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ASPEN Consensus Recommendations for Refeeding Syndrome

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Abstract

Introduction: In the spring of 2017, the American Society for Parenteral and Enteral Nutrition (ASPEN) Parenteral Nutrition Safety Committee and the Clinical Practice Committee convened an interprofessional task force to develop consensus recommendations for identifying patients with or at risk for refeeding syndrome (RS) and for avoiding and managing the condition. This report provides narrative review and consensus recommendations in hospitalized adult and pediatric populations. *Methods:* Because of the variation in definitions and methods reported in the literature, a consensus process was developed. Subgroups of authors investigated specific issues through literature review. Summaries were presented to the entire group for discussion via email and teleconferences. Each section was then compiled into a master document, several revisions of which were reviewed by the committee. *Findings/Recommendations:* This group proposes a new clinical definition, and criteria for stratifying risk with treatment and screening strategies. The authors propose that RS diagnostic criteria be stratified as follows: a decrease in any 1, 2, or 3 of serum phosphorus, potassium, and/or magnesium levels by 10%–20% (mild), 20%–30% (moderate), or >30% and/or organ dysfunction resulting from a decrease in any of these and/or due to thiamin deficiency (severe), occurring within 5 days of reintroduction of calories. *Conclusions:* These consensus recommendations are intended to provide guidance regarding recognizing risk and identifying, stratifying, avoiding and managing RS. This consensus definition is additionally intended to be used as a basis for further research into the incidence, consequences, pathophysiology, avoidance, and treatment of RS. (*Nutr Clin Pract.* 2020;35:178–195)

Keywords

consensus; magnesium; nutrition assessment; nutrition support; phosphorus; potassium; refeeding syndrome

Introduction

In 2017, the American Society for Parenteral and Enteral Nutrition (ASPEN) Parenteral Nutrition (PN) Safety Committee and the Clinical Practice Committee convened an interprofessional task force composed of dietitians, nurses, pharmacists, and physicians charged with developing consensus recommendations for screening and managing patients who are at risk of or have developed refeeding syndrome (RS). This paper summarizes the findings and consensus of the task force. Because of the heterogeneity of the literature, this report focuses on RS in hospitalized adult and pediatric populations. The following includes a proposed unifying clinical definition of RS as well as proposed updated criteria for RS risk. These consensus recommendations are intended to provide clinical guidance regarding preventing and managing RS for healthcare organizations and clinical professionals. The literature surrounding neonatal malnutrition and RS is complex. Specific recommendations for this population were deemed to be beyond the scope of this project, and the authors have made only general commentary.

These recommendations do not constitute medical or other professional advice and should not be taken as such.

To the extent that the information published herein may be used to assist in the care of patients, this is the result of the sole professional judgment of the attending healthcare professional whose judgment is the primary component of quality medical care. The information presented in these recommendations is not a substitute for the exercise of such judgment by the healthcare professional. Circumstances in clinical settings and patient indications may require actions different from those recommended in this document. In those cases, the judgment of the treating professional should prevail. This paper has been approved by the ASPEN Board of Directors.

Refeeding Syndrome Definition and Background

RS is historically described as a range of metabolic and electrolyte alterations occurring as a result of the reintroduction and/or increased provision of calories after a period of decreased or absent caloric intake. In this context, calories may be from any source: oral diet, enteral nutrition (EN), PN, or intravenous (IV) dextrose (eg, 5% dextrose solution). Despite the long-standing recognition of RS as a mechanism for potential serious complication of nutrition intervention, high-quality scientific evidence regarding the clinical syndrome is lacking. Most reports rely on retrospective, observational data and utilize widely discordant definitions of the syndrome. The lack of a standard definition impedes estimations of RS incidence, as well as efforts to develop well-designed, controlled trials that may lead to effective strategies for its recognition, avoidance, and treatment.

Hypophosphatemia is often considered the hallmark of this syndrome, and some authors have suggested that hypophosphatemia is the most common abnormal electrolyte in suspected cases.[1-3] However, this may be the result of definition bias or the relatively fewer causes of hypophosphatemia, compared with hypokalemia, making RS a more important cause of hypophosphatemia than it is of hypokalemia. Other electrolyte changes may be equally important.

RS was first described during World War II. Prisoners of war, concentration camp survivors, and victims of famine experienced unexpected morbidity and mortality during nutrition repletion.[4-6] In 1944, Keys et al reported[7] the results of a prospective, randomized control trial evaluating the physiologic effects of prolonged starvation on conscientious objectors and their subsequent rehabilitation. These were adults with strong antiwar sentiments who were allowed to substitute serving a social good rather than being drafted into the military. This landmark study, known as the Minnesota Starvation Experiment, stands as one of only a few studies to directly evaluate the symptoms seen during nutrition rehabilitation of malnourished patients and served as one of the bases of how clinicians understand RS today. It is unlikely that such a study would pass institutional review board scrutiny in the current era.

Since these initial reports, reporting on RS has focused mainly on those with eating disorders (particularly anorexia nervosa [AN]), adult patients who are severely malnourished because of underlying medical conditions, or geriatric patients with chronically decreased oral intake.

Case Reports

Numerous reports of RS have been published. Examples of these are presented here for illustration. A 28-year-old woman was admitted for severe progressive weight loss with lifelong history of idiopathic diarrhea, abdominal pain, nausea, and vomiting. Her admission weight of 23 kg was 40% of her ideal body weight, or estimated body mass index (BMI) < 10 kg/m^2. Initial laboratory tests included

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potassium of 2.9 mEq/L, and a phosphorus of 2.7 mg/dL (reference range not given; serum phosphorus levels can be reported in mmol and mg; normal serum phosphorus range is 2.5–4.5 mg/dL or 0.81–1.45 mmol/L).[8] PN (dextrose 500 g, potassium 130 mEq, phosphate 30 mmol, magnesium 16 mEq, thiamin 135 mg, and other vitamins) was initiated the night of admission. Twenty hours after the start of PN, the patient reported chest pain, and her phosphorus level was 1.1 mg/dL. Several hours later, she developed hypotension, cardiac arrhythmias, and metabolic acidosis. The infusion rate of PN was reported reduced in a stepwise fashion (details not provided). She received no supplemental phosphate, and her serum phosphorus level decreased further to 0.4 mg/dL. She developed respiratory failure requiring ventilator support, pulmonary infections, myocardial instability, and marked hypotension and died during the third week of hospitalization.[9]

A 66-year-old woman was admitted at 36 kg (70% of ideal body weight) with abdominal pain, a 6-week history of poor oral intake, and 3 months of profuse diarrhea following ileal conduit surgery for ureteral obstruction. She had diffuse muscle wasting and anasarca, potassium was 3.4 mEq/L, and phosphorus was 3.4 mg/dL (no reference range). Within 12 hours of admission, PN (dextrose 750 g, potassium 20 mEq, phosphate 15 mmol, and multivitamins) was initiated. After 48 hours, she became lethargic, hypotensive, and tachycardic. Her phosphorus was 0.7 mg/dL, potassium 1.4 mEq/L, and magnesium 1.8 mg/dL. Shortly thereafter, she became apneic, requiring intubation, and PN was held. Her hospital course was complicated by bilateral pneumonia, acute respiratory distress syndrome, and persistent hypotension and finally death on hospital day 6.[9]

These cases exemplify the most extreme forms of RS, in which organ failure and death ensue. It should also be noted that these patients were refed in a manner far more aggressive than is our current practice, and both had low levels of potassium and/or phosphorus before the initiation of calorie support. Low electrolyte levels, however, may not be present when RS ensues, so attention to other risk factors is likely important.

