Invited Review

Review of the Refeeding Syndrome

Michael D. Kraft, PharmD*†; Imad F. Btaiche, PharmD, BCNSP*†; and Gordon S. Sacks, PharmD, BCNSP‡

*Department of Clinical Sciences, College of Pharmacy, University of Michigan, Ann Arbor, Michigan; †Department of Pharmacy Services, University of Michigan Health System, Ann Arbor, Michigan; and the ‡Pharmacy Practice Division, School of Pharmacy, University of Wisconsin–Madison, Madison, Wisconsin

ABSTRACT: Refeeding syndrome describes a constellation of metabolic disturbances that occur as a result of reinstitution of nutrition to patients who are starved or severely malnourished. Patients can develop fluid and electrolyte disorders, especially hypophosphatemia, along with neurologic, pulmonary, cardiac, neuromuscular, and hematologic complications. We reviewed literature on refeeding syndrome and the associated electrolyte abnormalities, fluid disturbances, and associated complications. In addition to assessing scientific literature, we also considered clinical experience and judgment in developing recommendations for prevention and treatment of refeeding syndrome. The most important steps are to identify patients at risk for developing refeeding syndrome, institute nutrition support cautiously, and correct and supplement electrolyte and vitamin deficiencies to avoid refeeding syndrome. We provide suggestions for the prevention of refeeding syndrome and suggestions for treatment of electrolyte disturbances and complications in patients who develop refeeding syndrome, according to evidence in the literature, the pathophysiology of refeeding syndrome, and clinical experience and judgment.

The term refeeding syndrome (RS) is generally reserved to describe the metabolic alterations that occur during nutrition repletion of underweight, severely malnourished, or starved individuals. The hallmark sign of RS is severe hypophosphatemia and its associated complications. However, RS actually encompasses a constellation of fluid and electrolyte abnormalities affecting multiple organ systems, including neurologic, cardiac, hematologic, neuromuscular, and pulmonary function. This article will review the pathophysiology of RS, its physiologic complications, the treatment of associated metabolic disturbances, and provide guidelines for its recognition and prevention.

The classic study describing RS was conducted by Keys and colleagues1 in 1944 on male conscientious objectors of World War II. The participants had undergone semistarvation for 6 months and upon nutrition replenishment, some subjects developed cardiac failure. With the advent of modern-day parenteral nutrition (PN) and enteral nutrition (EN), reports of similar complications were noted in severely undernourished patients who received aggressive nutrition supplementation. Weinsier and Krumdieck2 reported cardiopulmonary failure resulting in death of 2 chronically undernourished women who received aggressive PN. Both patients were well below ideal body weight (IBW; 40% and 70%, respectively) and exhibited low serum concentrations of potassium and phosphorus before PN initiation. Large amounts of carbohydrate and protein were delivered (approximately 75 kcal/kg from dextrose and 3.5 g/kg of protein) at PN initiation, rather than gradually increasing PN calories to goal over the following days. Within 48 hours, both patients experienced cardiac abnormalities and pulmonary failure requiring mechanical ventilation. Severe hypophosphatemia, hypokalemia, and hypomagnesemia occurred despite the presence of supplemental electrolytes in the PN formulations. One patient died on hospital day 6 and the other died during the third week of hospitalization. These outcomes represent the most severe responses to refeeding but underscore the importance of understanding this syndrome, recognizing patients at risk, and providing appropriate treatment in the event of its occurrence.

Overview of Refeeding Syndrome

Starvation

Understanding the physiology of starvation provides insight into the morbid sequelae associated with refeeding a severely undernourished individ-
ual. During the initial period of starvation (24–72 hours), the liver uses glycogen stores for energy and skeletal muscle to provide amino acids as a source for new glucose production (ie, gluconeogenesis) for glucose-dependent tissues, such as the brain, renal medulla, and red blood cells. After 72 hours of starvation, metabolic pathways shift to derive energy from ketone production as a result of free fatty acid oxidation while sparing protein mobilization from skeletal muscle. Other adaptive mechanisms include an overall decrease in liver gluconeogenesis, a decline in basal metabolic rate, reduction in the secretion of insulin, and an increased use of free fatty acids by the brain as the primary energy source in place of glucose.

Refeeding

With the reintroduction of carbohydrate via oral feeding, EN, or PN, there is a sudden shift back to glucose as the predominant fuel source, creating a high demand for the production of phosphorylated intermediates of glycolysis (ie, red blood cell adenosine triphosphate [ATP] and 2,3-diphosphoglycerate [DPG]) with inhibition of fat metabolism. This results in hypophosphatemia, the hallmark sign of RS. Additional mechanisms identified as contributing to low serum phosphorus concentrations include preexisting low total body stores of phosphorus during starvation and enhanced cellular uptake of phosphorus during anabolic refeeding. Phosphate is necessary for accrual of lean tissue mass and is a vital component of metabolic pathways involving the production of ATP and 2,3-DPG. Potassium and magnesium also shift intracellularly in response to anabolism and increased insulin release. Magnesium is a cofactor for the Na-K ATPase pump, so uncorrected hypomagnesemia can complicate potassium repletion. Other metabolic alterations that may occur include fluid imbalance and vitamin deficiencies. An expansion of the extracellular water compartment occurs during refeeding of the malnourished individual. Although the exact mechanism of fluid imbalance in RS is unknown, sodium and water retention may be due to an antinatriuretic effect from hyperinsulinemia or a possible interaction between the water, sodium, and carbohydrate homeostasis. Although it is difficult to determine whether thiamine deficiency is a result of RS or is a preexisting deficiency due to starvation, it is reasonable to presume that an undernourished individual is at risk for thiamine deficiency. Thiamine is an essential cofactor involved in the metabolism of carbohydrates. The phosphorylated form of glucose is converted to pyruvate, which undergoes decarboxylation in the presence of pyruvate dehydrogenase and thiamine. Acetyl coenzyme A is produced for entrance into the Krebs cycle and generation of ATP as an energy source for all living cells. High doses of carbohydrate can increase the demand for thiamine use in undernourished subjects with decreased baseline thiamine stores, thus precipitating thiamine deficiency and its associated complications. As a result, thiamine administration prior to and during carbohydrate intake is recommended in patients at risk for RS.

Clinical Manifestations

Clinical manifestations of RS are related to the electrolyte and vitamin deficiencies that are present and the subsequent abnormalities that develop with the initiation of nutrition support. Clinical manifestations of RS are summarized in Table 1.

