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Invited Review

Review of the Refeeding Syndrome

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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 colleagues[1] 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 Krumdieck[2] 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.

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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.[3] 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[4] or a possible interaction between the water, sodium, and carbohydrate homeostasis.[5] 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.[6] 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.[6] 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).[2,7–15] Severe hypophosphatemia in these patients has also led to neurologic symptoms, including paresthesias, weakness, confusion, disorientation, encephalopathy, areflexic paralysis, seizures, coma, and death.[8–10,12,13,16,17] Silvas and Paragas[8] 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 show to impair cardiac function[18] and respiratory function.[14,19,20] O'Connor et al[18] 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 =

Table 1
Clinical manifestations of refeeding syndrome

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

1.6–4.7 mg/dL). Severe hypophosphatemia has also been shown to impair diaphragmatic contractility[20] and lead to acute respiratory failure requiring intubation and mechanical ventilation.[14,19] Youssef[14] described a case of a woman with multiple intestinal fistulae who underwent a laparotomy and then began PN. She developed respiratory failure on postoperative day 2 (her second day of PN) and went on to develop generalized convulsions, coma, and required intubation and mechanical ventilation.

Hypophosphatemia can lead to decreases in ATP and 2,3-DPG as described previously. This may lead to further abnormalities in oxygen transport and delivery,[7,11,21–23] and impaired glucose metabolism.[7] Hypophosphatemia and a subsequent decrease in 2,3-DPG increase the affinity of hemoglobin for oxygen and shifts the oxygen dissociation curve to the left.[21–23] Sheldon and Grzyb[11] described hypophosphatemia and associated abnormalities in a series of 19 trauma patients, 8 of whom inadvertently were given PN without phosphate supplementation. 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[7] 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). Hypophosphatemia also led to reductions in erythrocyte ATP and 2,3-DPG, with an associated increase of hemoglobin affinity for oxygen (P_{50} = 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.[24,25] 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.[24–27] 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.[26–29] Patients

with severe hypokalemia may develop electrocardiograph 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, bradycardia, 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 patients[34–37] 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.[43] 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

Table 2
Identification of patients at risk for refeeding syndrome

Anorexia nervosa
Classic marasmus/kwashiorkor
Residents admitted from skilled nursing facilities
Unfed for 7–10 days with evidence of stress/depletion
Chronic diseases causing undernutrition (eg, cancer or cardiac cachexia, chronic obstructive pulmonary disease, cirrhosis)
History of excessive alcohol intake
Morbid obesity with massive weight loss

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).[11] 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 $\leq$20 mEq/day, total fluid of $\leq$1000 mL/day).[56] 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.[56]

Vitamin supplementation should also be provided. Parenteral multivitamin preparations provide daily requirements as recommended by the American Medical Association.[57] 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.[58] 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 $\leq$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 $\geq$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,[59–63] 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

Table 3
Treatment of hypophosphatemia[64–70]*

Degree of hypophosphatemia	IV phosphate replacement dosage*†
2.3–2.7 mg/dL (mild hypophosphatemia, asymptomatic)	0.08–0.16 mmol/kg
1.5–2.2 mg/dL (moderate hypophosphatemia, asymptomatic)	0.16–0.32 mmol/kg
<1.5 mg/dL (Severe symptomatic hypophosphatemia)	0.32–0.64 mmol/kg

*In patients with normal renal function; patients with renal insufficiency should receive ≤50% of the initial empiric dose. Maximum infusion rate = 7 mmol phosphate/h.
†We suggest using adjusted body weight (AdjBW) in patients who are significantly obese (weight >130% of IBW or BMI ≥30 kg/m^2): AdjBW (men) = ([wt (kg) − IBW(kg)] × 0.3) + IBW; AdjBW (women) = ([wt (kg) − IBW(kg)] × 0.25) + IBW.

not correlate with total body phosphorus stores. Suggested IV phosphate dosing is provided in Table 3.[64–70] We recommend providing ≤50% of the initial empiric phosphate dose in patients with impaired renal function who are not treated with CRRT. Patients treated with CRRT have continuous phosphorus clearance and may require higher initial doses, depending on the degree of hypophosphatemia and whether or not phosphate is used in the dialysate/replacement fluid. Further phosphate supplementation should be guided by clinical response to the initial dose.