Methodology

Because of the heterogeneity of the definitions, the multitude of topics, and the paucity of high-quality controlled studies, multiple systematic reviews were not deemed feasible. Thus, the task force authors were divided into topical work groups. Each group conducted exhaustive literature reviews and held meetings via email and teleconference to review and reach consensus. Article searches were conducted through PubMed using keywords relevant to the topic at hand, such as "refeeding syndrome," refeeding hypophosphatemia," and "starvation." These sections were compiled into a master document and reviewed by the entire committee. The consensus process included teleconferences, surveys of the entire PN safety committee, and input from multiple ASPEN committees and the ASPEN Board of Directors. ASPEN defines the adult population to be above the age of 18 years old, the pediatric population to be between 28 days and 18 years old, and the neonatal population to be younger than 28 days.

Pathophysiology of Refeeding Syndrome

Under conditions of normal energy intake, metabolic substrates will change diurnally, cycling through postprandial, postabsorptive, and fasting states. With extended periods of nutrition deprivation, survival depends on the ability to efficiently use and preserve available energy reserves. As starvation becomes more profound, these energy stores, as well as vitamins and intracellular electrolytes, are depleted. The depletion of electrolytes is further exacerbated by conditions such as diarrhea, loss of intestinal contents (eg, fistula, vomiting, gastric drainage), or diuretic use, which cause additional losses.

When glucose appears in the bloodstream, insulin secretion rises in response.[10-12] In the presence of a total-body deficit of potassium, phosphorus, or magnesium, a drop in serum concentrations may occur because of rising insulin levels.[13-15] Rising insulin levels drive phosphorus and potassium intracellularly both by demand (ie, phosphorylation of glucose as glycolysis is initiated) and through the direct effects of insulin (ie, stimulation of the sodium-potassium adenosine triphosphatase [ATPase]). The mechanism for decrements in magnesium levels in this context has not been well elucidated. These decreases may occur even if serum levels are initially normal. The decrease in serum electrolytes may be sudden and severe and can be deadly for an individual who has been in a starved or catabolic state.[3,9,15]

Phosphorus is the principal ion implicated in many published reports related to RS. As stated, the focus on phosphorus may result from definition bias, and potassium and magnesium may be equally important. Phosphate is a vital component of adenosine triphosphate (ATP), the main storage form of energy in humans. As malnutrition progresses, the body will continuously draw on existing stores of phosphate to continue ATP production. Phosphate depletion can lead to respiratory muscle dysfunction, progressing to acute respiratory failure in severe cases.[16] It can also cause decreased cardiac contractility. Since phosphorus is important in the conduction of electrical impulses, low serum concentrations can also result in cardiac arrhythmias.[17,18] Depletion of phosphorus also decreases the production of 2,3-diphosphoglycerate, causing an increase in hemoglobin oxygen affinity, reduced oxygen release to tissues, and tissue hypoxia.[19]

Serum concentrations of potassium decrease because of insulin stimulation of the Na^+/K^+ ATPase,[16,20] a cell-wall enzyme that is responsible for flux of potassium into the cell and sodium out[18] and is essential in transmission of nerve impulses and contraction of muscles.[21,22] Hypokalemia may then result in impaired transmission of electrical impulses, increasing the risk of potentially lethal cardiac arrhythmias.[23,24] Hypokalemia may also manifest as weakness, hyporeflexia, respiratory depression, and paralysis.[25-27]

Hypomagnesemia has been identified as a feature of RS. As stated, neither the mechanism for its development in RS nor its direct importance in the morbidity of the syndrome have been elucidated. Hypomagnesemia impairs potassium reuptake in the nephron, resulting in excess losses, and may also impair cellular transport of potassium, all through impact on magnesium dependent enzymes such as Na-K-ATPase.[28]

Thiamin deficiency may also manifest as a result of RS. The demand for thiamin greatly increases during transition from starvation to feeding, as it is a cofactor for glucose-dependent metabolic pathways.[29,30] Thiamin deficiency can result in neurological abnormalities, including confusion, encephalopathy (Wernicke's syndrome and Korsakoff psychosis), oculomotor abnormalities (mainly horizontal ophthalmoplegia), hypothermia, and even coma.[31-33] Thiamin also plays a role in the conversion of lactate to pyruvate, and lactic acidemia may occur in those with thiamin deficiency, without acute liver injury.[34-36] Thiamin deficiency can also lead to a decreased production of ATP in cardiac myocytes, which may result in congestive heart failure, or wet beriberi. Inadequate ATP production in cardiac tissue can lead to release of adenosine into the plasma. Adenosine causes peripheral vasodilatation, elevated cardiac output, decreased cardiac contractility, dysrhythmias, and low diastolic blood pressure.[37-39]

Concerns about intravascular overload and congestive heart failure are sometimes reported in reviews of RS. However, these are not based on directly reported episodes and may be the result of a change in terminology related to heart failure. At the time of the first descriptions of RS, "heart failure" was used to describe what is now called "sudden death," or "lethal arrhythmia." Today, the term "heart failure" is solely associated with congestive heart failure and intravascular volume overload. Heart failure (meaning sudden death) was part of the original descriptions of RS. When the terminology shifted, congestive heart failure substituted for sudden death in the published definitions of RS. This substitution included the explanation that the sodium released into the extracellular space by the activation of Na^+/K^+-ATPase resulted in an osmotic shift of fluid into the extracellular space. However, this ignores the osmotic effect of potassium, exchanged for sodium, as it shifts into the cells. Although the exchange of sodium and potassium is not equal, favoring sodium, intravascular volume overload has not been reported. Furthermore, a large subcutaneous sodium storage system has been recently described.[40] Any acute addition of sodium, except for in sodium-avid patients (eg, those with preexisting congestive heart failure), is rapidly scavenged and made non-osmotic. It is not felt that intravascular fluid overload should be considered a sequela of RS.

Subacute or refeeding edema has been observed as a late manifestation associated with RS in patients with starvation, mainly in patients with AN, but this is believed to be due to capillary leak or inactivation of natriuretic peptide from hyperinsulinemia rather than due to volume overload.[41]

Screening and Assessment

Screening strategies to identify patients at risk for RS are imprecise and poorly validated, made worse by lack of a consensus definition for RS. Typically, RS risk is identified subjectively by a clinician at the time of enteral or PN evaluatión and initiation.[42,43]

Criteria specifically developed for predicting RS have been published. Britain's National Institute for Health and Care Excellence (NICE) is one example.[44] These recommendations were formulated based on previously published reviews and the expertise of the authors and agreed on by informal consensus. Screening criteria developed for malnutrition have also been tested for predictive value in RS. One such example is the Short Nutritional Assessment Questionnaire (SNAQ), which is validated for diagnosing malnutrition and a test for the screening of risk for RS.[45]

The value of these screening tools for predicting severe hypophosphatemia is poor. Their utility in predicting less severe hypophosphatemia or for predicting hypokalemia or hypomagnesemia is unknown, and their utility has been questioned.[46] Both NICE and SNAQ scored poorly for sensitivity or specificity on retrospective validation analyses. In a 2011 review of 321 hospitalizations, only about 25% of 92 patients deemed at risk by NICE criteria developed severe hypophosphatemia (<0.6 mmol/L; reference range 0.74–1.52 mmol/L) during refeeding (sensitivity = 50% and specificity = 76% for PN, and sensitivity = 38% and specificity = 73% for nasogastric (NG) feeds).[47] The validity of both NICE and SNAQ were reported in 2016. An "at-risk" SNAQ score had a positive predictive value of 13%; however, low SNAQ had a negative predictive value of 95%.[48]

Other criteria sets for diagnosing malnutrition, such as that proposed by ASPEN and the Academy of Nutrition and Dietetics[49] and the newer guideline from the Global Leadership Initiative on Malnutrition (GLIM),[50] may be predictive of RS. But these have not been studied for their predictive value.