Hypophosphatemia

Phosphorus is the major intracellular anion, and it is important for many metabolic processes involving ATP and 2,3-DPG as described previously. Severe hypophosphatemia (eg, serum phosphorus concentration <1–1.5 mg/dL) can lead to severe neurologic, cardiac, respiratory, and hematologic abnormalities and possibly death. Several reports describe hypophosphatemia associated with the initiation of nutrition support (oral, enteral, and parenteral). Severe hypophosphatemia in these patients has also led to neurologic symptoms, including paresthesias, weakness, confusion, disorientation, encephalopathy, areflexic paralysis, seizures, coma, and death. Silvas and Paragas described RS in 3 patients with severe malnutrition who received aggressive PN for repletion. All 3 adult patients were significantly underweight (~50%–60% of usual body weight, or reported weight loss of approximately 22–30 kg [50–65 pounds]); PN was initiated at a high rate (~37–40 kcal/kg/day on day 1), and advanced rapidly over the course of 2–5 days (up to ~65–100 kcal/kg/day). Patients developed paresthesias, weakness, somnolence, lethargy, restlessness, and muscle aches around day 5 of PN. Two patients became unresponsive, developed seizures (on days 8 and 16 of PN) and coma; 1 patient expired 5 days after the initial seizure (4 days after PN was discontinued). Serum phosphorus concentrations decreased over the first 5–8 days and reached a nadir of 0.1–0.5 mg/dL. Of note, 2 of the patients gained approximately 1.8 kg (4 pounds) relatively quickly after initiation of PN, likely reflecting fluid retention.

Severe hypophosphatemia has also been shown to impair cardiac function and respiratory function. O’Connor et al described diminished cardiac function in patients with serum phosphorus concentrations of 0.7–1.4 mg/dL. Stroke volume (SV), mean arterial pressure (MAP), and left ventricular stroke work (LVSW) were all decreased and pulmonary artery wedge pressure (PAWP) was increased. SV, MAP, and LVSW increased significantly, with a significant decrease in PAWP, after phosphate repletion over 8 hours (serum levels =
hypophosphatemia also led to reductions in erythrocyte ATP and 2,3-DPG, with an associated increase of hemoglobin affinity for oxygen (P50 = 19.5 mm Hg, normal ~27 ± 1.1 mm Hg). Furthermore, hypophosphatemia led to significant decreases in erythrocyte glucose-6-phosphate and fructose-6-phosphate, and a significant increase in total triose phosphates (eg, glyceraldehyde-3-phosphate, dihydroxyacetone phosphate), suggesting a decrease in erythrocyte glycolysis. These decreases in oxygenation and glucose metabolism may also lead to central nervous system and respiratory symptoms, as discussed.

**Hypokalemia**

Potassium is the major intracellular cation, with approximately 98% of total body potassium residing in the intracellular space but also in bone and cartilage. Potassium has many important physiologic functions, including regulation of electrical cellular membrane potential, cellular metabolism, glycogen synthesis, and protein synthesis. Hypokalemia alters the electrical action potential across cell membranes and leads to membrane hyperpolarization and impaired muscular contraction.

Mild to moderate hypokalemia (eg, serum potassium concentration = 2.5–3.5 mEq/L) can cause nausea, vomiting, constipation, and weakness. If left untreated, severe hypokalemia (eg, serum potassium concentration <2.5 mEq/L) can lead to paralysis, respiratory compromise, rhabdomyolysis, muscle necrosis, and changes in myocardial contraction and signal conduction.

**Table 1**

<table>
<thead>
<tr>
<th>Clinical manifestations of refeeding syndrome</th>
<th>Hypophosphatemia</th>
<th>Hypokalemia</th>
<th>Hypomagnesemia</th>
<th>Vitamin/Thiamine Deficiency</th>
<th>Sodium Retention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired oxygen transport and delivery, hypoxia</td>
<td>Nausea</td>
<td>Vomiting</td>
<td>Weakness</td>
<td>Weakness</td>
<td>Encephalopathy (eg, Wernicke-Korsakoff encephalopathy)</td>
</tr>
<tr>
<td>Impaired cardiac function</td>
<td>Vomiting</td>
<td>Constipation</td>
<td>Paralysis</td>
<td>Muscle twitching</td>
<td>Lactic acidosis</td>
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<tr>
<td>Impaired diaphragm contractility</td>
<td>Weakness</td>
<td>Respiratory compromise</td>
<td>Rhabdomyolysis</td>
<td>Tremor</td>
<td>Death</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>Muscle necrosis</td>
<td>Muscle</td>
<td>Nausea</td>
<td>Altered mental status</td>
<td></td>
</tr>
<tr>
<td>Paresthesias</td>
<td>Alternations in myocardial contraction</td>
<td>Vomiting</td>
<td>Diarrhea</td>
<td></td>
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<tr>
<td>Weakness</td>
<td>Electrocardiograph changes</td>
<td>Refractory hypophosphatemia and hypocalcemia</td>
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<tr>
<td>Lethargy</td>
<td>ST-segment depression</td>
<td>Electrocardiograph changes</td>
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<tr>
<td>Somnolence</td>
<td>T-wave flattening</td>
<td>Prolonged PR</td>
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<tr>
<td>Confusion</td>
<td>T-wave inversion</td>
<td>Widened QRS</td>
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<tr>
<td>Disorientation</td>
<td>Presence of U-waves</td>
<td>Prolonged QT</td>
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<tr>
<td>Restlessness</td>
<td>Cardiac arrhythmias</td>
<td>ST depression</td>
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<tr>
<td>Encephalopathy</td>
<td>Atrial tachycardia</td>
<td>Peaked T-wave</td>
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<tr>
<td>Areflexic paralysis</td>
<td>Bradycardia</td>
<td>T-wave flattening</td>
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<tr>
<td>Seizures</td>
<td>Atrioventricular block</td>
<td>Cardiac arrhythmias</td>
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<tr>
<td>Coma</td>
<td>Premature ventricular contractions</td>
<td>Atrial fibrillation</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Death</td>
<td>Ventricular tachycardia</td>
<td>Torsade de pointes</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Death</td>
<td>Ventricular fibrillation</td>
<td>Ventricular arrhythmias</td>
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<tr>
<td></td>
<td>Sudden death</td>
<td>Ventricular tachycardia</td>
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</table>

1.6–4.7 mg/dL). Severe hypophosphatemia has also been shown to impair diaphragmatic contractility and lead to acute respiratory failure requiring intubation and mechanical ventilation. Youssef described a case of a woman with multiple intestinal fistulae who underwent a laparotomy and then required intubation and mechanical ventilation. Sheldon and Grzyb described a case of a woman with multiple intestinal fistulae who underwent a laparotomy and then required intubation and mechanical ventilation. Patients who developed hypophosphatemia also had decreased levels of ATP and 2,3-DPG. The authors further found a significant correlation between total calories administered and the fall in serum phosphorus concentration, and a significant correlation between the amount of phosphate administered and the increase in serum phosphorus concentration. Travis et al found that within 5–7 days of PN initiation (3–4 L/day) that did not contain phosphate, 5 of 8 patients developed severe hypophosphatemia (serum phosphorus concentration <1 mg/dL, mean = 0.5 mg/dL).
with severe hypokalemia may develop electrocardiographic changes such as ST-segment depression, T-wave flattening, T-wave inversion, or the presence of U-waves.26,27,29 Patients may also develop cardiac arrhythmias, including atrial tachycardia, bradyarrhythmias, atrioventricular block, premature ventricular contractions, ventricular tachycardia, ventricular fibrillation, and possibly sudden death.25–28

