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Review article

Refeeding syndrome: Treatment considerations based on collective analysis of literature case reports

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Abstract Refeeding syndrome (RFS) represents a group of clinical findings that occur in severely malnourished individuals undergoing nutritional support. Cardiac arrhythmias, multisystem organ dysfunction, and death are the most severe symptoms observed. As the cachectic body attempts to reverse its adaptation to the starved state in response to the nutritional load, symptoms result from fluid and electrolyte imbalances, with hypophosphatemia playing a central role. Because guidelines for feeding the malnourished patient at risk for refeeding syndrome is scarce, we have provided management recommendations based on the knowledge derived from a collection of reported English literature cases of the RFS. A MEDLINE search using keywords including ''refeeding syndrome,'' ''RFS,'' and ''refeeding hypophosphatemia'' was performed. References from initial cases were utilized for more literature on the subject. We have emphasized the continued importance of managing patients at risk for RFS, compared how management of the severely malnourished patients have evolved over time, and provided comprehensive clinical guidelines based on the sum of experience documented in the case reports for the purpose of supplementing the guidelines available. Based on our review, the most effective means of preventing or treating RFS were the following: recognizing the patients at risk; providing adequate electrolyte, vitamin, and micronutrient supplementation; careful fluid resuscitation; cautious and gradual energy restoration; and monitoring of critical laboratory indices.

Keywords: Refeeding syndrome; Nutritional support; Micronutrient supplementation; Parenteral nutrition; Anorexia nervosa; Refeeding in anorexia nervosa; Refeeding complications; Hypophosphatemia; Arrhythmia; Nutritional support

Introduction

Refeeding syndrome (RFS) represents a group of clinical symptoms and signs commonly observed in severely malnourished and cachectic patients. Symptoms of RFS occur from fluid and electrolyte imbalances resulting from nutritional supplementation via oral, enteral, or parenteral routes following a period of adaption to a prolonged starvation or malnourishment. Multiple organ systems including cardiac, respiratory, neurologic, and hematologic can be affected and may lead to multisystem organ failure and death in the most severe of cases. The most common cause of death is cardiac arrhythmias (Table 1). The hallmark findings in RFS are fluid and electrolyte dysregulation including hypophosphatemia,

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Table 1
Manifestation of RFS in various organ systems as reported in case reports

System	Sign/Symptom	Authors
Cardiovascular	Sudden death Arrhythmias Hypertension Congestive heart failure	Kohn [68], Heymsfield [8]
Gastrointestinal	Anorexia Abdominal pain Constipation Vomiting	Knochel [40], Betro [75], Havala [45], Faintuch [76]
Musculoskeletal	Weakness Myalgias Rhabdomyolysis Osteomalacia	Subramanian [16], Silvis [77], Stoff [78]
Respiratory	Dyspnea Respiratory failure Ventilator dependency Diaphragm/Intercostal muscle weakness	Patel [30]
Neurologic	Weakness Parasthesias Tremors Ataxia Delirium Acute encephalopathy Coma Guillan-Barré-like syndrome Central pontine myelinolysis	Solomon [36], Mezoff [79], Weinsier [3], Kohn [68], Chudley [80], Patel [27]
Metabolic	Metabolic alkalosis Metabolic acidosis Respiratory alkalosis hyperglycemia	Weinsier [3], Btaiche [57]
Hematologic	Infections Thrombocytopenia Hemolysis Anemia	Litchman [81], Betro [75], Yawata [82], Craddock [31], Azumagawa [33]
Others	Acute tubular necrosis Wernicke's encephalopathy Liver failure	Stubbs [58], Mattlioli [29], Azumagawa [33], Saito [83]

Table 2
Conditions that increase the risk for RFS

Condition	Example	Authors
Psychiatric	Eating disorders e.g. anorexia nervosa Chronic alcoholism Depression in the elderly	Weinsier [3], Azumagawa [33], Beumont [44], Fisher [73], Kohn [68], Isner [70]
Malnourishment	Kwashiorkor Marasmus Prolonged fasting Prolonged vomiting Dysphagia and esophageal dysmotility Crohn's disease Malabsorptive states	Crook [9], Hernando [11], Mallet [18], McCray [14], Marinella [35], Patrick [62], Faintuch [76], Worley [84]
Neoplasm	Chemotherapy	McCray [14], González Ávila [22]
Surgical	Short bowel syndrome Prolonged NPO status Bariatric surgery	Weinsier [3], Silvis [77]
Metabolic	Diabetes mellitus (poorly controlled) Hemodialysis	Lin [41]
Physiologic	Pregnancy	Chiarenza [28]

NPO, nil per os (clinical order to allow nothing by mouth).

hypokalemia, hypomagnesemia, abnormalities in glucose metabolism, vitamin (importantly thiamine), and trace element deficiencies. RFS can be viewed as a spectrum disorder where symptoms range from mild to severe depending on the degree of starvation or malnourishment and the form of management employed.