IV phosphate formulations are available as potassium or sodium salts. One mmol of potassium phosphate contains 1.47 mEq of potassium, and 1 mmol of sodium phosphate contains 1.33 mEq of sodium. Potassium phosphate can be used in patients with simultaneous hypokalemia; otherwise sodium phosphate should be used. Total phosphate dose should be infused over 4–6 hours to minimize adverse effects (eg, thrombophlebitis from potassium phosphate) and to reduce the risk of calcium-phosphate precipitation. Doses can be infused up to a rate of 7 mmol of phosphate per hour (or about 10 mEq of potassium per hour).[69,70] Serum phosphorus concentration should be checked 2–4 hours after a dose and additional phosphate supplementation provided until the patient is asymptomatic or the serum phosphorus concentration is in the normal range. Serum phosphorus concentration should be monitored at least daily for the first week of nutrition support. More frequent monitoring may be indicated in the first several days of nutrition support, especially in patients who manifest signs or symptoms of hypophosphatemia.

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. Suggestions for potassium dosing are provided in Table 4.[71–73] We would also recommend that patients with impaired renal function who are not being treated with CRRT receive ≤50% of the recommended initial dose. 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

Table 4
Treatment of hypokalemia[71–73]*

Degree of hypokalemia	IV potassium replacement dosage*	Rate of IV infusion†	Maximum concentration
Serum potassium concentration = 2.5–3.4 mEq/L (mild to moderate hypokalemia, asymptomatic)	20–40 mEq	10–20 mEq potassium/h; maximum of 40 mEq potassium/h	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)
Serum potassium concentration <2.5 mEq/L, or if symptomatic (severe symptomatic hypokalemia)	40–80 mEq		

*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.

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 slow[32,84] 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
Treatment of hypomagnesemia[39,41,75–83]*

Degree of hypomagnesemia	IV magnesium replacement dosage*†
Serum magnesium concentration = 1–1.5 mg/dL (mild to moderate hypomagnesemia, asymptomatic)	1–4 g magnesium sulfate (8–32 mEq magnesium), up to 1 mEq/kg‡
Serum magnesium concentration <1 mg/dL (severe symptomatic hypomagnesemia)	4–8 g magnesium sulfate (32–64 mEq magnesium), up to 1.5 mEq/kg‡
Rate of IV infusion	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

*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/m^2): 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