**Hypomagnesemia**

Magnesium is the second most abundant intracellular cation, with most of the total body magnesium found in bone, muscle, and soft tissue.30–32 Approximately 1% of the total body magnesium resides in the extracellular fluid.30–32 Magnesium is an important cofactor for many enzymes and in many biochemical reactions, including reactions during oxidative phosphorylation and those involving ATP.30,32,33

Hypomagnesemia (serum magnesium concentration <1.5 mg/dL) is frequently observed in critically ill patients34–36 and has been associated with increased morbidity and mortality.35,36,38,39 Signs and symptoms of hypomagnesemia can resemble those of hypokalemia or hypophosphatemia. Patients with mild to moderate hypomagnesemia can experience weakness, muscle twitching, tremor, altered mental status, anorexia, nausea, vomiting, and diarrhea.30–32,35,40,41 Moderate to severe hypomagnesemia (eg, serum magnesium concentration <1.0 mg/dL) can manifest such signs and symptoms as electrocardiographic changes (eg, prolonged PR, widened QRS, prolonged QT, ST depression, peaked T-wave, or T-wave flattening),30–32,42 cardiac arrhythmias (eg, atrial fibrillation, torsade de pointes, ventricular arrhythmias, ventricular tachycardia),32,35,39 tetany, convulsions, seizures, coma, and even death.30–32,35,41 Hypomagnesemia, if left untreated, can also complicate the treatment of coexisting hypokalemia and hypocalcemia. Hypomagnesemia-induced hypokalemia is likely due to impaired Na+/K+-ATPase activity.42 Hypomagnesemia-induced hypocalcemia is likely a result of impaired parathyroid hormone release and/or activity.44–46

**Vitamin/Thiamine Deficiency**

Thiamine is an important cofactor in carbohydrate metabolism.6 Thiamine is a water-soluble vitamin, and total body stores can quickly become depleted with weight loss and malnutrition. With carbohydrate intake, there is an increased demand for thiamine, a cofactor in glycolysis. Thiamine deficiency in malnourished patients has led to Wernicke’s encephalopathy in patients who were given PN with high carbohydrate loads.12,17,47 With thiamine deficiency, pyruvate is then converted to lactate.48 Excessive lactate formation leading to lactic acidosis and death was reported in patients who received PN without thiamine supplementation.49–52

The role of other vitamin deficiencies (especially water-soluble vitamins) in RS is less clear.

**Sodium Retention/Fluid Overload**

Sodium retention and expansion of extracellular water that may occur in the early phases of RS can lead to fluid overload, pulmonary edema, and cardiac decompensation.53,54 This may be especially devastating to patients at risk for RS (eg, patients with severe malnutrition) because they may have reduced cardiac mass and function.53,55 Fluid and sodium restriction are indicated when initiating nutrition support in patients at risk for RS. Patients should be monitored closely for signs of fluid accumulation and overload.

**Prevention**

Clearly, preventing RS is the primary goal when initiating nutrition support in severely malnourished and cachectic patients. There are several key steps that clinicians should take to avoid RS and the morbidity and mortality associated with RS. It is essential to first identify patients who are at risk for RS before initiating nutrition support (Table 2). Regardless of the method used to estimate caloric goals (eg, Harris-Benedict equation, kcal/kg, etc), it is essential to avoid overfeeding. The minimum glucose requirement for a 70-kg adult to suppress gluconeogenesis, spare proteins, and supply fuel to the central nervous system is approximately 100–150 g/day.3 A reasonable goal for protein intake in adults is approximately 1.5 g/kg/day, although some patients may have increased (eg, severe trauma, severe burns, continuous renal replacement therapy, hepatic dysfunction or cirrhosis with encephalopathy [CRRT]) or decreased requirements (eg, renal failure with uremia).

When initiating nutrition support in patients at risk for RS, the rule of thumb is to “start low and go slow.” Nutrition support should be initiated cautiously (eg, approximately 25% of estimated goal needs on day 1), and gradually increased to goal over the course of 3–5 days. Any electrolyte abnormalities (especially hypophosphatemia, hypokalemia, and hypomagnesemia) should be corrected before nutrition support is initiated. Providing empiric

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**Table 2**

**Identification of patients at risk for refeeding syndrome**

<table>
<thead>
<tr>
<th>Anorexia nervosa</th>
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<tbody>
<tr>
<td>Classic marasmus/kwashiorkor</td>
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<tr>
<td>Residents admitted from skilled nursing facilities</td>
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<tr>
<td>Unfed for 7–10 days with evidence of stress/depletion</td>
</tr>
<tr>
<td>Chronic diseases causing undernutrition (eg, cancer or cardiac cachexia, chronic obstructive pulmonary disease, cirrhosis)</td>
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<tr>
<td>History of excessive alcohol intake</td>
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<tr>
<td>Morbid obesity with massive weight loss</td>
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</table>
electrolyte supplementation (in patients with normal renal function) before and during nutrition support is advisable. Increasing total caloric load may decrease serum phosphorus concentration, and it is necessary to provide a minimum of approximately 10–15 mmol of phosphate per 1000 kcal to maintain normal serum concentrations (in patients with normal renal function). Patients with severe malnutrition, critical illness, severe trauma, and burns will also likely have a depletion of total body phosphorus (even if serum concentrations are normal), and their phosphate requirements will be higher. The same may be true for potassium and magnesium in these patients as well. After nutrition support is initiated and titrated upward, electrolytes should be supplemented according to serum electrolyte concentrations and response to therapy. Because patients at risk for RS may also have diminished cardiac reserve and can develop fluid overload, fluid and sodium should be minimized during the first few days of nutrition support (eg, sodium ≤20 mEq/day, total fluid of ≤1000 mL/day). Patients should gain no more than 1 kg per week during repletion. Any weight gain >1 kg/week would likely be attributed to fluid retention.

Vitamin supplementation should also be provided. Parenteral multivitamin preparations provide daily requirements as recommended by the American Medical Association. These preparations contain 3 mg or 6 mg of thiamine daily. However, thiamine requirements are increased in cachectic patients, and additional supplementation has been suggested. Supplemental thiamine at 50–100 mg/day IV, or 100 mg PO for 5–7 days should be provided to patients at risk for thiamine deficiency or RS. Most reports have focused on thiamine deficiency, but other vitamins may also be deficient in the malnourished patient. Although the importance of other vitamin deficiencies in RS is less clear, administering supplemental vitamins (especially folic acid) to patients at risk for RS is a reasonable approach. In addition to thiamine, 1 mg/day folic acid may also be provided for 5–7 days. Alternatively, providing a supplemental multivitamin PO daily in addition to EN for 5–7 days is reasonable. These steps can be done safely and inexpensively and may prevent patient morbidity. Patients should be monitored closely for signs and symptoms of RS. Vital signs, including heart rate, blood pressure, respiratory rate, mental status, and neurologic function, should be monitored routinely, especially during the first several days of nutrition support until goal is reached. Finger pulse oximetry should be used if available, and patients should also be monitored for any electrocardiographic changes if possible. In addition, patients should be evaluated for any neuromuscular signs and symptoms during daily physical examinations. Patients should also be assessed for fluid balance, signs of edema, fluid overload, and weighed on a regular basis.