One of the earliest accounts of RFS was in the 1940s when Brozek and colleagues documented cardiovascular failure in semi-starved patients, after they were abruptly fed a normal diet [1]. After World War II, Schnitker and colleagues documented that following liberation, 21% of chronically starved Japanese prisoners died despite the provision of ''adequate diet'' that included vitamin supplementation [2]. The term ''refeeding syndrome'' was coined and brought to attention by Weinsier and Krumdieck in 1981 when they reported the untimely death of two malnourished patients who were fed ''overzealously'' [3].

The predisposing conditions in patients at risk for developing RFS are listed in Table 2. Nutritional depletion is a common denominator and hallmark finding in patients with RFS. In prolonged starvation (weeks to months), glycogen stores are expended while proteins are conserved for intracellular enzymatic and structural functions, leaving fats as the predominant source of energy. During this time absolute size and volume of cells of the liver, heart, brain, and more importantly muscle decreases probably due to a combination of an energy deficient state, loss of intracellular storage macromolecules such as protein and glycogen, and adaptation to fat metabolism. For example, the brains of anorexia nervosa patients have significantly tropic changes and decreased hippocampal volume [4,5]. Without replacement, intracellular and extracellular ions including PO_4^{3-}, K^+, Mg^{2+}, and Na^+ are lost over time, although their measured concentrations may remain falsely normal mainly because of concurrent loss of total body water that also accompanies malnourishment. Importantly, the falsely normal concentration of these ions is not simply due to excess total body water, since they may occur in normally hydrated individuals or individuals with only mild water retention. Once adaptation has occurred, survival can be effectively sustained for months, the exact duration being variable among individuals and proportional to amount of available fat stores [6]. Sudden introduction of seemingly adequate nutrition during this time can be interpreted by the body as ''stressful.'' Dormant enzymes are suddenly activated in the context of relative nutrient and

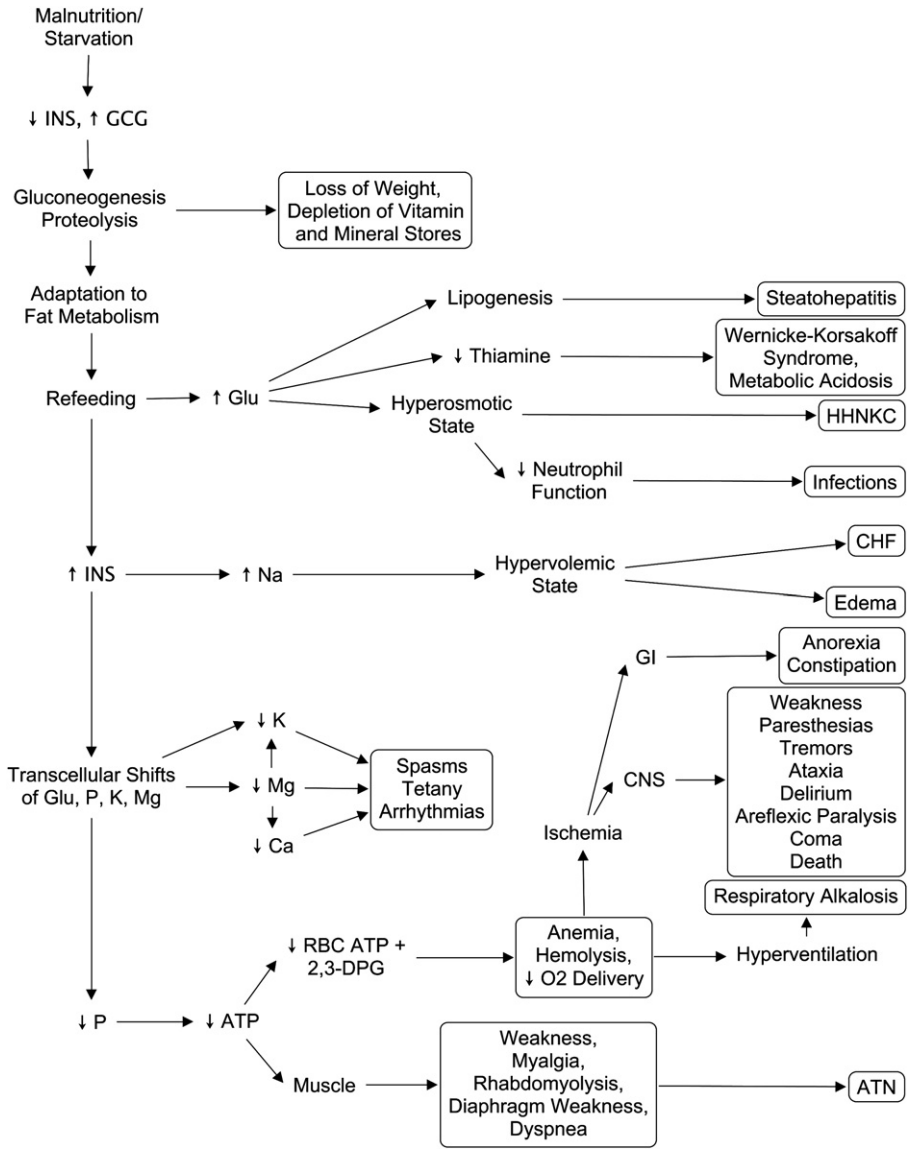

Fig. 1. Pathophysiology of refeeding syndrome. INS, insulin; GCG, glucagon; Glu, glucose; P, phosphorus; K, potassium; Na, sodium; Ca, calcium; ATP, adenosine triphosphate; RBC, red blood cell; CHF, congestive heart failure; ATN, acute tubular necrosis; HHNKC, hyperosmolar hyperglycemic nonketotic coma; GI, gastrointestinal system; CNS, central nervous system.