1. Keys A, Brozek J, Henschel A, Mickelson O, Taylor HD, eds. *The Biology of Human Starvation, Vols. 1, 2.* Minneapolis, MN: University of Minnesota Press; 1950.
2. Weinsier RL, Krumdieck CL. Death resulting from overzealous total parenteral nutrition: the refeeding syndrome revisited. *Am J Clin Nutr.* 1980;34:393–399.
3. Cahill GF. Starvation in man. *N Engl J Med.* 1970;282:668–675.
4. DeFronzo RA, Cooke CR, Andres R, Faloona GR, Davis PJ. The effect of insulin on renal handling of sodium, potassium, calcium, and phosphate in man. *J Clin Invest.* 1975;55:845–855.
5. Guirao X, Franch G, Gil MJ, Garcia-Domingo MI, Girvent M, Sitges-Serra A. Extracellular volume, nutritional status, and refeeding changes. *Nutrition.* 1994;10:558–561.
6. Van Way CW, Longoria M, Sacks GS. Do surgeons need to worry about vitamin deficiencies? *Nutr Clin Pract.* 2001;16(suppl):S5–S7.
7. 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;285:763–768.
8. Silvis SE, Paragas PD. Paresthesias, weakness, seizures, and hypophosphatemia in patients receiving hyperalimentation. *Gastroenterology.* 1972;62:513–520.
9. Sand DW, Pastore RA. Paresthesias and hypophosphatemia occurring with parenteral alimentation. *Am J Dig Dis.* 1973;18:709–713.
10. Furlan AJ, Hanson M, Cooperman A, Farmer RG. Acute areflexic paralysis: association with hyperalimentation and hypophosphatemia. *Arch Neurol.* 1975;32:706–707.
11. Sheldon GF, Grzyb S. Phosphate depletion and repletion: relation to parenteral nutrition and oxygen transport. *Ann Surg.* 1975;182:683–689.
12. 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.
13. Silvis SE, DiBartolomeo AG, Aaker HM. Hypophosphatemia and neurological changes secondary to oral caloric intake. *Am J Gastroentenerol.* 1980;73:215–222.
14. Youssef HAE. Hypophosphatemic respiratory failure complicating PN: an iatrogenic potentially lethal hazard [letter]. *Anesthesiology.* 1982;57:246.
15. Hayek ME, Eisenberg PG. Severe hypophosphatemia following the institution of enteral feedings. *Arch Surg.* 1989;124:1325–1328.
16. Vanneste J, Hage J. Acute severe hypophosphatemia mimicking Wernicke's encephalopathy [letter]. *Lancet.* 1986;1:44.
17. Mattioli S, Miglioli M, Montagna P, Lerro MF, Pilotti V, Gozzetti G. Wernicke's encephalopathy during PN: observation in one case. *JPEN J Parenter Enteral Nutr.* 1988;12:626–627.
18. O'Connor LR, Wheeler WS, Bethune JE. Effect of hypophosphatemia on myocardial performance in man. *N Engl J Med.* 1977;297:901–903.
19. Newman JH, Neff TA, Ziporin P. Acute respiratory failure associated with hypophosphatemia. *N Engl J Med.* 1977;296:1101–1103.
20. 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.
21. Benesch R, Benesch RE. The effect of organic phosphates from the human erythrocyte on the allosteric properties of hemoglobin. *Biochem Biophys Res Commun.* 1967;26:162–167.
22. Lichtman MA, Miller DR, Cohen J, Waterhouse C. Reduced red cell glycolysis, 2,3-diphosphoglycerate and adenosine triphosphate concentration, and increased hemoglobin-oxygen affinity caused by hypophosphatemia. *Ann Intern Med.* 1971;74:562–568.