### Treatment

Treatment of RS includes supportive care and treatment of any electrolyte disorders. If the patient exhibits any signs or symptoms consistent with RS, nutrition support should be interrupted immediately. Dextrose 10% in water can be initiated instead at the same rate to avoid rebound hypoglycemia if desired. A “stat” laboratory assessment should be made to evaluate serum electrolyte and glucose levels. If the patient exhibits any neurologic changes (eg, mental status changes, encephalopathy), a single dose of IV thiamine 100 mg should be given. If respiratory distress or other respiratory symptoms are present, supplemental oxygen should be provided, and an arterial blood gas obtained. Cardiovascular changes should be addressed and treated immediately. Any evidence of fluid overload should also be treated appropriately (eg, diuretic therapy).

The following sections provide suggestions for treatment of specific electrolyte abnormalities. We would recommend administering ≤50% of the initial empiric doses of electrolytes (phosphate, potassium, and magnesium) in patients with impaired renal function (eg, creatinine clearance <50 mL/min, serum creatinine ≥2 mg/dL, patients who are oliguric [urine output <400 mL/day] or anuric [urine output <100 mL/day]) who are not treated with CRRT. In addition, when using weight-based dosing, there are no definitive data or recommendations for “adjusting” weight in patients who are significantly obese. There is also debate on when clinicians should use an “adjusted” body weight (eg, using a percentage above IBW or according to body mass index [BMI]). Adipose tissue is estimated to be composed of approximately 10%–30% water, and total body water in men is slightly higher that that in women. Often in clinical practice, an “adjustment” of 25%–40% of the difference between actual weight and IBW is added to the IBW to determine the “adjusted” body weight or dosing weight. Even though this practice is controversial, adjusting body weight in obese patients may minimize the risk of overdosing and complications.

### Treatment of Hypophosphatemia

Treatment of hypophosphatemia depends on the magnitude of hypophosphatemia, whether or not the patient is symptomatic, and the route of administration that is available (ie, enteral or parenteral). Patients with mild hypophosphatemia who are asymptomatic and have a functioning gastrointestinal tract may be treated with oral phosphates. However, oral absorption can be unreliable, and oral phosphate products may cause diarrhea. Asymptomatic patients with moderate to severe hypophosphatemia who cannot receive oral medications and patients who are symptomatic should receive IV phosphate supplementation. Phosphate dosing is largely empiric because serum concentrations may...
Serum potassium concentration

Potassium phosphate can be used in patients with hypophosphatemia and whether or not phosphate is used in the dialysate/replacement fluid. Further phosphate supplementation should be guided by clinical response and serum concentrations. Suggestions for potassium dosing are provided in Table 3. We recommend providing ≤50% of the initial empiric dose. Maximum infusion rate = 7 mmol phosphate/h. 

<table>
<thead>
<tr>
<th>Degree of hypophosphatemia</th>
<th>IV phosphate replacement dosage*†</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.3–2.7 mg/dl (mild hypophosphatemia, asymptomatic)</td>
<td>0.08–0.16 mmol/kg</td>
</tr>
<tr>
<td>1.5–2.2 mg/dl (moderate hypophosphatemia, asymptomatic)</td>
<td>0.16–0.32 mmol/kg</td>
</tr>
<tr>
<td>&lt;1.5 mg/dl (Severe symptomatic hypophosphatemia)</td>
<td>0.32–0.64 mmol/kg</td>
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</table>

*In patients with normal renal function; patients with renal insufficiency should receive ≤50% of the initial empiric dose. †We suggest using adjusted body weight (AdjBW) in patients who are significantly obese (weight >130% of IBW or BMI >30 kg/m²): AdjBW (men) = ([wt (kg) – IBW(kg)] × 0.3) + IBW; AdjBW (women) = ([wt (kg) – IBW(kg)] × 0.25) + IBW.

Table 4

<table>
<thead>
<tr>
<th>Degree of hypokalemia</th>
<th>IV potassium replacement dosage*</th>
<th>Rate of IV infusion†</th>
<th>Maximum concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum potassium concentration = 2.5–3.4 mEq/L (mild to moderate hypokalemia, asymptomatic)</td>
<td>20–40 mEq</td>
<td>10–20 mEq potassium/h; maximum of 40 mEq potassium/h</td>
<td>80 mEq/L via a peripheral vein; up to 120 mEq/L via a central vein (admixed in 0.9% sodium chloride in water, or 0.45% sodium chloride in water)</td>
</tr>
<tr>
<td>Serum potassium concentration &lt;2.5 mEq/L, or if symptomatic (severe symptomatic hypokalemia)</td>
<td>40–80 mEq</td>
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</table>

*In patients with normal renal function; patients with renal insufficiency should receive ≤50% of the initial empiric dose. †Continuous cardiac monitoring and infusion via a central venous catheter are recommended for infusion rates >10 mEq potassium per hour.

Treatment of Hypokalemia

Hypokalemia can be treated with potassium supplementation via the oral or IV route. The IV route should be used when treating patients with symptomatic or severe hypokalemia (eg, serum potassium concentration <2.5 mEq/L), or when the gastrointestinal tract cannot be used. Dosing of potassium is largely empiric and based on clinical response and serum concentrations. Patients receiving CRRT may have higher clearance of potassium and require higher initial doses. Serum potassium concentration should be checked within 1–4 hours after a dose, and multiple doses of potassium may be required for full repletion. Potassium can be safely administered in adult patients at rates of 10–20 mEq/h. Rates >20 mEq/h are rarely needed, except in emergent situations. Patients should receive potassium via a central venous catheter and should have continuous cardiac monitoring for infusion rates >10 mEq/h. Potassium should never be given as a rapid infusion to avoid serious or fatal consequences. Potassium concentration in solutions for continuous infusion via a peripheral vein should be limited to 80 mEq/L, and up to 120 mEq/L can be used for infusion via a central vein. These standard recommendations are provided for safety, although...
individual recommendations and practices may vary slightly.

Oral potassium supplementation can be provided, but oral supplements can cause gastrointestinal side effects (eg, cramping, diarrhea), and oral liquid formulations have an unpleasant taste. We recommend an oral potassium dose of 20–40 mEq, or a total dose of 40–100 mEq/day as an initial regimen to correct hypokalemia. Oral doses should be divided into 2–4 doses to minimize gastrointestinal side effects.