Incidence of Refeeding Syndrome

In the absence of a universally accepted definition for RS, descriptions of incidence are fraught. It is generally agreed that hypophosphatemia is one of the hallmarks of the syndrome. Thus, many studies in which the authors have created their own definitions use hypophosphatemia as the sole diagnostic criteria. In a 1996 study in which RS was defined as hypophosphatemia within 72 hours of starting nutrition, and hypophosphatemia defined as serum phosphorus level that fell by >0.16 mmol/L to <0.65 mmol/L, RS was present in 34% of critically ill patients.[51] Using the same definition, a subsequent study reported an incidence of RS of 8% in their at-risk (by SNAQ) population.[51] In a prospective cohort study using severely low electrolytes (potassium, magnesium, and phosphorus), fluid overload, and disturbance of organ function as diagnostic criteria, a rate of 2% out of 243 at-risk patients (by NICE criteria) was seen.[52] Clearly, these studies are not comparable.

Reporting of RS incidence in the pediatric population is even more sparse. A report by Dunn et al,[53] in 2003, is one of the only such studies. In their cohort of 164 consecutive intensive care unit (ICU) patients started on PN, 15 were deemed at risk for RS using criteria developed at their institution. They report the incidence of "electrolyte shifts" within 72 hours of the initiation of nutrition support in the entire population to be 27% and 8 of 15 in the at-risk population, despite cautious feeding tactics. Of those who developed hypophosphatemia, 3 developed cardiac abnormalities and lethargy.[53]

The neonatal time period is generally accepted to be the interval from birth to 4 weeks of age. However, significant physiologic differences exist between neonates before and after 2 weeks of age. Studies examining rates of electrolyte abnormalities in the neonate have focused mainly on neonates that are small for gestational age (SGA; equivalent to less than the 10th percentile on the standard growth curve), those with intrauterine growth retardation (IUGR), those with extreme prematurity (24–27 weeks), and those with very low birth weight (VLBW; <1500 g). IUGR can be the result of chronic malnutrition in utero or the result of acute or late-onset placental insufficiency. Inadequate growth before birth may be related to placental insufficiency or a maternal comorbid diagnosis such as preeclampsia.[54]

Several studies have reported electrolyte abnormalities in neonates. Two have reported that rates of hypophosphatemia were significantly higher in patients that were SGA.[55,56] Those with a high umbilical artery resistance index (UA-RI; defined as a value above the 95th percentile) were also at risk for developing early hypophosphatemia. Urinary excretion of phosphorus and potassium was lower in these patients, suggesting that low levels were not caused by urinary loss.[55] In a subsequent observation, higher rates of electrolyte abnormalities were found, including hypophosphatemia, in patients with IUGR and VLBW.[57] Others have reported hypophosphatemia and hypokalemia in neonates receiving PN. These authors have stressed the importance of close monitoring and electrolyte repletion.[58,59]

Predictive Biomarkers

The use of biomarkers for screening, risk assessment, and monitoring of clinical improvement might be useful in clinical decision making. Conversely, routine use of low-sensitivity screening techniques may lead to unnecessary interventions, such as slow advancement of feedings toward the nutrition goal. Further, routine use of nonspecific screening has been shown to increase hospital length of stay and mortality.[60-63]

Currently, the literature is too spare to recommend the routine use of biomarkers for clinical use for predicting RS. For the most part, biomarkers have only been studied for predicting risk of malnutrition and, by extension, are theorized to identify risk for RS. Thus, the weak sensitivity of these markers (eg, Insulin-like growth factor 1 (IGF-1) and leptin) for malnutrition also makes them currently inappropriate as screening tools for RS.

Populations Potentially at Risk for Refeeding Syndrome

In the hospital setting, where close attention to electrolyte levels is standard of care, complications of refeeding may, in fact, be rare.[64,65] Until a unifying definition for RS is used in studies, the incidence will be poorly understood and identifying characteristics of patients at risk very challenging. However, the consistent characteristic of risk that emerge from clinical experience and scientific observation include prolonged undernourishment, particularly in the face of ongoing electrolyte loss. The following describe populations identified as potentially at risk or unlikely to be at risk. It should again be stressed that the incidence of RS in these populations is not known. Published case reports are provided for illustration.

Anorexia Nervosa

AN is associated with self-inflicted energy restriction resulting in weight loss and malnutrition and is one of the population groups most studied for incidence of RS. These patients have isolated starvation, mostly in the absence of other medical comorbidities, which distinguishes them from other hospitalized patients. There have been several reports on the incidence of different components of RS in this population.[1,54,66-69] Predictably, these are quite variable. For example, one series reported a rate of hypophosphatemia of 5.8% in their study group of 69 patients (mean age 15.5 years old). Importantly, degree of malnourishment correlated with severity of hypophosphatemia.[70] In another series, the

authors report a 38% incidence of mild hypophosphatemia (2.5–3.4 mg/dL) and no severe hypophosphatemia (<1.0 mg/dL) during initiation of nourishment in 46 patients (mean age 15.7 years, mean body weight = 72.9% of ideal).[71]

Mental Health Disorders

Patients with severe mental disorders may be at elevated risk for RS due to poor nourishment resulting from self-neglect, medication side effects, food avoidance due to hallucinations, avoidance of attending meals with others due to social anxiety, lack of skills of daily living (such as shopping and cooking skills), and homelessness with inconsistent access to nutritious meals.[72,73]

A 25-year-old woman with schizophrenia was admitted to a medical ward with a BMI of 12.5 and a history of significant weight loss over the past year. Phosphorus was not measured at admission. Slow initiation of intake was recommended because of perceived risk for RS. On day 2, she ingested approximately 670 calories, consisting mainly of simple sugars and fats, in addition to her daily approved meals of 600 kcal/d. The day following this binge meal, she developed severe hypokalemia and severe hypophosphatemia, psychiatric imbalance, lower extremity edema, and ophthalmoplegia. After several days of repletion, she had improved enough to be transferred to the psychiatric ward.[74]

Alcohol and Substance-Use Disorders

An elevated risk for RS in patients with alcohol-use disorder is believed to originate in a diet deficient in essential vitamins and minerals. Studies of the incidence of RS in alcoholic patients are lacking. However, the authors recommend that risk for RS be considered in alcoholic patients with evidence of global malnourishment. Similarly, patients who abuse methamphetamine, heroin, and other mood-altering substances are also at higher risk of undernourishment[75] and may, therefore, be at higher risk for RS.