23. Thomas HM, Lefrak SS, Irwin RS, Fritts Jr HW, Caldwell PRB. The oxyhemoglobin dissociation curve in health and disease: role of 2,3-diphosphoglycerate. *Am J Med.* 1974;57:331–348.
24. Mandal AK. Hypokalemia and hyperkalemia. *Med Clin North Am.* 1997;81:611–639.
25. Halperin ML, Kamel KS. Potassium. *Lancet.* 1998;352:135–140.
26. Freedman BI, Burkart JM. Hypokalemia. *Crit Care Clin.* 1991;7:143–153.
27. Brophy DF, Gehr TWB. Disorders of potassium and magnesium homeostasis. In: Dipiro JT, Talbert RL, Yee GC, et al, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 5th ed. New York, NY: McGraw-Hill; 2002:981–993.
28. Gennari FJ. Hypokalemia. *N Engl J Med.* 1998;339:451–458.
29. Agarwal A, Wingo CS. Treatment of hypokalemia. *N Engl J Med.* 1999;340:154–155.
30. Wacker WEC, Parisi AF. Magnesium metabolism. *N Engl J Med.* 1968;278:658–663, 712–717, 772–776.
31. Graber TW, Yee AS, Baker FJ. Magnesium: physiology, clinical disorders, and therapy. *Ann Emerg Med.* 1981;10:49–57.
32. Reinhart RA. Magnesium metabolism: a review with special reference to the relationship between intracellular content and serum levels. *Arch Intern Med.* 1988;148:2415–2420.
33. Wacker WE. The biochemistry of magnesium. *Ann N Y Acad Sci.* 1969;162:717–726.
34. Reinhart RA, Desbiens NA. Hypomagnesemia in patients entering the ICU. *Crit Care Med.* 1985;13:506–507.
35. Ryzen E, Wagers PW, Singer FR, Rude RK. Magnesium deficiency in a medical ICU population. *Crit Care Med.* 1985;13:19–21.
36. Chernow B, Bamberger S, Stoiko M, et al. Hypomagnesemia in patients in postoperative intensive care. *Chest.* 1989;95:391–397.
37. Frankel H, Haskell R, Lee SY, et al. Hypomagnesemia in trauma patients. *World J Surg.* 1999;23:966–969.
38. Rubiez GJ, Thill-Baharozian M, Hardie D, Carlson RW. Association of hypomagnesemia and mortality in acutely ill medical patients. *Crit Care Med.* 1993;21:203–209.
39. Ceremuzynski L, Hao NV. Ventricular arrhythmias late after myocardial infarction are related to hypomagnesemia and magnesium loss: preliminary trial of corrective therapy. *Clin Cardiol.* 1993;16:493–496.
40. Kingston ME, Al-Siba'I MB, Skooge WC. Clinical manifestations of hypomagnesemia. *Crit Care Med.* 1986;14:950–954.
41. Salem M, Munoz R, Chernow B. Hypomagnesemia in critical illness: a common and clinically important problem. *Crit Care Clin.* 1991;7:225–252.
42. Seelig MS. Electrographic patterns of magnesium depletion appearing in alcoholic heart disease. *Ann N Y Acad Sci.* 1969;162:906–917.
43. Skou JC. Further investigations on a Mg^{++} + Na^{+}-activated adenosine triphosphate, possibly related to the active, linked transport of Na^{+} and K^{+} across the nerve membrane. *Biochem Biophys Acta.* 1960;42:6–23.
44. Weisinger JR, Bellorin-Font E. Magnesium and phosphorous. *Lancet.* 1998;352:391–396.
45. Anast CS, Winnacker JL, Forte LR, Burns TW. Impaired release of parathyroid hormone in magnesium deficiency. *J Clin Endocrinol Metab.* 1976;42:707–717.
46. Fatemi G, Ryzen E, Flores J, Endres DB, Rude RK. Effect of experimental human magnesium depletion on parathyroid hormone secretion and 1,25-dihydroxyvitamin D metabolism. *J Clin Endocrinol Metab.* 1991;73:1067–1072.