Serum potassium concentration should be monitored at least daily during the first several days of nutrition support. Because hypomagnesemia may cause refractory hypokalemia, magnesium deficiency should be corrected, along with potassium supplementation, in order to facilitate the correction of hypokalemia.74

Treatment of Hypomagnesemia

Magnesium deficiency has been associated with a total body magnesium deficiency of 1–2 mEq/kg.75 IV treatment of hypomagnesemia should be the preferred route in patients at risk for RS if symptomatic and when the gastrointestinal tract cannot be used. Oral magnesium supplements have a slow onset and are associated with diarrhea and gastrointestinal intolerance. Suggestions for empiric IV dosing of magnesium (for patients with normal renal function) are listed in Table 5.39,41,75–83 Because magnesium distribution and equilibration between serum and intracellular spaces and tissues are slow32,84 but renal elimination is rapid (with up to 50% of an IV dose of magnesium excreted in the urine)31,32,75–77,80,82 infusion time of IV magnesium is important. In nonemergent situations, we recommend infusing doses of ≤6 g of magnesium sulfate over 6–12 hours and infusing higher doses over 12–24 hours, with a maximum of 1 g magnesium sulfate (~8.1 mEq elemental magnesium) over 1 hour. More rapid administration rates may simply increase urinary loss of magnesium. Additional supplementation may be required, and total repletion of magnesium may take several days. Severe symptomatic hypomagnesemia may require more aggressive dosing in the acute setting (eg, 4 g magnesium sulfate [~32 mEq elemental magnesium] over 4–5 minutes has been used in patients with preeclampsia or eclampsia).75,80

For patients with impaired renal function, we recommend using ≤50% of the suggested empiric magnesium dose. The patient must be monitored carefully, especially when magnesium doses approach the maximum recommendations (approximately 12 g magnesium sulfate [~97 mEq elemental magnesium] over 12 hours).75 Serum magnesium concentration should be checked approximately 12–24 hours after magnesium repletion. Serum magnesium concentrations can be monitored more frequently in the acute setting; however, because of the slow magnesium equilibrium,32,84 serum magnesium concentration can seem artificially high if measured too soon after a dose.79 Serum concentrations should be monitored at least once daily during the first several days of nutrition support in patients at risk for RS.

Restarting Nutrition Support

If a patient manifests signs and symptoms of RS, nutrition support should be restarted with great caution. All electrolyte abnormalities should be adequately treated and supplemental electrolytes provided in the nutrition formulation above what was previously provided when RS symptoms developed. Multivitamins should also be supplemented as described earlier. The patient should be free of symptoms and stable before restarting nutrition support. We suggest initiating nutrition support at ≤50% of the previous rate when symptoms develop, and advance nutrition to goal cautiously over at least 4–5 days. The patient should be monitored closely for further signs and symptoms of RS.

### Table 5

<table>
<thead>
<tr>
<th>Degree of hypomagnesemia</th>
<th>IV magnesium replacement dosage*†</th>
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</thead>
<tbody>
<tr>
<td>Serum magnesium concentration = 1–1.5 mg/dL (mild to moderate hypomagnesemia, asymptomatic)</td>
<td>1–4 g magnesium sulfate (8–32 mEq magnesium), up to 1 mEq/kg†</td>
</tr>
<tr>
<td>Serum magnesium concentration &lt;1 mg/dL (severe symptomatic hypomagnesemia)</td>
<td>4–8 g magnesium sulfate (32–64 mEq magnesium), up to 1.5 mEq/kg‡</td>
</tr>
<tr>
<td>Rate of IV infusion</td>
<td>Maximum of 1 g magnesium sulfate/h (8 mEq magnesium/h), up to 12 g magnesium sulfate (97 mEq magnesium) over 12 h if asymptomatic; up to 32 mEq magnesium over 4–5 min in severe symptomatic hypomagnesemia</td>
</tr>
</tbody>
</table>

*In patients with normal renal function; patients with renal insufficiency should receive ≤50% of the initial empiric dose.
†We suggest using adjusted body weight (AdjBW) in patients who are significantly obese (weight >130% of IBW or BMI = 30 kg/m²): AdjBW [men] = [(wt [kg] – IBW[kg]) × 0.3] + IBW; AdjBW [women] = [(wt [kg] – IBW[kg]) × 0.25] + IBW.
‡One gram magnesium sulfate = 8.1 mEq magnesium.
Summary

RS is a serious condition that can develop in underweight, severely malnourished, or starved individuals during nutrition repletion. RS involves significant electrolyte, fluid, and vitamin abnormalities that can lead to significant morbidity and mortality. Clinicians should be aware of RS, identify patients at risk of developing RS, and most importantly take steps to prevent RS. Patients who develop signs and symptoms of RS require aggressive electrolyte supplementation, vitamin supplementation, and supportive care, and nutrition support should be restarted with great caution.

 References

Refeeding in the ICU: an adult and pediatric problem
Matthew C. Byrnes and Jessica Stangenes

Division of Surgical Critical Care, University of Minnesota, Minneapolis, Minnesota, USA

Correspondence to Matthew C. Byrnes, MD, Division of Surgical Critical Care, University of Minnesota, MMC 11, 420 Delaware Street SE, Minneapolis, MN 55455, USA
Tel: +1 612 625 7911; fax: +1 612 626 0439; e-mail: mbyrnes150@yahoo.com

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Purpose of review
To describe the etiology and complications of the refeeding syndrome.

Recent findings
Complications of the refeeding syndrome can include electrolyte abnormalities, heart failure, respiratory failure, and death. This syndrome is of particular importance to critically ill patients, who can be moved from the starved state to the fed state rapidly via enteral or parenteral nutrition. There are a variety of risk factors for the development of the refeeding syndrome. All of these risk factors are tied together by starvation physiology. Case reports and case series continue to be reported, suggesting that this entity continues to exist in critically ill patients. Initiation of enteral nutrition to patients with starvation physiology should be gradual and careful monitoring of electrolytes and organ function is critical during the early stages of refeeding.

Summary
The refeeding syndrome remains a significant issue in critically ill patients. Knowledge of the risk factors and the clinical signs of the refeeding syndrome is important to optimize outcomes.

Keywords
hypomagnesemia, hypophosphatemia, refeeding syndrome, starvation

Introduction
The refeeding syndrome is a constellation of signs and symptoms that occurs after the abrupt provision of nutrition to patients who have been in a starved state. Complications of the refeeding syndrome can include electrolyte abnormalities, heart failure, respiratory failure, and death [1,2,3,4]. This syndrome is of particular importance to critically ill patients, who can be moved from the starved state to the fed state rapidly via enteral or parenteral nutrition.

The refeeding syndrome was initially noted, though not recognized, during World War II [4]. Emaciated prisoners of war inexplicitly died after they were provided a regular diet. The cause of the lethal cardiac failure was not apparent for many years thereafter. During the subsequent decades, understanding of electrolytes and vitamins improved. It has become clear that the abrupt introduction of nutrition to starved patients carries specific perils. This review will describe the physiology of the refeeding syndrome as well as discuss the clinical implications and methods to prevent and treat the syndrome.