cofactor deficiency. This deficiency of micro- and macromolecules is enhanced at the onset of increased enzymatic activity, precipitating signs and symptoms of RFS. The hemodynamic and metabolic sequelae that transpires is described below [6–9]:

- *Hypophosphatemia* results from cellular uptake of phosphorus (P) and inorganic phosphates (PO_4^{3-}) under the influence of insulin for the synthesis of ATP, DNA, RNA, proteins, and 2,3-diphosphoglycerate, and from the increased phosphorylation of glucose. Regulation of cellular function such as leukocyte chemotaxis, phagocytosis, and platelet clot formation requires PO_4^{3-} and contributes to its depletion. Anabolic processes such as cell membrane formation by phospholipids, and cellular growth and replication by nucleoproteins and nucleic acids, further deplete PO_4^{3-}. Lack of red cell PO_4^{3-} leads to hemolysis, anemia, susceptibility to infections, inadequate oxygen delivery to tissues, generalized ischemia, diminished cellular regulation, and growth, which may cause multiple organ failure and death. A pathophysiological diagram is provided (Fig. 1).
- *Hyperglycemia* results from glucose introduction into a starved system adapted to fat metabolism. Infections become more common as hyperglycemia disrupts neutrophilic function, leading to a functional neutropenic state. Hyperosmosis from hyperglycemia may lead to coma and death.

- *Hypomagnesemia* results from cellular uptake of magnesium (Mg) after feeding. Mg is essential for many cellular process and all cellular processes involving ATP. Hypomagnesemia is an important mediator of both hypocalcemia and hypokalemia.
- *Hypokalemia* results from cellular uptake of potassium (K), induced by insulin produced in response to the nutritional load.
- *Fluid overload* occurs from the sodium (Na) retention effects of hyperglycemia and hyperinsulinemia.
- *Vitamin deficiency* results from the rapid depletion of vitamins after onset of refeeding due to their role in various biochemical functions. For example, thiamine is necessary for glucose metabolism but its stores are depleted during starvation. Sudden introduction of glucose drives already depleted thiamine stores to a nadir, precipitating Wernicke's encephalopathy and lactic acidosis.
- *Trace element deficiency* also results from increased enzymatic activity during the anabolic process. For example, the importance of trace elements such as zinc and selenium as functional components of many enzymes involved in DNA/RNA metabolism and oxidative-reduction processes is well known.

Anorexia nervosa is the modern prototypical predisposing condition [10]. Other notable conditions are malabsorptive syndromes [11,12], cancer [13], chronically uncontrolled diabetes mellitus [14], alcoholism [15,16], status post surgery [17], and infirmities of advanced age [18] (Table 2) .

The incidence of RFS in severely malnourished patients who are being refed is 48% [19]. It is found in 34% of all ICU patients [20], 9.5% of patients hospitalized for malnutrition from gastrointestinal fistulae [21], and 25% of cancer inpatients [22]. Not all patients at risk will experience symptoms of RFS [23].

Until recently, because of the difficulty in its recognition, the management of RFS was based on clinical experience. Numerous cases have been reported since the syndrome was first recognized. Some authors have provided management recommendations based on the clinical outcomes [24]. Some hospitals and communities have centralized guidelines for managing the malnourished or cachectic patient [25,26], although they may be intended for regional use and may not have widespread application. They also fail to provide guidelines for vitamin and trace element supplementation, which is part and parcel of managing the malnourished patient. In the absence of guidelines based on a collection of reported clinical cases, we have reviewed English literature case reports and highlighted the appropriate management of patients at risk for developing RFS. We have also illustrated how management of the cachectic patient has evolved over time and provided practical clinical guidelines based on the sum of experience documented in the case reports to supplement the guidelines mentioned above.

Methods and materials

English language case reports of RFS from January 1966 to September 2008 of children and adults were searched using the PubMed database and the following keywords: ''refeeding syndrome,'' ''refeeding complications,'' ''refeeding case report,'' and ''refeeding hypophosphatemia.'' Cases that did not clearly demonstrate complications as a result of nutritional supplementation were excluded. Fifty-four individual case reports from 36 authors were included in our review ranging from 1969 to 2008. To understand the evolution of management of RFS over time, two groups were compared: An ''earlier experience'' group, from cases ranging from 1969 to 1989 and a ''modern experience'' group, from 1990 to 2008.