A cachectic (BMI 16 kg/m^2) 44-year-old homeless man had an initial phosphorus level in the low normal range (0.84 mmol/L; reference range: 0.80–1.50 mmol/L). After 4 days of a standard diet supplemented with IV saline, potassium, oral multivitamins, and 100 mg of intramuscular thiamin, the patient's phosphorus level dropped to 0.15 mmol/L. Coincident with this precipitous drop, he complained of lower-limb myalgias and paresthesias and diarrhea. He was noted to have mood lability and QTc prolongation on electrocardiogram (ECG). In total, he required 42 mmol of phosphorus given intravenously over 36 hours. His symptoms improved with continued nourishment and electrolyte repletion, and he was eventually discharged to a rehabilitation facility.[76]

Bariatric Surgery and Bowel Resections

RS has been described in obese patients who have underdone bariatric surgical procedures.[77,78] As with other conditions, the incidence and risk factors are unknown. One such case described a 48-year-old woman, admitted at 117 kg and a BMI of 41.5 for lithium overdose and protracted diarrhea, vomiting, and confusion. She had several bariatric surgeries in the 13 years antecedent, including gastric banding with subsequent slippage and removal and biliopancreatic diversion and revision. She had been lost to follow-up for the 2 years before admission, and her weight during that period unknown, but her admission weight was higher than the 98 kg last measured. Deficiencies of vitamins B1, B6, B12, D, and K and zinc, selenium, and iron, as well as severe hypoproteinemia, were noted. Based on physical findings, she was diagnosed with Wernicke's encephalopathy. She initially received PN, vitamin supplementation, and high-dose thiamin supplementation and was then converted to tube feeding providing 1200 kcal/d (10 kcal/kg). Over the next 10 days, she developed severe hypophosphatemia (0.9 mg/dL; normal range 2.5–4.5 mg/dL), as well as hypokalemia and hypomagnesemia (levels not specified) and pulmonary edema resulting in respiratory failure. She improved after aggressive electrolyte repletion and continued nutrition support.[79]

This case highlights that RS can develop in the setting of elevated BMI. These patients may have chronic malnutrition and malabsorption. Furthermore, it is believed that the rapid changes in weight that occur initially after bariatric surgery may predispose to RS if a sudden increase in intake (eg, from nutrition support) is experienced, especially in the presence of electrolyte loss (eg, from vomiting). Patients who have undergone bowel resections (eg, for mesenteric ischemia) can also exhibit similar patterns of malnutrition and refeeding difficulties that can predispose to RS.[80]

Malabsorption

Adults and pediatric patients with malabsorptive syndromes, such as celiac disease, may also be at elevated risk for RS. Electrolyte and vitamin stores may be rapidly depleted in an acute crisis. A 28-year-old woman with refractory celiac disease was admitted with severe dehydration, diarrhea, malnutrition, and hypovolemic shock that was suspected to be due to nonadherence to a gluten-free diet. At admission, her BMI was 14 kg/m^2, and her labs were significant for renal insufficiency, metabolic acidosis, and hypokalemia. Phosphorus and glucose levels were within normal ranges. Electrolyte disturbances and acid-base disorders were corrected over the first 2 days. PN providing 450 kcal/d was started on day 3. On day 5, the patient developed psychomotor agitation, respiratory distress, and cardiogenic shock with an ejection fraction of 20%.

Phosphorus and potassium levels were severely low. Mechanical ventilation and inotropic agents were started; however, the patient died 2 days later with multiple-organ failure.[81] Additional cases of RS in pediatric patients with celiac disease have been described.[82,83]

Starvation in Protest, Famine, and Migration

Starvation related to protest or activism places individuals at risk for RS. For example, a 30-year-old man undertook a well-publicized, voluntary protest in the form of a 44-day fast in 2007. Over the course of the protest, he lost 25% of his original body weight and drank only water. Refeeding was done orally using a commercial 1.2-kcal/mL oral feeding supplement, along with 50-mg thiamin twice a day and a daily multivitamin. He received approximately 570 kcal overnight on day 0 and on day 1, 1140 kcals on day 2, and 1710 kcal on day 3, and then the feeds stopped and a 1500 kcal light diet was started on day 4. On the evening of day 1, his phosphorus dropped from its initial level of 1.0 to 0.46 mmol/L (reference range: 1.2–1.7 mmol/L), which prompted administration of 1 unit of a phosphate infusion (phosphate 50 mmol, potassium 9.5 mmol, and sodium 81 mmol per 500 mL) over 12 hours and oral phosphate (16 mmol) twice daily on days 2–4. Although he had no serious clinical sequelae, he had multiple laboratory derangements, including elevated bilirubin and liver enzymes.[84]

Child Abuse and Starvation

Victims of child abuse and starvation are at risk for malnutrition and, by proxy, for RS during their recovery period. Starvation affects millions of children throughout the world, in developing and developed countries. Child starvation often results from neglect by the child's caregivers when not due to economic factors or famine.[85]

Military Recruits

Malnutrition in military recruits may be overlooked, since this is an otherwise healthy population. A 26-year-old male Marine recruit had been in training for 10 weeks when he presented to the emergency department (ED). His superiors found him fatigued, hypothermic, and confused during a march. After initial resuscitation and rewarming, his confusion resolved, and he reported losing approximately 20 lb (9.1 kg) over the 3 months before starting training because he was over the weight standards. He also reported a further 35 lb (15.9 kg) weight loss during the 10 weeks of training due to a severely restricted diet. On admission, he was found to have rhabdomyolysis and developed pneumonia. He was not considered to be at risk for RS, as he had been on a regular diet, and was discharged after 3 days. On day 4, he began to complain of increasing weakness and edema and was found to have a critical hypophosphatemia. Despite IV repletion, phosphorus levels did not normalize for 3 days. In total, he received 9 doses of 12 mmol of phosphate, 8 g of magnesium, and 200 mEq of potassium. His symptoms began to resolve around day 9, and he was discharged on limited duty.[86] This highlights that large amounts of repletion may be required to return serum levels to normal. Although it is highly likely that this is rare among military recruits, and very few are at risk for malnutrition, this case is highlighted to remind clinicians to avoid missing the diagnosis of malnutrition and RS because of the youth and overall health of the patient.

Athletes

Athletes are highlighted for the same reasons as the military population. A 28-year-old male bodybuilder with no past medical or surgical history presented to the ED with a 2-day history of severe, progressive bilateral lower-leg weakness and reduced handgrip strength. Laboratory values were significant for extremely low phosphorus, magnesium, and potassium. He had just finished a fitness competition 2 days prior and had lost 19 kg (≈14% of his body weight) during the 4-month period leading up to the competition. On competition days, the patient's diet consisted primarily of simple carbohydrates (eg, chocolate bars) followed by 800 g of a variety of carbohydrates thereafter for 5 days. He was admitted to the ICU for a total of 2 days for aggressive electrolyte repletion and was discharged on hospital day 4.[87]

Renal Failure/Hemodialysis

Although malnutrition is prevalent in patients receiving hemodialysis (HD) for advanced renal dysfunction[88,89] and is associated with increased mortality,[90,91] RS is likely uncommon in patients dependent on HD, even in the face of malnutrition, because of the poor clearance of phosphorus and potassium via HD. Hyperphosphatemia and high potassium levels are common.

RS may be more likely to occur in patients receiving continuous venovenous hemofiltration and peritoneal dialysis, because clearance of phosphorus and potassium is significantly greater than with intermittent HD, but the incidence is not known. Hypophosphatemia may occur in patients on intermittent HD in the presence of significant 1,25-hydroxy-vitamin D deficiency.