Level of evidence
The refeeding syndrome was initially noted by clinical observation. Subsequently, numerous case reports and case series have been published. Although our understanding of the syndrome has been refined significantly, there are no randomized trials upon which to base recommendations and only minimal nonrandomized prospective studies. As such, the recommendations in this review are based primarily upon case series and case reports as well as our experience in the ICU.

Epidemiology
It is critical to identify patients at risk for the refeeding syndrome prior to initiating any nutrition therapy (Table 1). The majority of these disease states have been described in case reports and case series and have a common thread of starvation physiology [1,3,5–9,10]. Common conditions associated with refeeding syndrome include anorexia nervosa, hyperemesis, alcoholism, cancer, and abused and neglected adults and children. There are a variety of malabsorptive syndromes, such as short bowel syndrome, inflammatory bowel disease, cystic fibrosis, chronic pancreatitis and various forms of bariatric surgery that can lead to refeeding syndrome after the initiation of aggressive parenteral nutrition and occasionally enteral nutrition [11–14]. Hospitalized patients that have had nutrition withheld for 7–10 days are also at risk. Individuals experiencing starvation due to famine, hunger strikes, or imprisonment during war times can also develop the refeeding syndrome. Case reports continue to emerge in the literature documenting that the refeeding syndrome continues to be a complication that cannot
be ignored in an array of patient populations [15,16]. Some elements of the refeeding syndrome can be seen in up to half of the highest risk patients [17,18]. Fatalities are uncommon but are well described.

Patients with anorexia nervosa represent the prototypical population of refeeding syndrome. Numerous case reports have noted this complication during nutritional rehabilitation of patients with eating disorders [19,20,21,22]. A case report by Altinyazar et al. [19] noted the risk of Wernicke–Korsakoff’s syndrome from thiamine deficiency in patients with anorexia nervosa. This illustrates the importance of ongoing monitoring for refeeding syndrome to prevent neurological derangements in this population. Kishibe et al. [22] reported a case of acute edema/cutaneous distention syndrome (AECDS) thought to be associated with refeeding an anorexic patient. Cutaneous symptoms associated with AECDS (erythema, linear crazes, erosions, and bullae) manifested after the patient was aggressively refed. Another case report demonstrated acute hypoxic respiratory failure in a bulimic female due to severe hypophosphatemia (phosphorus <1 mg/dl) [23].

Whitelaw et al. [20] evaluated the incidence of hypophosphatemia in eating disordered adolescent patients undergoing nutritional rehabilitation. A retrospective chart review of 29 patients diagnosed with anorexia nervosa, bulimia, or restrictive-subtype eating disorder was conducted. Patients were assessed for anticipated risk of refeeding syndrome and prescribed varying caloric regimens. Caloric prescription was reduced for one patient suspected to be at high risk for refeeding syndrome. It was noted that patients with a body weight at <68% of ideal body weight or a BMI of 15.1 kg/m² were most likely to develop hypophosphatemia and were the most appropriate patients for reductions in initial energy prescription and close electrolyte monitoring. The authors reiterated the need for clinical trials comparing various caloric regimens to determine the risk of refeeding complications versus the risks of delayed nutritional support in the eating disorder population.

A multicenter study was recently published that reported the epidemiology of the refeeding syndrome among anorexic patients admitted to the ICU in France [24]. The incidence of the refeeding syndrome among these patients was 10%. Among the seven deaths, five were attributed to multisystem failure secondary to severe metabolic disturbances. Notably, caloric intake was significantly higher on day 1 among patients who developed the refeeding syndrome (14 versus 23 kcal/kg).

There is also likely to be a risk of refeeding syndrome among patients who have been fasted for several days in the hospital before receiving intravenous dextrose infusions. The clearest evidence comes from studies among postmyocardial infarction patients receiving glucose–insulin–potassium (GIK) infusions for myocardial protection [25,26]. Several studies have demonstrated the onset of hypophosphatemia with this regimen, which may represent an unacknowledged form of the refeeding syndrome. The specific amount of glucose required to induce the condition is unknown; however, clinicians should be aware that both full nutrition and simple intravenous dextrose infusions can result in the refeeding syndrome.

### Pathophysiology

A thorough understanding of the refeeding syndrome requires a description of the physiology of different nutritional states [27]. The hormonal milieu shifts during the conversion from the starved state to the fed state (Fig. 1). These hormonal alterations account for the electrolyte and fluid shifts that are seen in the syndrome.

### Starvation

Liver glycogen is depleted within 24 h of entering a fasting state. The major hormonal shift during starvation

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**Table 1 Conditions associated with the refeeding syndrome**

<table>
<thead>
<tr>
<th>Conditions associated with increased risk for refeeding syndrome</th>
<th>Symptoms associated with increased risk for refeeding syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eating disorders (anorexia nervosa and bulimia)</td>
<td>Unintentional weight loss &gt;10% within a 1–3 months period</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>&lt;70–80% ideal body weight</td>
</tr>
<tr>
<td>Kwashiorkor</td>
<td>Muscle wasting</td>
</tr>
<tr>
<td>Marasmus</td>
<td>Chronic dysphagia</td>
</tr>
<tr>
<td>Oncology patients</td>
<td>Persistent nausea, vomiting or diarrhea limiting oral intakes</td>
</tr>
<tr>
<td>Uncontrolled diabetes</td>
<td>Prolonged fasting or nil per os (NPO) status &gt;7–10 days</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>Inadequate nutrition therapy (EN or PN) intakes &gt;10 days</td>
</tr>
<tr>
<td>Congential heart disease</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td></td>
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<tr>
<td>HIV/AIDS</td>
<td></td>
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<tr>
<td>Bariatric surgery</td>
<td></td>
</tr>
<tr>
<td>Malabsorptive conditions (short bowel syndrome, cystic fibrosis, pancreatic insufficiency, inflammatory bowel disease)</td>
<td></td>
</tr>
<tr>
<td>Hyperemesis gravidarum</td>
<td></td>
</tr>
<tr>
<td>Neglected children and adults</td>
<td></td>
</tr>
<tr>
<td>Food insecurity and homeless</td>
<td></td>
</tr>
</tbody>
</table>

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**Refeeding in the ICU** Byrnes and Stangenes 187

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is a reduction of insulin combined with a relative increase in glucagon [2,3,28]. There is also an increase in growth hormone. The primary sources of energy substrates during starvation are fat and protein. Catabolism of protein and hydrolysis of triglycerides provides necessary precursors for hepatic gluconeogenesis, which provide a source of glucose for hematologic and neurologic cells. Gluconeogenesis peaks at day 7 of starvation, then slowly decreases. Lipolysis also peaks at 7 days, then plateaus. During prolonged starvation, there are additional mechanisms to produce glucose and conserve substrates. Glucose is converted anaerobically to ATP, This yields less ATP per unit of glucose, but it produces lactate, which can be recycled back to glucose in the liver (Cori cycle).