47. Reuler JB, Girard DE, Cooney TG. Wernicke's encephalopathy. *N Engl J Med.* 1985;312:1035–1039.
48. Romanski SA, McMahon MM. Metabolic acidosis and thiamine deficiency. *Mayo Clin Proc.* 1999;74:259–263.
49. Kitamura K, Takahashi T, Tanaka H, et al. Two cases of thiamine deficiency-induced lactic acidosis during PN. *Tohoku J Exp Med.* 1993;171:129–133.
50. Barrett TG, Forsyth JM, Nathavitharana KA, Booth IW. Potentially lethal thiamine deficiency complicating parenteral nutrition in children. *Lancet.* 1993;341:901–902.
51. Centers for Disease Control and Prevention. Deaths associated with thiamine-deficient PN. *MMWR Morb Mortal Wkly Rep.* 1989;38:43–46.
52. Centers for Disease Control and Prevention. Lactic acidosis traced to thiamine deficiency related to nationwide shortage of multivitamins for PN. *MMWR Morb Mortal Wkly Rep.* 1997;46: 523–528.
53. Heymsfield SB, Bethel RA, Ansley JD, Gibbs DM, Felner JM, Nutter DO. Cardiac abnormalities in cachectic patients before and during nutritional repletion. *Am Heart J.* 1978;95:584–594.
54. Huang YL, Fang CT, Tseng MC, Lee YJ, Lee MB. Life-threatening refeeding syndrome in a severely malnourished anorexia nervosa patient. *J Formos Med Assoc.* 2001;100:343–346.
55. Gottdiener JS, Gross HA, Henry WL, Borer JS, Ebert MH. Effects of self-induced starvation on cardiac size and function in anorexia nervosa. *Circulation.* 1978;58:425–433.
56. Apovian CM, McMahon MM, Bistran BR. Guidelines for refeeding the marasmic patient. *Crit Care Med.* 1990;18:1030–1033.
57. Nutrition Advisory Group, AMA Department of Foods and Nutrition. Multivitamin preparations for parenteral use, 1975. *JPEN J Parenter Enteral Nutr.* 1979;3:258–262.
58. Brooks MJ, Melnik G. The refeeding syndrome: an approach to understanding its complications and preventing its occurrence. *Pharmacotherapy.* 1995;15:713–726.
59. Hankin ME, Munz K, Steinbeck AW. Total body water content in normal and grossly obese women. *Med J Aust.* 1976;2:533–537.
60. 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.
61. 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.
62. 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;38: 299–306.
63. Foster GD, Wadden TA, Mullen JL, et al. Resting energy expenditure, body composition, and excess weight in the obese. *Metabolism.* 1988;37:467–472.
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, Papper S. 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, Enow NB, Shin B. Intravenous phosphate repletion regimen for critically ill patients with moderate hypophosphatemia. *Crit Care Med.* 1995;23:1204–1210.
70. Clark CL, Sacks GS, Dickerson RN, Kudsk KA, Brown RO. Treatment of hypophosphatemia in patients receiving specialized nutrition support using a graduated dosing scheme: results from a prospective clinical trial. *Crit Care Med.* 1995;23:1504–1511.
71. Kruse JA, Carlson RW. Rapid correction of hypokalemia using concentrated intravenous potassium chloride infusions. *Arch Intern Med.* 1990;150:613–617.
72. Hamill RJ, Robinson LM, Wexler HR, Moote C. Efficacy and safety of potassium infusion therapy in hypokalemic critically ill patients. *Crit Care Med.* 1991;19:694–699.
73. Kruse JA, Clark VL, Carlson RW, Geheb MA. Concentrated potassium chloride infusions in critically ill patients with hypokalemia. *J Clin Pharmacol.* 1994;34:1077–1082.
74. Ryan MP. Interrelationships of magnesium and potassium homeostasis. *Mineral Electrolyte Metab.* 1993;19:290–295.
75. Flink EB. Therapy of magnesium deficiency. *Ann N Y Acad Sci.* 1969;162:901–905.
76. Heaton FW. The kidney and magnesium homeostasis. *Ann N Y Acad Sci.* 1969;162:775–785.
77. Martin HE. Clinical magnesium deficiency. *Ann N Y Acad Sci.* 1969;162:891–900.
78. Dickerson RN, Brown RO. Hypomagnesemia in hospitalized patients receiving nutritional support. *Heart Lung.* 1985;14:561–569.
79. Rasmussen HS, McNair P, Norregard P, Backer V, Lindeneg O, Balslev S. Intravenous magnesium in acute myocardial infarction. *Lancet.* 1986;1:234–236.
80. Oster JR, Epstein M. Management of magnesium depletion. *Am J Nephrol.* 1988;8:349–354.
81. Sacks GS, Brown RO, Dickerson RN, et al. Mononuclear blood cell magnesium content and serum magnesium concentration in critically ill hypomagnesemic patients after replacement therapy. *Nutrition.* 1997;13:303–307.
82. Hebert P, Mehta N, Wang J, Hindmarsh T, Jones G, Cardinal P. Functional magnesium deficiency in critically ill patients identified using a magnesium-loading test. *Crit Care Med.* 1997;25: 749–755.
83. Huycke MM, Naguib MT, Stroemmel MM, et al. A double-blind placebo-controlled crossover trial of intravenous magnesium sulfate for foscarnet-induced ionized hypocalcemia and hypomagnesemia in patients with AIDS and cytomegalovirus infection. *Antimicrob Agents Chemother.* 2000;44:2143–2148.
84. Barnes BA. Magnesium conservation: a study of surgical patients. *Ann N Y Acad Sci.* 1969;162:786–801.