The Critically Ill

The critically ill patient is often without adequate nourishment for extended periods of time and so can be assumed to be at risk for RS when calories are reintroduced. This is true for medical and surgical patients. da Silva described a critically ill patient with a past medical history of alcohol and opioid use disorder and with malnutrition. She was admitted for altered mental status after a presumed

overdose. On arrival to the ED, she was in hypercapnic respiratory failure and was intubated. Initial potassium was low at 2.4 mEq/L (normal: 3.5–50 mEq/L), and phosphorus concentration was normal (normal: 2.5–4.5 mg/dL). EN was started after several days of mechanical ventilation in the ICU. Prefeeding electrolytes showed potassium slightly elevated at 5.5 mEq/L and a normal phosphorus of 2.5 mg/dL. The following morning, the patient suffered a brief cardiac arrest with an electrocardiogram showing a polymorphic, wide complex ventricular tachycardia indicative of torsades de pointes. Repeat labs showed a potassium of 2.6 mEq/L and a phosphorus of 2 mg/dL. Although the rate of EN was reduced by 50% and her electrolytes were aggressively replaced, the patient did not survive the hospitalization.[92]

Malignancy

Patients with malignancy can be at risk for RS due to prolonged starvation and/or electrolyte losses. Chemotherapy induces nausea, vomiting, anorexia, mucositis, and diarrhea, all of which increase losses of electrolytes. Radiation induces gastrointestinal (GI) toxicity and mucositis, as well as anorexia. Comorbidities specific to the type of malignancy (such as bowel obstructions) can also contribute to global malnutrition.[93]

A patient receiving chemotherapy for adenocarcinoma of the esophagus was admitted with severe mucositis. The patient had lost 18% of his body weight (BMI 21.9 kg/m^2) over the previous 3 months and ate minimally for 8 days before admission. Electrolytes were initially normal. He became septic on day 4 and was transferred to the ICU, where PN was started at 15 kcal/kg/d. After 2 days of PN, phosphorus became extremely low. PN was held and serum phosphorus concentration improved to some extent with parenteral replacement. PN was restarted 3 days later at 15 kcal/kg/d. Serum electrolyte concentrations decreased again a week later, and the patient gained 9 kg, presumably fluids. Electrolytes were normalized with repletion during continued nourishment, and the patient was discharged after 3 weeks.[63] Additional case reports of RS in this population have been published.[1,94]

Patients in the Emergency Department

The ED is often the first contact patients have with hospital care. RS and Wernicke's encephalopathy may ensue if patients at risk are not identified before the initiation of calories. Patients may also present to the ED with RS with altered mental status, if due to Wernicke's or severe metabolic derangement, and a history may be difficult to obtain. The care of patients with undifferentiated altered mental status or patients with electrolyte abnormalities should follow current best practices. In patients who have risk for thiamin deficiency, such as chronic alcohol users, or those with severe chronic starvation from any cause, thiamin supplementation should be considered by the emergency room clinician. Generally, however, the patient will only be in the ED long enough for a single dose, and repletion of thiamin, or other vitamins and minerals, may take up to several weeks. In patients that are cachectic or in whom there are concerns for significant malnutrition, caution in administration of glucose-containing fluids is warranted, although it is likely unusual that significant RS would be seen after a short period of infusion of dextrose-containing fluids.

Obtaining a thiamin level is also not an appropriate test to be performed for ED management but may be helpful for subsequent care. In most institutions, the test is performed at an independent laboratory, with results returning several days later. Decisions about preemptive thiamin supplementation should be made based on clinical judgment of risk for Wernicke's, until better screening techniques are available.

Avoidance of Refeeding Syndrome

There is poor consensus and conflicting research to drive decisions related to feeding rates for avoiding RS. Moreover, research evaluating aggressive refeeding rates has been performed in patients with AN and focused on adolescents with isolated starvation. Studies examining conservative approaches focus on patients who are older, are much more acutely medically ill, and have multiple comorbidities and physiologic stressors. Overall, an individualized approach to refeeding patients is suggested.

Regardless of the route of energy intake, there are multiple factors to be considered when initiating and advancing energy intake in those at risk for RS. Crucial among these are physiologic response (eg, serum electrolyte changes and cardiac rhythm) and tolerance to the initial feeding.

As stated, there is currently no universal recommendation for how to advance the nutrition regimen in a safe way. Many of the available recommendations are general and vague, providing advice such as increase slowly,[43] advance gradually,[3] or provide modest energy increases[95] and obtain goal needs in 3–7 days.[96] For example, a review article by McCray et al recommended advancing feedings by 200–300 calories every 3–4 days. However, this recommendation stems solely from clinical experience.[97] Others recommend supplementing electrolytes while increasing energy with the addition of phosphate 10–15 mmol for every 1000 calories provided.[95] Table 1[44,97-100] outlines the multiple published proposed approaches for safely reintroducing energy to the high-risk patient.

Not only is the literature inconclusive, but reintroducing nutrition at a "low rate with slow advancement" may be at odds with the expedient weight gain desired in high-risk populations, such as those with AN.[101,102] Conversely, several recent randomized trials in the critically ill support

Table 1. Published Recommendations for Initiation and Advancement of Nourishment for Patients at Risk for RS.

	Initial Calories	Feeding Advancement	Other Recommendations
NICE[44]	• Maximum 10 kcal/kg/d • 5 kcal/kg/d in "extreme" cases (examples, BMI < 14 kg/m^2 or negligible intake for >15 days)	• Slowly to meet or exceed full needs by 4–7 days	• Restore circulatory volume
IrSPEN[98]	• Extreme risk: 5 kcal/kg/d • High risk: 10 kcal/kg • Moderate risk: 20 kcal/kg	• Slow initiation of feeding according to risk category	• Check electrolyte levels • Electrolyte replacement to correct deficiencies • Monitor fluid balance
CNSG[99]	• Extreme risk: consider providing only 5 kcal/kg/d • High risk: commence nutrition support at a maximum of 10 kcal/kg body weight • Moderate risk: introduce at a maximum of 50% of requirements for the first 2 days	• Extreme or high risk: slowly over 4–7 days as clinical and biochemical monitoring allows • Moderate risk: increase energy intake only as clinical conditions and electrolyte results allow	• Energy and fluid must be introduced very gradually • Check potassium, magnesium, phosphorus • Do not discontinue feeding if electrolyte levels fall • When serum potassium, magnesium, or phosphorus levels are significantly low, feeding should not be advanced further until supplementation has occurred
Cray[96]	• ≈10 kcal/kg/d for severe cases • 15–20 kcal/kg for others	• Increase calories cautiously in a stepwise manner by 200–300 kcal every 2–3 days	• Consider all sources of calories and fluids in your calculations (including dextrose) • Check baseline electrolytes (especially phosphorus, potassium, and magnesium) before initiating nutrition support, and replace any low levels promptly • Unless hemodynamically unstable, keep sodium-containing IV fluids to ≈1 L/d initially in severely malnourished patients, such as those with anorexia nervosa, who may have a component of cardiomyopathy
Friedli [100]	• Ranging from 5 to 25 kcal/kg/d depending on severity of RS risk	• Nutrition therapy should be started with reduced caloric targets and slow increase to the full caloric amount over 5–10 days according to the individual risk category for RS • Fluid overload should be prevented by restricted use of fluid and sodium restrict diet within the first 7 days	• Patients at high risk for RS should receive electrolytes substitution of lower than normal/in low normal range • Prophylactic supplementation of electrolytes