During the initial stages of starvation, urinary nitrogen is very high as a result of the conversion of amino acids to glucose. As starvation progresses, this process slows. With prolonged starvation past 10 days, the brain shifts its primary metabolic source to fat in the form of ketone bodies. Without this shift, the loss of lean body mass from muscle catabolism would be fatal in less than 1 month. There is also a reduction in the basal metabolic rate and a reduction in the amount of ATP produced in the body.

**Fed state**

With the reintroduction of nutrition, particularly carbohydrate, to individuals who have had a metabolic adaptation to starvation, there is a dramatic shift in macronutrient metabolism. There are four major changes that occur. First, insulin secretion is heightened. Second, glucagon release is inhibited. Third, there is an activation of previously slowed anabolic pathways. Fourth, there is a shift from lipolysis to lipogenesis. Although ordinary meals are associated with this shift in the hormonal milieu, starved patients have different metabolic characteristics that place them at risk for developing the refeeding syndrome. They have a depletion of ATP; they have reduced whole body levels of electrolytes and vitamins; and they have less physiologic reserve to tolerate insults. The hyperinsulinemic response causes a migration of critical electrolytes to intracellular locations. The severity of these fluctuations largely depends on the severity of malnutrition and electrolyte depletion experienced prior to the refeeding period. Several physiologic alterations can be observed as a result of these metabolic changes and are outlined as follows [28].

**Hypophosphatemia**

The most prominent electrolyte abnormality of the refeeding syndrome is hypophosphatemia [8,9,17,29–31]. Serum phosphorus is tightly regulated between 2.5 and 4.5 mg/dl during wellness. The starved state leads to a total body loss of phosphorus; however, serum levels may still be normal. The abrupt introduction of a carbohydrate diet shifts energy metabolism to an anabolic state. During refeeding, the phosphorus demand significantly exceeds the available supply. Insulin levels increase, which causes intracellular migration of phosphorus. Furthermore, phosphorus is also required for structural incorporation into phospholipids, nucleoproteins and nucleic acids. There is also incorporation of phosphorus into ATP and 2,3-DPG, which further accentuates hypophosphatemia [2,32].

**Hypokalemia**

Depletion of potassium during the refeeding process is attributed to the reintroduction of carbohydrate and the
subsequent increase in insulin secretion that drives cellular uptake of potassium. There is typically a whole-body reduction of potassium during starvation, which accentuates the problems of hypokalemia during refeeding [1,30].

**Hypomagnesemia**
Depletion of magnesium during the refeeding process is multifactorial. As with phosphorus and potassium, there is a total body depletion of magnesium during starvation. Serum levels may be deceptively normal due to concurrent dehydration. During the refeeding process, there can be a massive shift of magnesium to intracellular locations. Additionally, magnesium is a co-factor for a number of metabolic processes, so demand exceeds supply during refeeding.

**Hyperglycemia**
Upon reintroduction of carbohydrate to a patient experiencing starvation, gluconeogenesis is initially suppressed. However, as refeeding continues, glucocorticoid circulation increases leading to exacerbation of hyperglycemia.

**Sodium retention and fluid imbalance**
The hyperinsulinemic response to carbohydrate in the starved patient causes decreased renal excretion of sodium and water. The retention of sodium and water causes an expansion of the extracellular fluid compartment and can potentially lead to significant fluid retention, pulmonary edema, and possibly congestive cardiac failure [33].

**Thiamine deficiency**
Vitamin and mineral deficiencies may already be present in a patient experiencing starvation from prolonged inadequate intake [34]. Thiamine, in particular, is a co-factor required in the metabolism of carbohydrate and is rapidly utilized during glycolysis. Limited thiamine stores can be utilized early in the refeeding process.

**Clinical implications**
There are a number of clinical consequences to the refeeding syndrome. Most of these are the result of electrolyte shifts and vitamin depletion. Nearly every organ system can be affected by this syndrome. The characteristics of the refeeding syndrome are as follows:

1. Electrolyte abnormalities:
   - hypokalemia,
   - hypomagnesemia, and
   - hypophosphatemia.
2. Hyperglycemia.
3. Cardiac:
   - heart failure, and
   - arrhythmia.
4. Respiratory:
   - diaphragm fatigue,
   - respiratory failure, and
   - prolonged ventilatory weaning.
5. Hematologic:
   - anemia and
   - red blood cell lysis.
6. Immunologic:
   - immune suppression, and
   - infectious complications.
7. Neurologic:
   - Wernicke’s encephalopathy.
8. Musculoskeletal:
   - weakness, and
   - rhabdomyolysis.

**Weakness**
Muscular weakness is commonly seen in the refeeding syndrome. This weakness can be synergistic with weakness associated with critical illness or starvation. It is mainly driven by electrolyte aberrations, primarily hypophosphatemia [32]. Rhabdomyolysis is also occasionally seen.

**Arhythmia**
Both hypomagnesaemia and hypokalemia are associated with cardiac arrhythmias [35]. This includes atrial as well as potentially lethal ventricular arrhythmias [36,37]. Prolongation of the QT interval on an EKG may precede ventricular arrhythmias.

**Dysxia**
Hypophosphatemia limits the production of 2,3-DPG [9,38]. This enzyme is required for efficient offloading of oxygen to peripheral tissues. As a result, even in the presence of normal gas exchange, delivery of oxygen to cells may be inhibited.

**Cardiac dysfunction**
The introduction of adequate nutrition places significant metabolic stress on marginalized myocardium. The already poorly functioning heart may be unable to handle the additional volume from the fluid retention associated with the refeeding syndrome [7,39,40]. Cardiac dysfunction represented the causes of death among prisoners in World War II that died of the refeeding syndrome [41].

**Respiratory failure**
Hypophosphatemia is a well known mediator of diaphragmatic fatigue. The refeeding syndrome can lead to new respiratory failure or prolonged ventilator weaning [8,23].

**Cerebral effects**
Thiamine stores are depleted with starvation. The remaining thiamine is used up very rapidly after the introduction of a glucose source. This has led to Wernicke’s encephalopathy [19,34].
Anemia
The anemia associated with refeeding syndrome is multifactorial. There is increased red blood cell lysis and there is also an inability to shift metabolic demands to increase red cell production.

Infection
Infectious complications can be seen with the refeeding syndrome [10,29]. These issues likely stem from hyperglycemia but there may also be intrinsic immunologic dysfunction.

Prevention and treatment
Multidisciplinary teams consisting of nurses, pharmacists, dietitians, and physicians are commonplace in ICUs today. These teams play a critical role in identifying and preventing complications associated with refeeding syndrome. Historically, management of refeeding syndrome was largely based upon case reports and clinical experience. As the recognition of refeeding syndrome improved, guidelines on the management of this syndrome have evolved but optimal treatment has not been confirmed through clinical trials.