Statistical analyses including mean, median, and range were performed using Microsoft Excel 2003® software. Ages given in months were approximated to the nearest whole number for statistical calculation. Thirty-one of the 54 case reports either provided actual patient body mass index (BMI) or had enough information to calculate the BMI. The normal BMI is between 18.5 and 25 kg/m^2. Twenty-two was used to represent the ideal body weight (IBW) because it is the approximate result of averaging out the normal BMI range. We used the IBW to calculate the degree of obesity or malnourishment for each individual case subject. IBWs provided in the case reports were preferred over our calculated ones. Forty-seven of the 54 case reports provided sufficient data to calculate the onset of symptoms and signs. Symptoms that occurred in 2 and 3 wk were taken as 14 and 21 d, respectively. To assess the differences in nutrition supplementation between the two groups, we defined ''overzealous feeding'' as the lack of documentation of incremental feeding in the initial refeeding period by the authors. We compared ''attempts at supplementation'' of electrolytes and micronutrients between the two groups.

Five representative case reports that contributed greatly in developing the guidelines are summarized and discussed in detail below. They were chosen for their ability to illustrate the key aspects of RFS and its management. Following each case report, a ''Take Home Message (THM)'' highlights the important lessons to be learned.

Selected case reports

Case 1—Pontine myelinolysis as a complication of RFS

A 23-y-old female with a past medical history of anorexia nervosa was found unresponsive in her bed. She had been vomiting for 2 wk, and her presenting signs and symptoms were seizures, hyponatremia, hypokalemia, and alkalemia with a pH of 7.62. She was given parenteral nutrition and her Na levels were corrected from 108 mM/L to 130 mM/L within 12 h. Her neurologic symptoms improved rapidly by

24 h but showed signs of neurologic deterioration. She became confused, ataxic, mute, bedridden, and eventually comatose. She was later diagnosed with central pontine myelinolysis [27].

THM: Patients with anorexia nervosa are at increased risk for RFS. Persistent vomiting leads to hypokalemia, which may worsen at the onset of refeeding. Hypovolemic hyponatremia is a common finding in anorexia nervosa and makes rehydration in such patients very difficult. Thus, specific guidelines must be employed to avoid irreversible, devastating complications of abrupt reversal of hyponatremia such as central pontine myelinolysis.

Case 2—RFS and pregnancy

A 23-y-old primigravida in her second trimester presented with hyperemesis gravidarum and poor nutritional intake of 2-mo duration secondary to untreated Crohn's disease. Cortisone and total parenteral nutrition (TPN) with unknown electrolyte composition were administered as part of her treatment. Three days later, she became delirious, agitated, and comatose. Her symptoms were accompanied by hypophosphatemia, hypomagnesemia, hypoalbuminemia, and thrombocytopenia, not present on admission. An initial dose of thiamine, followed by high doses of multivitamins and B-complex vitamins, reversed her symptoms in 3–4 h. TPN was begun at 530 kcal/d and continued for 3 d, while varying the electrolyte content to keep serum levels normal. On day 5, TPN was increased to 675 kcal/d and then 1050 kcal/d on day 6. The patient responded well to this form of management [28].

THM: RFS has been reported in association with pregnancy. Hypophosphatemia is considered a significant underlying pathophysiological mechanism of RFS as it explains most of the symptomatology. Neurologic, hematologic, respiratory, and metabolic abnormalities are common features of RFS (Table 1). The importance of vitamins in the pathogenesis of RFS is illustrated here especially since vitamin provisions led to acute symptom reversal. Very ill patients, especially pregnant women, may benefit from meticulous micronutrient supplementation. For optimal nutrition management, patients at risk for RFS must be started on a low-calorie diet, followed by gradual increments to achieve adequate energy requirements.

Case 3—Death from RFS

A 66-y-old woman underwent an ileal conduit operation for ureteral obstruction. She developed abdominal pain, profuse diarrhea, and food intolerance for 3 mo prior to re-admission. She lost significant weight and was at 70% of her IBW. TPN with dextrose 750 g/d and amino acids 120 g/d, supplemented with 60 mEq/kg/d of Na, 20 mEq/kg/d of K, 15 mM/kg/d of P, and multivitamins was started. Twenty-four hours later, she became hypophosphatemic, acidotic, and apneic and required mechanical ventilation. Nutrition administration was stopped and P infusion was begun. She became acutely hypoglycemic and, despite rise in serum P level, she died later due to acute respiratory distress syndrome and bilateral pneumonia [3].

THM: RFS has been reported in the elderly. They are predisposed to developing RFS by virtue of their sensitivity to malnourishment. Malabsorptive syndromes such as ulcerative colitis, Crohn's disease, and short bowel syndrome are also reported predispositions to RFS. Respiratory decline is common as RFS develops (Table 1). Nutritional support must be reduced when symptoms of RFS become evident and stopped completely when they become severe. Importantly, the amount of energy in the form of glucose in this case is substantially high when compared with modern recommendations. Supplementation of appropriate vitamins, minerals, and electrolytes is an essential part of management of the patient at risk and may help reverse some symptoms of RFS (Table 3). Death is a possible outcome of severe RFS, most commonly by cardiopulmonary complications. TPN poses the greatest risk for severe complications from RFS when compared with nutritional supplementation via oral or enteral routes.