BMI, body mass index; CNSG, clinical nutrition steering group; IrSPEN, Irish Society for Clinical Nutrition and Metabolism; IV, intravenous; NICE, National Institute for Health and Care Excellence; RS, refeeding syndrome.

a slow initiation and advancement of nutrition support therapy.[103-105]

Aggressive Refeeding Protocols

For the most part, studies of aggressive refeeding have focused on patients with AN. A retrospective comparison reviewed the effect of a lower vs relatively higher-caloric diet in patients with AN.[106] Three hundred ten patients between the ages of 10 and 21 years with an average BMI of approximately 16 kg/m^2 were included. The average premorbid dietary intake was approximately 900 kcal/d and weight loss was 1.6 kg/mo. The interventional diet in the high-calorie group (222 patients) provided a mean of 1557

Table 2. Signs and Symptoms of Severe Refeeding Syndrome.[a]

Hypophosphatemia	Hypokalemia	Hypomagnesemia	Thiamin Deficiency	Sodium Retention
Neurological	Neurological	Neurological	Encephalopathy	Fluid overload
Paresthesias	Paralysis	Weakness	Lactic acidosis	Pulmonary edema
Weakness	Weakness	Tremor	Nystagmus	Cardiac decompensation
Delirium	Cardiac	Muscle twitching	Neuropathy	
Disorientation	Arrhythmias	Changed mental status	Dementia	
Encephalopathy	Contraction changes	Tetany	Wernicke's syndrome	
Areflexic paralysis	Respiratory failure	Convulsions	Korsakoff psychosis	
Seizures	Gastrointestinal	Seizures	Wet and dry beriberi	
Coma	Nausea	Coma		
Tetany	Vomiting	Cardiac		
Cardiac	Constipation	Arrhythmias		
Hypotension	Other	Gastrointestinal		
Shock	Rhabdomyolysis	Anorexia		
Decreased stroke volume	Muscle necrosis	Nausea		
Decreased mean arterial Pressure		Vomiting		
Increased wedge pressure Pulmonary		Constipation		
Diaphragmatic weakness				
Respiratory failure				
Dyspnea				
Hematologic				
Hemolysis				
Thrombocytopenia				
Leukocyte dysfunction				

Adapted with permission from Reference 96. Kraft MD, Btaiche IF, Sacks GS. Review of the refeeding syndrome. *Nutr Clin Pract*. 2005;20(6):625-633.

[a] In the pediatric population, manifestations of end organ involvement more commonly cause bradycardia, temperature abnormalities, and involvement of the respiratory system.

calories, and the lower-calorie group received a mean of 1163 calories. There was a trend toward more frequent hypophosphatemia, hypomagnesemia, and hypokalemia in the high-calorie group, but the difference was not statistically significant. Their findings suggested that higher-caloric diets on admission were associated with reduced length of stay, without a statistically significant increase in hypokalemia, hypophosphatemia, and hypomagnesemia.[106]

In another cohort of 361 patients (461 admissions) with an average BMI of 16.1 kg/m^2, all patients initially received 1200–1500 calories/d and were aggressively advanced to 3500–4000 calories over 10–13 days. In total, 7.9% of cases had hypophosphatemia at admission, and 18.5% developed it during the treatment. With refeeding, 54 patients developed mild hypophosphatemia (>2.0 mg/dL), 16 developed moderate hypophosphatemia (1–1.9 mg/dL), and none developed severe hypophosphatemia (<1.0 mg/dL). Mean weight gain was 1.98 kg/wk, with 71.8% of patients reaching a BMI kg/m^2 of 19 and 58.5% reaching a BMI kg/m^2 of 20. They found that lower admission BMI was more predictive of hypophosphatemia than rate of weight gain. There were no deaths or serious morbidity. The study was limited in that not all patients had serum phosphorus, magnesium, and/or potassium levels drawn on admission, nor did all patients have these values monitored consistently during their hospital stay.[107]

Cautious Refeeding Protocols

Judicious refeeding rates have also been studied for the most part in the critically ill. In one of the only randomized control trials, Doig et al in 2015 studied RS in critically ill patients from 13 tertiary-care hospitals across Australia. Their definition of RS was new-onset hypophosphatemia developing <72 hours after initiation of nutrition. They measured hospital morbidity and mortality as well as mortality at 60-day follow-up in 339 patients who had phosphorus levels drop to <0.65 mmol/L within 72 hours after initiation of nutrition support. The intervention group received energy restricted to 20 kcal/h for at least 2 days, and if no phosphate repletion was required in those 2 days, then energy intake was returned to normal over 2–3 days. The return to normal was defined as 40 kcal/h for 24 hours, then increased goals to 60 kcal/h for 24 hours, followed by 80% of calculated energy goals for another 24 hours, with 100% of goals achieved by day

Table 3. ASPEN Consensus Criteria for Identifying Adult Patients at Risk for Refeeding Syndrome.[49,71,110]

	Moderate Risk: 2 Risk Criteria Needed	Significant Risk: 1 Risk Criteria Needed
BMI	16–18.5 kg/m^2	<16 kg/m^2
Weight loss	5% in 1 month	7.5% in 3 months or >10% in 6 months
Caloric intake	None or negligible oral intake for 5–6 days **OR** <75% of estimated energy requirement for >7 days during an acute illness or injury **OR** <75% of estimated energy requirement for >1 month	None or negligible oral intake for >7 days **OR** <50% of estimated energy requirement for >5 days during an acute illness or injury **OR** <50% of estimated energy requirement for >1 month
Abnormal prefeeding potassium, phosphorus, or magnesium serum concentrations[a]	Minimally low levels or normal current levels and recent low levels necessitating minimal or single-dose supplementation	Moderately/significantly low levels or minimally low or normal levels and recent low levels necessitating significant or multiple-dose supplementation
Loss of subcutaneous fat	Evidence of moderate loss	Evidence of severe loss
Loss of muscle mass	Evidence of mild or moderate loss	Evidence of severe loss
Higher-risk comorbidities (see Table 4)	Moderate disease	Severe disease

ASPEN, American Society for Parenteral and Enteral Nutrition; BMI, body mass index.
[a]Please note that electrolytes may be normal despite total-body deficiency, which is believed to increase risk of refeeding syndrome.

Table 4. Diseases and Clinical Conditions Associated With an Increased Risk of Refeeding Syndrome.[15,109-111]

Acquired immunodeficiency syndrome
Chronic alcohol or drug use disorder
Dysphagia and esophageal dysmotility (eg, eosinophilic esophagitis, achalasia, gastric dysmotility)
Eating disorders (eg, anorexia nervosa)
Food insecurity and homelessness
Failure to thrive, including physical and sexual abuse and victims of neglect (particularly children)
Hyperemesis gravidarum or protracted vomiting
Major stressors or surgery without nutrition for prolonged periods of time
Malabsorptive states (eg, short-bowel syndrome, Crohn's disease, cystic fibrosis, pyloric stenosis, maldigestion, pancreatic insufficiency)
Cancer
Advanced neurologic impairment or general inability to communicate needs
Postbariatric surgery
Postoperative patients with complications
Prolonged fasting (eg, individuals on hunger strikes, anorexia nervosa)
Refugees
Protein malnourishment

4. If the patient's phosphorus did drop to <0.71 mmol/L at any time during nutrition advancement, then calories were restricted to the initiation level (20 kcal/h) and the process restarted. Patients in the control group received approximately 69 kcal/h. Caloric restriction resulted in an improvement of mortality at 60 days, without any change in morbidity.[108]

