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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.

Overview of Refeeding Syndrome

Starvation

Understanding the physiology of starvation provides insight into the morbid sequelae associated with refeeding a severely undernourished individ-

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

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 $\sim 27 \pm 1.1$ 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 ≤20 mEq/day, total fluid of ≤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 ≤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,[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.

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