Refeeding in the ICU: an adult and pediatric problem

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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

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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

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Table 1 Conditions associated with the refeeding syndrome

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

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/m^2 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.

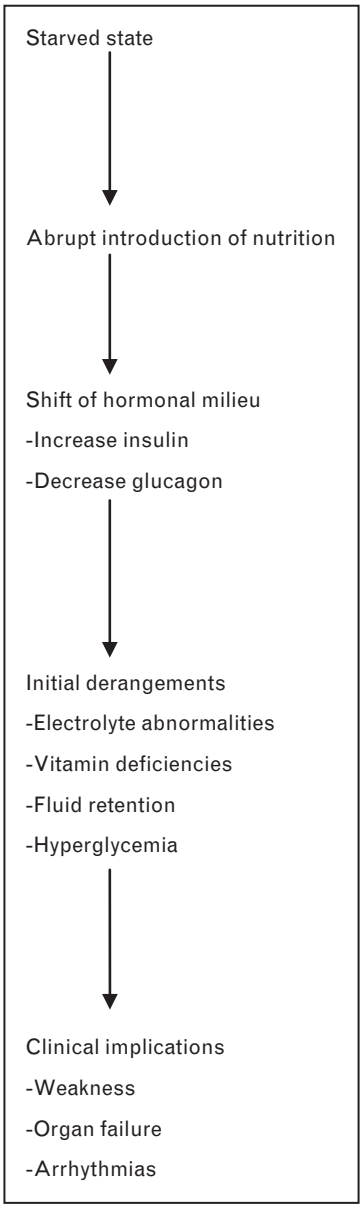
Pathophysiology

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

Figure 1 Steps in the refeeding syndrome



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. Gluconeogesis 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, gluconeogensis 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:
  (a) hypokalemia,
  (b) hypomagnesemia, and
  (c) hypophospatemia.
(2) Hyperglycemia.
(3) Cardiac:
  (a) heart failure, and
  (b) arrhythmia.
(4) Respiratory:
  (a) diaphragm fatigue,
  (b) respiratory failure, and
  (c) prolonged ventilatory weaning.
(5) Hematologic:
  (a) anemia and
  (b) red blood cell lysis.
(6) Immunologic:
  (a) immune suppression, and
  (b) infectious complications.
(7) Neurologic:
  (a) Wernicke's, encephalopathy.
(8) Musculoskeletal:
  (a) weakness, and
  (b) 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 hypophospatemia [32]. Rhabdomyolysis is also occasionally seen.

Arrhythmia

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.

Dysoxia

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 2 Guidelines for electrolyte replacement

Lab value	Adult replacement	Pediatric i.v. replacement	Recommended monitoring
Hypophosphatemia			
General (<2.7 mg/dl)	0.08–0.0.16 mmol/kg[a]	0.08–0.24 mmol/kg	Obtain serum phosphate level 2 h after completion of infusion
Mild 2.3–2.7 mg/dl	0.16–0.32 mmol/kg[a]		
Moderate 1.5–2.2 mg/dl	0.32–0.64 mmol/kg[a]		
Severe <1.5 mg/dl			
Hypokalemia			
General (<3.4–3.5 mEq/l)		0.3–0.5 mEq/kg/dose (infuse over at least 1 h)	Obtain serum potassium level 2 h after completion of infusion
Mild to moderate 2.5–3.4 mEq/l	20–40 mEq[b]		ECG to rule out arrhythmias
Severe <2.5 mEq/l	Up to 1–1.5 mEq[b]/kg/day		
Hypomagnesemia			
General (<1.8 mg/dl)		25–50 mg/kg up to max single dose of 2 g	Monitor serum magnesium levels every 8–12 h
Mild to moderate (1–1.8 mg/dl)	1 g i.v. magnesium sulfate every 6 h		
Severe (<1 mg/dl)	If symptomatic, treat with 8–12 g daily in divided doses		

Should reduce dose in the presence of renal dysfunction.
[a] Can be given as either intravenous NaPhos or KPhos.
[b] 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), cobalamine (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/m^2 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).