These findings were corroborated by a subsequent study of 337 critically ill patient intubated for >7 days. They defined RS, in the same manner as in the prior trial, as new-onset hypophosphatemia <72 hours after initiation of nutrition. The primary outcome was 6-month mortality and ICU length of stay. The low-calorie group received <50% of their goal calories for the first 3 days, with an increase in 25% of calorie target per day after. The control group received >50% their calorie goal. RS was observed in 36.8% of patients, with no statistically significant difference in hospital morbidity, and with a trend toward reduced length of stay, in the lower-calorie group. They also found that low calorie intake was associated with an increased overall survival at day 180.[109]

ASPEN Consensus Definitions

Refeeding Syndrome

This paper describes RS, conceptually, as a measurable reduction in levels of 1 or any combination of phosphorus, potassium, and/or magnesium, or the manifestation of thiamin deficiency, developing shortly (hours to days) after initiation of calorie provision to an individual who has been exposed to a substantial period of undernourishment. RS may manifest in a wide variety of severities, from slight, clinically insignificant decrements in electrolyte levels to severe and sudden decreases, which lead to, or risk development of, end organ failure if not preempted or corrected. Although many prior definitions have, for historic reasons, focused solely on hypophosphatemia, it is

Table 5. ASPEN Consensus Criteria[a] for Identifying Pediatric Patients at Risk for Refeeding Syndrome.[112-114]

	Mild Risk: 3 Risk Categories Needed	Moderate Risk: 2 Risk Criteria Needed	Significant Risk: 1 Risk Criteria Needed
Weight-for-length *z*-score(1–24 months) or BMI-for-age *z*-score(2–20 years)	−1 to −1.9 *z*-score that is a change from baseline	−2 to −2.9 *z*-score that is a change from baseline	−3 *z*-score or greater that is a change from baseline
Weight loss	<75% of norm for expected weight gain	<50% of norm for expected weight gain	<25% of norm for expected weight gain
Energy intake	3–5 consecutive days of protein or energy intake <75% of estimated need	5–7 consecutive days of protein or energy intake <75% of estimated need	>7 consecutive days of protein or energy intake <75% of estimated need
Abnormal prefeeding serum potassium, phosphorus, or magnesium concentrations[b]	Mildly abnormal or decreased to 25% below lower limit of normal	Moderately/significantly abnormal or down to 25%–50% below lower limit of normal	Moderately/significantly abnormal or down to 25%–50% below lower limit of normal
Higher-risk comorbidities (see Table 4)	Mild disease	Moderate disease	Severe disease
Loss of subcutaneous fat	Evidence of mild loss **OR** Mid-upper arm circumference *z*-score of −1 to −1.9 *z*-score	Evidence of moderate loss **OR** Mid-upper arm circumference *z*-score of −2 to −2.9	Evidence of severe loss **OR** Mid-upper arm circumference *z*-score of −3 or greater
Loss of muscle mass		Evidence of mild or moderate loss **OR** Mid-upper arm circumference *z*-score of −2 to −2.9	Evidence of severe loss **OR** Mid-upper arm circumference *z*-score of −3 or greater

ASPEN, American Society for Parenteral and Enteral Nutrition; BMI, body mass index.
[a]Not intended for use in patients at ≤28 days of life or ≤44 weeks' corrected gestational age.
[b]Please note that electrolytes may be normal despite total-body deficiency, which is believed to increase risk of refeeding syndrome.

proposed here that the decrement in any of the 3 electrolytes may signal total-body deficit and warrant monitoring or intervention.

Specifically, RS diagnostic criteria are outlined as the following:

- A decrease in any 1, 2, or 3 of serum phosphorus, potassium, and/or magnesium levels by 10%–20% (mild RS), 20%–30% (moderate RS), or >30% and/or organ dysfunction resulting from a decrease in any of these and/or due to thiamin deficiency (severe RS).
- And occurring within 5 days of reinitiating or substantially increasing energy provision.

Examples of signs and symptoms of end organ disturbance related to RS can be found in Table 2.[71,110] The criteria for severity stratification are arbitrary but chosen to align with published severity stratifications for electrolyte decrements.

Risk of Refeeding Syndrome

As previously indicated, the incidence of RS is unknown. Thus, any quantification of risk is not currently possible. However, certain characteristics have been identified as likely predisposing to RS.

Table 3 contains characteristics recommended, by consensus, for inclusion in assessment of risk of RS for adults. Again, because incidence is unknown, this list cannot be considered exhaustive, nor is the strength of impact of each or multiple characteristics known. The list includes several additions to the previous NICE criteria,[44] such as the addition of physical exam findings including loss of subcutaneous fat and muscle mass. The characteristics of weight loss, intake, and loss of fat and muscle are consistent with the Academy/ASPEN adult malnutrition characteristics for adult patients with moderate and severe malnutrition.[49] For adults, risk is divided into moderate and severe. A definition for mild risk for adults is not provided. It was the consensus of the task force that to do so would risk the creation of an oversensitive definition, without evidence as to the degree of clinical risk or the risk of excessive intervention. Further, it is unlikely, by definition, that mild risk would be of clinical significance or would require a change in management. Many disease processes that increase risk for developing malnutrition are included in the updated risk criteria. Table 4[15,111-113] includes some

Table 6. ASPEN Consensus Recommendations for Avoidance and Treatment of RS in At-Risk Adults.

Aspect of Care	Recommendations
Initiation of calories	• Initiate with 100–150 g of dextrose or 10–20 kcal/kg for the first 24 hours; advance by 33% of goal every 1 to 2 days. This includes enteral as well as parenteral glucose. • In patients with moderate to high risk of RS with low electrolyte levels, holding the initiation or increase of calories until electrolytes are supplemented and/or normalized should be considered. • Initiation of or increasing calories should be delayed in patients with severely low phosphorus, potassium, or magnesium levels until corrected. • Calories from IV dextrose solutions and medications being infused in dextrose should be considered in the limits above and/or initiated with caution in patients at moderate to severe risk for RS. If a patient has received significant amounts of dextrose for several days, from maintenance IV fluids and/or medications in dextrose, and has been asymptomatic with stable electrolytes, calories from nutrition may be reintroduced at a higher amount than recommended above.
Fluid restriction	• No recommendation.
Sodium restriction	• No recommendation.
Protein restriction	• No recommendation.
Electrolytes	• Check serum potassium, magnesium, and phosphorus before initiation of nutrition. • Monitor every 12 hours for the first 3 days in high-risk patients. May be more frequent based on clinical picture. • Replete low electrolytes based on established standards of care. • No recommendation can be made for whether prophylactic dosing of electrolytes should be given if prefeeding levels are normal. • If electrolytes become difficult to correct or drop precipitously during the initiation of nutrition, decrease calories/grams of dextrose by 50% and advance the dextrose/calories by approximately 33% of goal every 1–2 days based on clinical presentation. Recommendations may be changed based on practitioner judgment and clinical presentation, and cessation of nutrition support may be considered when electrolyte levels are severely and/or life-threateningly low or dropping precipitously.
Thiamin and multivitamins	• Supplement thiamin 100 mg before feeding or before initiating dextrose-containing IV fluids in patients at risk. • Supplement thiamin 100 mg/d for 5–7 days or longer in patients with severe starvation, chronic alcoholism, or other high risk for deficiency and/or signs of thiamin deficiency. • Routine thiamin levels are unlikely to be of value. • MVI is added to PN daily, unless contraindicated, as long as PN is continued. For patients receiving oral/enteral nourishment, add complete oral/enteral multivitamin once daily for 10 days or greater based on clinical status and mode of therapy.
Monitoring and long-term care	• Recommend vital signs every 4 hours for the first 24 hours after initiation of calories in patients at risk. • Cardiorespiratory monitoring is recommended for unstable patients or those with severe deficiencies, based on established standards of care. • Daily weights with monitored intake and output. • Evaluate short- and long-term goals for nutrition care daily during the first several days until the patient is deemed stabilized (eg, no requirement for electrolyte supplementation for 2 days) and then based on institutional standards of care.