Case 4—RFS, a cause of Wernicke's encephalopathy

A 22-y-old man diagnosed with ulcerative colitis presented with vomiting, diarrhea, and severe rectal bleeding. He was severely malnourished and TPN was begun immediately after surgery with carbohydrates 50 g/d, lipids 135 g/d, proteins 77.5 g/d, electrolytes, and thiamine 3.2 mg daily. Five days later he reported visual loss and became drowsy with signs of diplopia, nystagmus, gaze paresis, tremors, brisk reflexes, and clonus. Lactic acidosis became evident. TPN was stopped and an unreported amount of ''high-dose'' thiamine was infused. The patient recovered without sequelae [29].

THM: Thiamine deficiency and its associated Wernicke's encephalopathy are recognized complications of RFS. Thiamine deficiency can manifest in the presence of low glucose intake as evident in this case, or even without glucose intake. Thiamine is necessary for glucose metabolism and must be given before and during nutritional support. Symptoms of thiamine deficiency such as lactic acidosis may occur despite thiamine administration, underlining the importance of adequate supplementation prior to nutrition support. Reduction of nutritional supplementation may be necessary to prevent progression of RFS.

Case 5—RFS despite hypocaloric nutrition

A 60-y-old obese man with esophageal cancer presented with progressive dysphagia. He had been intolerant to even liquids and lost 16% of his body weight unintentionally during this time, although he remained overweight. Ten percent

Table 3
Clinical considerations in management of refeeding syndrome based on reported cases

I. Recognize patients at risk
- Identification of high-risk patients
- Cooperation among nutritionists and physicians
- Recognition that parenteral nutrition carries a greater risk than oral or enteral, although all three can cause RFS

II. Electrolyte deficiency and replacement
- Prior to initiating feeds in at-risk patients, the level of essential electrolytes must be known and replaced accordingly
- Hypophosphatemia (<3 mg/dL or <1 mM/L)
  - P can be given either as a Na or K preparation depending on K levels
  - *Mild* (2.3–3 mg/dL or 0.75–1 mM/L): Replace with 0.32 mM/kg/d of IV or PO K-Phos
  - *Moderate* (1.6–2.2 mg/dL or 0.5–0.74 mM/L): Replace with 0.64 mM/kg/d of IV K-Phos
  - *Severe* (<1.6 mg/dL or <0.5 mM/L): Replace with 1 mM/kg/d of IV K-Phos [38]
  - Monitoring phosphate levels is important since IV replacement is associated with neurological symptoms [44]
- Hypokalemia (<3.5 mEq/L or <3.5 mM/L)
  - 1–4 mEq/kg/d in the form of oral K (as KCl or other K formularies). Symptomatic or more severe deficiency may require IV supplementation with care to avoid hyperkalemia [24,26,35]
  - Monitor K levels with IV replacement or concurrent diuretic use. Consider ECG to rule out arrhythmias if levels are high or low
- Hypomagnesemia (<1.7 mg/dL or 0.7 mM/L)
  - *Mild to Moderate* (1.2–1.7 mg/dL or 0.5–0.7 mM/L): Replace with 10–15 mM daily with oral Mg oxide or Mg citrate [51]
  - *Severe* (<1.2 mg/dL or <0.5 mM/L): If asymptomatic, treat as above. If symptomatic, treat with 25 mM/d of parenteral Mg with reassessments every 8–12 h [14,51]

III. Vitamins [61]
- B_1 (thiamine): Give loading dose of thiamine 300 mg IV *before* starting nutrition. Give maintenance dose of 100 mg/d *during* nutrition.
- Vitamins B_6 (pyridoxine): 1.7 mg/d
- B_{12} (cobalamine): 2.4 μg/d
- Folate: 400 μg/d, not to exceed 1 mg daily

IV. Micronutrients–Give loading doses where appropriate, followed by maintenance dose [61]
- Selenium (Se): Loading dose of 100–400 μg/d; maintenance dose of 20–70 μg/d
- Zinc (Zn): Loading dose of 10–30 mg/d; maintenance dose of 2.5–5 mg/d
- Iron (Fe): Loading doses not needed. A maintenance dose of 10–15 mg/d via the oral route is sufficient. Parenteral iron in the form of dextran can be added safely to TPN

V. Fluid and sodium balance
- Provide 20–30 mL/kg/d of NS. Adjust as needed to achieve adequate hydration. Measure daily weights to prevent fluid overload.
- Hyponatremia (<135 mEq/L or <135 mM/L)
  - Goal of treatment is to avoid rapid correction while preventing permanent neurological sequelae.
  - Fluid restriction is adequate if mild. Assess Na levels frequently and replete at less than 12 mEq/L (12 mM/L) within 24 h to avoid risk for central pontine myelinolysis [27,65]
  - Symptomatic hyponatremia responds better to normal or hypertonic saline therapy versus fluid restriction [85,86]