1 Fuentebella J, Kerner JA. Refeeding syndrome. Pediatr Clin North Am 2009; 56:1201–1210.

2 • Boateng AA, Sriram K, Meguid MM, *et al.* Refeeding syndrome: treatment considerations based on collective analysis of literature case reports. Nutrition 2010; 26:156–167.

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

3 Crook MA, Hally V, Panteli JV. The importance of the refeeding syndrome. Nutrition 2001; 17:632–637.

4 Miller SJ. Death resulting from overzealous total parenteral nutrition: the refeeding syndrome revisited. Nutr Clin Pract 2008; 23:166–171.

5 Best C, Hitchings H. Enteral tube feeding: from hospital to home. Br J Nurs 2010; 19:174; 176–179.

6 Majumdar S, Dada B. Refeeding syndrome: a serious and potentially life-threatening complication of severe hyperemesis gravidarum. J Obstet Gynaecol 2010; 30:416–417.

7 O'Connor G, Goldin J. The refeeding syndrome and glucose load. Int J Eat Disord 2010. [Epub ahead of print]

8 Patel U, Sriram K. Acute respiratory failure due to refeeding syndrome and hypophosphatemia induced by hypocaloric enteral nutrition. Nutrition 2009; 25:364–367.

9 Marinella MA. Refeeding syndrome: an important aspect of supportive oncology. J Support Oncol 2009; 7:11–16.

10 • Lubart E, Leibovitz A, Dror Y, *et al.* Mortality after nasogastric tube feeding initiation in long-term care elderly with oropharyngeal dysphagia: the contribution of refeeding syndrome. Gerontology 2009; 55:393–397.

This study evaluated a series of elderly patients and noted the incidence of hypophosphatemia and infectious complications.

11 Silk Z, Jones L, Heath D. Refeeding syndrome: an important complication after bariatric surgery. Surg Obes Relat Dis 2010. [Epub ahead of print]

12 Vincent RP, Aylwin SJ, le Roux CW. When the brakes came off: re-feeding oedema after deflation of a gastric band – a case report. Obes Surg 2009; 19:1468–1470.

13 Benjamin J, Singh N, Makharia GK. Enteral nutrition for severe malnutrition in chronic intestinal pseudo-obstruction. Nutrition 2010; 26:502–505.

14 Akobeng AK, Thomas AG. Refeeding syndrome following exclusive enteral nutritional treatment in Crohn disease. J Pediatr Gastroenterol Nutr 2010; 51:364–366.

15 Al Sharkawy I, Ramadan D, El-Tantawy A. 'Refeeding syndrome' in a Kuwaiti child: clinical diagnosis and management. Med Princ Pract 2010; 19:240–243.

16 Harbottle L, Brache E, Clarke J. Audit of parenteral nutrition use in Guernsey. Int J Pharm Pract 2009; 17:293–298.

17 Marik PE, Bedigian MK. Refeeding hypophosphatemia in critically ill patients in an intensive care unit. A prospective study. Arch Surg 1996; 131:1043–1047.

18 Hernandez-Aranda JC, Gallo-Chico B, Luna-Cruz ML, *et al.* Malnutrition and total parenteral nutrition: a cohort study to determine the incidence of refeeding syndrome. Rev Gastroenterol Mex 1997; 62:260–265.

19 Altinyazar V, Kiylioglu N, Salkin G. Anorexia nervosa and Wernicke Korsakoff's syndrome: atypical presentation by acute psychosis. Int J Eat Disord doi: 10.1002/eat.20783.

20 • Whitelaw M, Gilbertson H, Lam PY, *et al.* Does aggressive refeeding in hospitalized adolescents with anorexia nervosa result in increased hypophosphatemia? J Adolesc Health 2010; 46:577–582.

This study represented a series of patients that describes risk factors for the development of hypophosphatemia.

21 •• Gentile MG, Pastorelli P, Ciceri R, *et al.* Specialized refeeding treatment for anorexia nervosa patients suffering from extreme undernutrition. Clin Nutr 2010; 29:627–632.