Electrolyte repletion
A complete electrolyte panel should be obtained in patients at high risk for refeeding syndrome prior to starting nutritional intake [1,2,3,42]. Electrolyte deficiencies should be replaced prior to initiating nutritional support. Recent guidelines in electrolyte replacement are summarized in Table 2 [1,2,43]. Intravenous replacement is preferred initially in critically ill patients to avoid issues with malabsorption. In our hospital, we have had success utilizing a combination of intravenous and enteral phosphorus replacement in adults (i.e. i.v. NaPhos as prescribed by electrolyte replacement protocols with an additional 1–3 packets of generic sodium phosphate daily) to more rapidly replace phosphorus levels of less than 2 mg/dl back to normal levels.

Caloric support
Lack of consensus exists regarding the appropriate initial caloric level to deliver to patients at high risk for the refeeding syndrome. Overall consensus, however, is to have gradual introduction and advancement of feeding. It is important, especially in critically ill patients, to account for all energy and carbohydrate intake sources, such as propofol and intravenous dextrose. Prudent initial caloric provision have been described to be 20–75% of estimated energy needs in the adult and pediatric populations or 5–20 kcal/kg/day for adult patients depending on the suspected severity of nutritional depletion prior to feeding [1,2,30,42,44].

Few recommendations exist on the percentage of calories that should come from carbohydrate versus protein or fat. Boateng et al. [2] recommend the following distribution:

<table>
<thead>
<tr>
<th>Table 2 Guidelines for electrolyte replacement</th>
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<tbody>
<tr>
<td>Lab value</td>
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<tr>
<td>----------------------</td>
</tr>
<tr>
<td><strong>Hypophosphatemia</strong></td>
</tr>
<tr>
<td>General (&lt;2.7 mg/dl)</td>
</tr>
<tr>
<td>Mild 2.3–2.7 mg/dl</td>
</tr>
<tr>
<td>Moderate 1.5–2.2 mg/dl</td>
</tr>
<tr>
<td>Severe &lt;1.5 mg/dl</td>
</tr>
<tr>
<td><strong>Hypokalemia</strong></td>
</tr>
<tr>
<td>General (&lt;3.4–3.5 mEq/l)</td>
</tr>
<tr>
<td>Mild to moderate 2.5–3.4 mEq/l</td>
</tr>
<tr>
<td>Severe &lt;2.5 mEq/l</td>
</tr>
<tr>
<td><strong>Hypomagnesemia</strong></td>
</tr>
<tr>
<td>General (&lt;1.8 mg/dl)</td>
</tr>
<tr>
<td>Mild to moderate (1–1.8 mg/dl)</td>
</tr>
<tr>
<td>Severe (&lt;1 mg/dl)</td>
</tr>
</tbody>
</table>

*Can be given as either intravenous NaPhos or KPhos.
*Given using intravenous KCl.
50–60% calories from carbohydrate, 15–25% calories from protein, and 20–30% calories from fat. The advancement of energy provisions should occur slowly over a period of 3–7 days. Caloric intake should increase by 10–25% per day or by 200–250 kcal/day after electrolytes have stabilized. Initiation of enteral nutrition is usually slow by necessity. Clinicians should be especially cautious with patients receiving parenteral nutrition, as full caloric replacement can be accomplished more easily, which likely increases the risk of the refeeding syndrome.

If symptoms of refeeding syndrome are observed, nutritional intakes should be reduced or halted until symptoms are corrected and resolved. Upon resolution of refeeding symptoms, it has been suggested that nutrition therapy should be restarted at 50% or less of the previous rate that precipitated the symptoms. Additionally, close monitoring of electrolytes and vital signs is critical. However, others have recommended that correction of fluid and electrolyte abnormalities can be done while continuing nutrition therapy intakes [27].

**Vitamin supplementation**

Little consensus exists as to the optimal vitamin and trace element supplementation that should be administered to patients suspected to be at risk for refeeding syndrome. Some authors recommend 50–300 mg of thiamine prior to starting a feeding regimen [2,3]. Furthermore, it is recommended to continue with 100 mg of enteral thiamine daily. In florid Wernicke’s encephalopathy, very high doses of thiamine (500–750 mg) may be warranted [19]. In the pediatric patients, thiamine should also be replaced, though at a lower dose of 10–25 mg/day initially and then 5–10 mg/day for 1 month [1].

Published guidelines recommend additional micronutrient supplementation in adults [2*]. This supplementation includes pyridoxine (vitamin B6), cobalamin (vitamin B12), folate, selenium, zinc, and iron. Most multivitamin–mineral combination pills are likely adequate to provide the additional recommended maintenance doses of these vitamins; however, clinicians should consult with their pharmacy to determine the specific contents of these combination pills.

**Volume**

Consideration should be given to sodium and fluid balance when initiating a feeding regimen in a patient at risk for refeeding syndrome. Some authors have recommended initial fluid restriction to prevent congestive heart failure after initiation of a feeding regimen [33]. Sodium levels should also be monitored closely, and hyponatremia should be slowly corrected to avoid permanent neurological sequelae. Daily weights, intakes and outputs, heart rate, and sodium values should be monitored to help identify and treat fluid overload associated with refeeding syndrome.

**Monitoring**

Recommendations have been made that heart rate and ECG monitoring also be monitored in the first week of nutritional therapy to detect cardiac complications from refeeding syndrome.

**Clinical pathway**

A retrospective study described a pathway of correcting undernutrition in anorexic patients while also avoiding refeeding syndrome [21**]. Thirty-three female patients, aged 22.8 years, diagnosed with anorexia nervosa and a BMI of 12 kg/m² or less were admitted to a specialized eating disorder unit from May 1999 through March 2009. Indirect calorimetry was used to more accurately determine each patient’s resting energy expenditure (REE), resulting in a mean measured REE of 27 kcal/kg/day. These authors began with a higher caloric prescription than that of previous recommendations; however, they primarily refed their patients with enteral nutrition therapy using fluid-restricted, high-calorie (1.7–2 kcal/ml), high-nitrogen formulas which tend to also be lower in carbohydrates. All patients were given thiamine and a B vitamin supplement on day 1 of admission. Prior to the initiation of a feeding regimen, electrolytes were evaluated and supplemented as needed. All patients experienced a significant increase in body weight while none experienced laboratory or clinical symptoms of refeeding syndrome. This study represents the largest case study known thus far for refeeding of patients with anorexia nervosa successfully without symptoms of refeeding syndrome.

**Conclusion**

In conclusion, the refeeding syndrome remains a significant issue in critically ill patients. Knowledge of the risk factors and the clinical signs of the refeeding syndrome is important to optimize outcomes. This can be most effectively accomplished with a multidisciplinary team that is attuned to nutritional needs and metabolic demands of this patient population.

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 217).


This review represents extensive guidelines for the prevention and treatment of the refeeding syndrome.


This study reported a method of refeeding patients with starvation physiology without the induction of the refeeding syndrome.


This study represents the most report of the refeeding syndrome in critically ill patients. This study also provides an excellent description of the morbidity and mortality of the refeeding syndrome in anorexic patients.


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