VI. Energy
- Start feeds at no more than 20% of basal energy expenditure in calories
- Start with 10 kcal/kg/d in first 3 d; use 5 kcal/kg/d in critically ill patients. Slowly increase to 15–20 kcal/kg/d from days 4 to 10. Note parenteral nutrition may carry greater risk for RFS [26]
- Ratio: 50–60% carbohydrate, 15–25% fats, 20–30% protein
- Increase or reduce energy provision based on resolution of symptoms and laboratory parameters

VII. Monitor
- Daily body weights, urine output, and careful chart monitoring to optimize fluid balance and to prevent fluid overload, pulmonary edema, or CHF
- Plasma electrolytes must be monitored daily for first week or until clinically stable
- ECG is advised in the first week of refeeding
- Daily vital signs is necessary as tachycardia may be a sign of impending cardiac decompensation
- Plasma glucose must be monitored and maintained between 100 and 150 mg/dL to prevent hypoglycemia and hyperglycemia
- Pre-albumin levels predict development of hypophosphatemia in the critically ill [20]
- Monitor CBC, BMP, ALT/AST daily and more frequently in the critically ill

VIII. Special considerations
- Pregnancy—high-dose multivitamins especially folate are beneficial in pregnant women [87]. Vitamin A has significant teratogenic properties at doses exceeding 10 000 IU/d (3 mg/d) [88]
- Infection—diligent search for source of infection. Antibiotics may be considered in febrile patients
- Children—in severely malnourished, assess for JVP elevation and hepatomegaly for early rapid insights into volume status. Diurese if clinical signs suggest volume overload [62]
- Chronic renal failure—in these patients P, Mg, and K, may be normal or even elevated. At first signs of normalization of these values, there is benefit from monitoring and supplementation as described above [89]

PN, parenteral nutrition; EN, enteral nutrition; IV, intravenous; PO, oral; K-Phos, potassium phosphate; DRI, Daily Reference Intake; ECG, electrocardiogram; NS, normal saline; CHF, congestive heart failure; CBC, complete blood count; BMP, basic metabolic panel; ALT, alanine transaminase; AST, aspartate transaminase; JVP, jugular venous pressure.

dextrose solution was administered via a jejunostomy tube at a slow rate of 10 mL/h with adequate IV supplementation of electrolytes and micronutrients. This was followed by enteral tube feeding of 4.4 kcal/kg/d at the same rate, again with adequate supplementation of electrolytes. The rate was gradually increased from 10 to 65 mL/h over 48 h. The patient complained of difficulty breathing and abdominal pain, accompanied by hypokalemia, hypomagnesemia, and hypophosphatemia. Tube feeding was ceased; his electrolytes were corrected, and he was treated successfully for acute respiratory failure with endotracheal intubation and mechanical ventilation. Feeding was resumed 36 h later with no sequelae [30].

THM: Dysphagia of any etiology may predispose to inadequate nutrition and heighten the risk for RFS. Obesity does not eliminate the risk for developing RFS especially when accompanied by significant malnourishment and weight loss. Although parenteral nutrition is the most common route associated with RFS, patients being fed orally or enterally can develop RFS and they must not be overlooked. Finally RFS can occur despite slow nutritional supplementation, thus monitoring of all indices during treatment is essential.

Results

Insight from analyses of case reports

Where values were reported, hypophosphatemia was present in 100% (49/49) of cases, a finding consistent with previous discussions of the syndrome. Of the cases reported, anorexia nervosa was the most common predisposing diagnosis for the RFS (21/54; 39%), followed by malabsorptive syndromes (12/54; 22%), dysphagia (7/54; 13%), and alcoholism (7/54; 13%). Females were twice as likely as men (36/54; 67% versus 18/54; 33%) to develop RFS owing in part to the propensity of anorexia nervosa in young girls. In the 47 cases where onset of symptoms were timed, RFS occurred and ranged from 0.5 to 21 d, with a median value of 3 d, supporting findings by Craddock and colleagues [31] and Hayek and Eisenberg [32] regarding onset of refeeding hypophosphatemia. RFS occurred from ages 11 m to 90 y, with a median age of 23.5 y. Body weight in 31 patients ranged from 11% to 61% below the IBW with one outlier at 58% above IBW. The median weight was at 39% below the IBW. Death occurred in 13 of 51 patients (25%) and was most often associated with parenteral nutrition (9/25; 36%), followed by enteral (4/19; 21%) and oral (2/16; 13%) routes. Death was almost three times as likely in ''earlier'' case reports (8/21; 38%), compared to ''modern'' ones (5/30; 17%). Reasons for this may include the fact that overzealous feeding—defined as non-incremental feeding—was more common in earlier case reports (17/19; 89%) compared to the modern ones (18/32; 56%). Supplementation of P and other electrolytes was readily observed in the majority of both sets of case reports. However, supplementation of multivitamins and micronutrients was attempted in recent case reports (8/31; 26%) less often compared to earlier ones (7/19; 37%). Because of limited information provided in some cases, the adequacy of supplementation could not be ascertained for all cases. Our analysis was thus limited to comparing groups that received electrolytes to those that did not. Plasma electrolytes were the most commonly monitored indices, seen in the vast majority of case reports, whereas others such as glucose, electrocardiogram (ECG), albumin, and body fluids were rarely monitored. Thus, although survival is being improved with modern treatment, clinicians need to be educated about optimal management of the malnourished patient to maximize this survival benefit.