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

22 Kishibe M, Sakai H, Iizuka H. Acute edema/cutaneous distention syndrome associated with refeeding in a patient with anorexia nervosa. Arch Dermatol 2009; 145:1202–1203.

23 Oud L. Transient hypoxic respiratory failure in a patient with severe hypophosphatemia. Med Sci Monit 2009; 15:CS49–CS53.

24 •• Vignaud M, Constantin JM, Ruivard M, *et al.* Refeeding syndrome influences outcome of anorexia nervosa patients in intensive care unit: an observational study. Crit Care 2010; 14:R172.

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

25 Elia M, De Silva A. Tight glucose control in intensive care units: an update with an emphasis on nutritional issues. Curr Opin Clin Nutr Metab Care 2008; 11:465–470.

26 Marwick TH, Woodhouse SP. Severe hypophosphataemia induced by glucose–insulin–potassium therapy. A case report and proposal for altered protocol. Int J Cardiol 1988; 18:327–330.

27 Mehanna HM, Moledina J, Travis J. Refeeding syndrome: what it is, and how to prevent and treat it. BMJ 2008; 336:1495–1498.

28 Adkins SM. Recognizing and preventing refeeding syndrome. Dimens Crit Care Nurs 2009; 28:53–58; quiz 9–60.

29 Heimburger DC, Koethe JR, Nyirenda C, *et al.* Serum phosphate predicts early mortality in adults starting antiretroviral therapy in Lusaka, Zambia: a prospective cohort study. PLoS One 2010; 5:e10687.

30 Tresley J, Sheean PM. Refeeding syndrome: recognition is the key to prevention and management. J Am Diet Assoc 2008; 108:2105–2108.

31 Grover Z, Ee LC. Protein energy malnutrition. Pediatr Clin North Am 2009; 56:1055–1068.

32 Worley G, Claerhout SJ, Combs SP. Hypophosphatemia in malnourished children during refeeding. Clin Pediatr (Phila) 1998; 37:347–352.

33 Sacks GS. Refeeding syndrome: awareness is the first step in preventing complications. J Support Oncol 2009; 7:19–20.

34 Saad L, Silva LF, Banzato CE, *et al.* Anorexia nervosa and Wernicke–Korsakoff syndrome: a case report. J Med Case Rep 2010; 4:217.

35 Heymsfield SB, Bethel RA, Ansley JD, *et al.* Cardiac abnormalities in cachectic patients before and during nutritional repletion. Am Heart J 1978; 95:584–594.

36 Osadchii OE. Mechanisms of hypokalemia-induced ventricular arrhythmogenicity. Fundam Clin Pharmacol 2010; 24:547–559.

37 Shechter M. Magnesium and cardiovascular system. Magnes Res 2010; 23:60–72.

38 Weisinger JR, Bellorin-Font E. Magnesium and phosphorus. Lancet 1998; 352:391–396.

39 Kohn MR, Golden NH, Shenker IR. Cardiac arrest and delirium: presentations of the refeeding syndrome in severely malnourished adolescents with anorexia nervosa. J Adolesc Health 1998; 22:239–243.

40 Casiero D, Frishman WH. Cardiovascular complications of eating disorders. Cardiol Rev 2006; 14:227–231.

41 Marinella MA. Refeeding syndrome and hypophosphatemia. J Intensive Care Med 2005; 20:155–159.

42 Bankhead R, Boullata J, Brantley S, *et al.* Enteral nutrition practice recommendations. JPEN J Parenter Enteral Nutr 2009; 33:122–167.

43 Gottschlich MM, editor. A.S.P.E.N. Nutrition Support Core Curriculum: a case-based approach – the adult patient. 1st ed. Silver Spring: American Society for Parenteral & Enteral Nutrition; 2007.

44 Mehanna H, Nankivell PC, Moledina J, *et al.* Refeeding syndrome: awareness, prevention and management. Head Neck Oncol 2009; 1:4.