad Med*. 1996;100:119-126.
109. Deftos LJ, First BP. Calcitonin as a drug. *Ann Intern Med*. 1989;95: 192-197.
110. Nierman DM, Mechanick JI. Biochemical response to treatment of bone hyperresorption in chronically critically ill patients. *Chest*. 2000;118: 761-766.