Discussion

Recommendations based on collective analyses of case reports

Given its non-specific presentation and presumed rarity, diagnosing RFS can be an arduous task for the physician. The reported incidence is likely an underestimate of the true value and thus clinicians must foremost be educated to recognize this syndrome [14]. In case 1, the patient had a clear psychiatric diagnosis of anorexia nervosa. When she became unable to eat, her caretakers wrongfully interpreted it as ''refusing to eat,'' which effectively delayed her diagnosis and treatment. Severe anorexia nervosa can present with edema, heart failure, and hypophosphatemia, which are also features of RFS [33]. This exemplifies how co-morbid conditions can complicate the timely recognition of RFS. The authors suggested the need for awareness of the possibility of RFS in high-risk patients, as well as better collaboration among caretakers from different specialties [27].

After successful identification of a patient at risk for RFS, the next step in management is to prevent the development of severe symptoms if possible, or to lessen the symptoms if RFS has already developed. It is possible to prevent or reverse symptoms of RFS with adequate management. As discussed below under ''Energy supplementation,'' slow nutritional supplementation is an essential component in the prevention of refeeding complications [13,14,26,34].

Pregnancy is associated with hemodynamic modifications and can complicate many clinical conditions including RFS. Case 2 was the only report found that observed RFS in the context of pregnancy [28]. In a pregnant woman who presented with RFS after TPN administration, an initial dose of vitamin B, followed by high doses of multivitamins, B-complex, and thiamine, were enough to reverse her symptoms in 3–4 h. The exact mechanism behind this finding is unknown but is thought to be due to increased requirements for vitamin supplementation during the pregnancy associated variability in basal metabolic rate. TPN was begun slowly with low caloric content and continued for 3 d while monitoring and correcting electrolytes. On

days 5 and 6, TPN was increased in a stepwise fashion and the patient responded well to this progressive increase of nutritional support. Thus, all patients at risk for RFS, and even pregnant women being refed, must be started on a low calorie diet with small increments and judicious monitoring of electrolytes (Table 3).

Weinsier and Krumdieck presented the first modern cases of RFS, from which one is summarized in case 3 [3]. This case illustrates that death is a possible outcome of RFS. The causes of death from RFS may be due to multiple organ dysfunction secondary to widespread deficiency of ATP or by cardiac arrhythmias from acute dyselectrolytemia, the most common cause [35] (Fig. 1).

Phosphorus

Serum phosphorus levels can be monitored along with Mg, K, Na, and Ca. Hypophosphatemia plays a key role in the pathogenesis of RFS [3,34–36] (Fig. 1). Thus maintenance of serum P levels in the normal range (3.0–4.5 mg/dL or 1–1.4 mM/L) is essential in the management of RFS and may resolve most of the symptoms [37]. Several means of P replacement exist, concisely summarized by the accompanying article [38]. A recent study of patients receiving parenteral nutrition recommends daily dosages of 0.32 mM/kg for mild hypophosphatemia (2.3–3 mg/dL or 0.75–1 mM/L), 0.64 mM/kg for moderate hypophosphatemia (1.6–2.2 mg/dL or 0.5–0.74 mM/L), and 1 mM/kg for severe hypophosphatemia (<1.6 mg/dL or <0.5 mM/L) [39]. Sodium phosphate is generally used when serum K is >4 mEq/L (>4 mM/L), while potassium phosphate is used when K is <4 mEq/L (<4 mM/L) to protect serum K concentration. Symptoms of hypophosphatemia are usually not seen until serum P levels fall below 1 mg/dL (0.3 mM/L) at which point they must be aggressively infused with 56 mg/dL (18 mM/L) within 12 h, with frequent level checks, until levels exceed 2 mg/dL (0.65 mM/L) or until symptoms resolve [9,14,26,40]. Patients who develop diarrhea following oral phosphate preparations may be treated parenterally [41,42]. Milk supplementation may be attempted in children who can tolerate oral feeds [43]. Oversupplemention of P may lead to hypocalcemia, hyperkalemia, and hypernatremia and their clinical consequences [40] pointing to the importance of monitoring P levels. For example, hypocalcemia-induced carpo-pedal spasms following IV replacement of phosphates have been described [44]. The importance of P replacement is elucidated in the fact that, even in end-stage renal disease patients who are commonly hyperphosphatemic, serious hypophosphatemia may develop when nutrition is initiated without adequate P supplementation [41].