ASPEN, American Society for Parenteral and Enteral Nutrition; IV, intravenous; MVI, multivitamin injectable; PN, parenteral nutrition; RS, refeeding syndrome.

conditions that are specific to the adult population; however, most apply to adults and children. Abnormal electrolyte values are expressed as percentages below the lower limit of normal, as different medical laboratories may have different values for the normal range.

Table 5[114-116] lists criteria recommended, by consensus, for inclusion in assessing risk of RS in the pediatric population. As with adults, this list cannot be considered exhaustive, nor is it known the strength of impact of each or multiple characteristics. There are a few important differences between the adult and pediatric populations. RS risk, in general, is believed to be closely associated with the degree of malnutrition, particularly starvation-related malnutrition. However, adults are believed to be more tolerant to longer periods of starvation. Short periods of nutrient deprivation may have a more significant effect in children because of the added metabolic demands of growth. For this reason, the pediatric criteria include a "mild risk" level. The velocity of weight gain, current height and length, current weight-for-length, or BMI-for-age *z*-score

Table 7. ASPEN Consensus Recommendations for Avoidance and Treatment of RS in At-Risk Pediatric Patients.

Aspect of Care	Recommendations
Initiation of nutrition	• Initiate nutrition at a maximum of 40%–50% goal, but usually starting the glucose infusion rate around 4–6 mg/kg/min and advancing by 1–2 mg/kg/min daily as blood glucose levels allow until you reach a max of 14–18 mg/kg/min. This includes enteral as well as parenteral glucose. • Calories from IV dextrose solutions and medications being infused in dextrose should be considered in the limits above and/or initiated with caution in patients at moderate to severe risk for RS. If the patient is already receiving IV dextrose for several days and/or medications in dextrose and has been asymptomatic with stable electrolytes, calories from nutrition may be reintroduced at a higher amount than recommended above.
Fluid restriction	• No recommendation
Sodium restriction	• No recommendation
Protein restriction	• No recommendation
Electrolytes	• Check serum potassium, magnesium, and phosphorus before initiation of nutrition. • Monitor every 12 hours for the first 3 days in high-risk patients. May be more frequent based on clinical picture. • Replete low electrolytes based on established standards of care. • No recommendation can be made for whether prophylactic dosing of electrolytes should be given if prefeeding levels are normal. • If electrolytes become difficult to correct or drop precipitously during the initiation of nutrition, decrease calories/grams of dextrose by 50% and advance the dextrose/calories by approximately 33% of goal every 1–2 days based on clinical presentation. Recommendations may be changed based on practitioner judgment and clinical presentation, and cessation of nutrition support may be considered when electrolyte levels are severely and/or life-threateningly low or dropping precipitously.
Thiamin and multivitamins	• Thiamin 2 mg/kg to a max of 100–200 mg/d before feeding commences or before initiating IV fluids containing dextrose in high-risk patients. • Continue thiamin supplementation for 5–7 days or longer in patients with severe starvation, chronic alcoholism, or other high risk for deficiency and/or signs of thiamin deficiency. • Routine thiamin levels are unlikely to be of value. • MVI is added to PN daily, unless contraindicated, as long as PN is continued. For patients receiving oral/enteral nourishment, add complete oral/enteral multivitamin once daily for 10 days or greater based on clinical status and mode of therapy. • Once patient is within adult weight ranges, refer to adult multivitamin recommendations.
Monitoring and long-term care	• Recommend vital signs every 4 hours for the first 24 hours after initiation in those at risk. • Cardiorespiratory monitoring is recommended for unstable patients or those with severe deficiencies, based on established standards of care. • Daily weights with monitored intake and output. • Estimation of energy requirements as needed for oral feeding patients. • Evaluate short- and long-term goals for nutrition care daily during the first several days until the patient is deemed stabilized (eg, no requirement for electrolyte supplementation for 2 days) and then based on institutional standards of care.

ASPEN, American Society for Parenteral and Enteral Nutrition; IV, intravenous; MVI, multivitamin injectable; PN, parenteral nutrition; RS, refeeding syndrome.

should be considered when assessing children for their risk of RS.

ASPEN Consensus Recommendations for the Avoidance and Treatment of RS

Adult and Pediatric Patients

The approaches to avoid causing RS and those for responding to and avoiding worsening of RS are often the same and are combined in these consensus recommendations. These recommendations (Table 6 for adults and Table 7 for children) may not apply to special populations, such as those with renal impairment; are meant as general guidelines; have not been tested in randomized studies; and should be adapted to the individual patient and/or institution.

Simply stated, patients deemed at risk for RS, apart from young patients with AN, should at first receive conservative calories. They should be monitored more closely for electrolyte abnormalities and receive appropriate treatment for electrolyte abnormalities following established standards of care. Treatment of established RS should be aimed at correcting the underlying electrolyte abnormalities to prevent sequelae and may additionally include either a

reduction of calories or a slowing of the advancement of calories toward eventual goals. Treatment should include both reactive and preemptive supplementation, dependent on the severity of RS, or the severity of risk for RS. Patients with low electrolyte levels before the initiation of feeding should undergo more aggressive supplementation than would be ordinary in the steady state. Consideration of the severity or rapidity of the electrolyte decrement and risk for RS may determine whether electrolytes should be normalized before initiation of any calories or calorie increase.

Neonates

Specific recommendations for neonates are not included in this paper. In general, SGA, IUGR due to maternal comorbidities, elevated high UA-RI, extreme prematurity, VLBW, and a z-score > -2 are examples of characteristics thought to put neonates at risk for RS. This is not an exhaustive list.

Future Research

Further research is needed in all areas related to RS, from validation and better identification of risk factors and definitions of RS and its severity to standardization of treatment protocols. This paper presents a unifying set of criteria such that research is made uniform and incidence of sequelae can be determined.

Although guidance has been provided, these criteria are based on consensus and will need to be tested in randomized trials in general, in specific populations, and with different comorbid conditions to determine their usefulness. For example, it is likely that the risk of RS is very different between patients with AN and those in the ICU; among adults, adolescents, children, and neonates; and between the hospitalized patient in an affluent city and the victim of famine or poverty-related starvation. Studies are required to compare initiation regimens and protocols for their effectiveness for avoiding RS and/or the sequelae of RS. Studies are also required to examine the use of prophylactic electrolyte supplementation before feeding patients deemed at high risk for RS but with normal prefeeding electrolyte levels.

Conclusion

This paper has provided a narrative review and consensus recommendations for risks, avoidance, and treatment of RS. In addition, it provides a unified consensus definition, updated consensus recommendations for screening and identifying patients at risk for RS, and guidance for avoiding and treating RS.

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