Potassium

Potassium deficiency and hypokalemia are implicated in cardiac and neurological electrical abnormalities seen in RFS [45]. Attention must be paid especially to anorexia nervosa patients, as they are K-depleted by their underlying condition. The importance of the supplementation of K in malnourished patients has been well established [46]. Correction of K is relatively simple to accomplish and the target level should be >3.5 mEq/L (3.5 mM/L) (normal level: 3.5–5.0). Supplementation with 1–4 mEq/kg/d in the form of KCl or other K-salts is sufficient to correct hypokalemia in many cases [24,26,35]. Oral replacement of K will suffice for stable patients but critical ones may require K parenterally. Care must be taken when K is replaced parenterally or used concurrently with potassium-sparing diuretics to prevent arrhythmias from the ensuing hyperkalemia [47,48].

Magnesium

Magnesium (Mg) has a normal range between 1.8 and 3.0 mg/dL (0.8–1.2 mM/L) and must be supplemented if plasma levels drop below 0.5 mg/dL (0.2 mM/L) because cardiac arrhythmias, abdominal discomfort, and neuromuscular abnormalities have been reported in this range [21]. Hypomagnesemia is a known mediator of hypokalemia and hypocalcemia [49,50]. The goal is to maintain plasma Mg levels >0.4 mg/dL (0.16 mM/L) at all times during treatment to avoid the associated clinical complications [51]. Oral replacement is the preferred route for the asymptomatic patient, while IV replacement is reserved for those who cannot tolerate oral feeds or are having severe symptoms. Mild to moderate hypomagnesemia [1.2–1.7 mg/dL (0.5–0.7 mM/L)] requires 10–15 mM daily of oral magnesium with Mg oxide or Mg citrate, while severe hypomagnesemia [<1.2 mg/dL (<0.5 mM/L)] must be treated with doses of 25 mM/d of parenteral Mg with stringent monitoring of values at least twice daily [51]. Others suggest replacing the Mg level of 1.0 to 1.4 mg/dL with 4 g/d (16 mM or 32 mEq) of $MgSO_4$ and treating the Mg level of 1.5–1.8 mg/dL with 2 g/d (8 mM or 16 mEq) [52].

Micronutrients (vitamins and minerals)

Vitamin deficiency as noted above contributes significantly to the symptomatology of RFS. Vitamin B_1 (thiamine) is not stored in sufficient amounts and, since it is needed for glycolysis [53], it must be provided before or along with glucose administration. When glucose is administered in excess of thiamine, symptoms of Wernicke's encephalopathy occur as illustrated in case 4. To avoid this, high loading doses (up to 300 mg) of thiamine is required [29]. Overadministration of thiamine is accompanied by few minor irritative symptoms and it is unlikely serious sequelae will result from its administration [54], although *repeated* IV administration of high-dose thiamine-containing products can cause anaphylaxis [55].

Thiamine is a component of several enzymes of the tricarboxylic acid cycle in glucose metabolism in man [56].

Deficiency in thiamine also causes a buildup of pyruvic and lactic acids and can lead to fatal metabolic acidosis [53,57], making monitoring of thiamine levels an essential role in the management of RFS. Rescue authorities who come in contact with trapped and/or starved patients must be educated to provide thiamine prior to food en route to the hospital to avoid refeeding complications [58].

Malabsorptive states including pancreatitis, gastrointestinal fistulas, bypass surgery, and short bowel syndrome cause various vitamin and cofactor derangements including deficiencies in water-soluble vitamins (B_1, B_6, B_{12}), fat-soluble vitamins (A, D, E, K), selenium (Se), zinc (Zn), and iron (Fe). Replacing vitamins and trace elements are important in the critically ill [59,60]. The clinician must keep in mind that it is often difficult when interpreting levels in patients with acute phase response. Detailed information on vitamin and micronutrient supplementation in nutritional support is available [61]. In addition to the recommended daily reference intake of supplements, it may be necessary to provide surplus amounts based on the clinical scenario. For instance, folate and thiamine may be needed in higher doses during the refeeding period in pregnancy [54]. Recommended doses of these micronutrients in patients at risk for RFS as provided by daily reference intake is adequate (Table 3).

Fluids and sodium balance

Plasma sodium levels are important to monitor because they provide insight into extracellular fluids and they can predict mortality. Patrick described a greater risk for sudden death following refeeding in malnourished children with low Na values compared to those without [62]. Edema, elevated jugular venous pressure, and hepatomegaly were reliable predicting signs of fluid overload in these children.

Immediately following carbohydrate load Na is retained and contributes to the fluid overload. Thus fluids must be administered in moderation or held and monitored judiciously during refeeding to avoid complications such as congestive heart failure [33,63]. Furthermore insulin induced by carbohydrate infusion has Na- and water-retaining effects in the renal tubules [57,64]. Rapid correction of hyponatremia may lead to central pontine myelinolysis as in case 1. Thus, it is recommended that Na levels are corrected to no more than 12 mM/L within a 24-h period [65].

Energy supplementation

The authors of case 3 document that nutrition was infused abruptly at twice the recommended level for that time period because the caretakers were eager to reverse the patient's cachectic state ''without delay.'' It has been documented many times that in nutritional repletion, meal administration must occur gradually [9,36]. Carbohydrate supplementation must not exceed 7 g/kg/d (28 kcal/kg/d) in the healthy individual [63]. Nutrition must be started at no more than 10 kcal/kg/d in patients at risk, and as low as 5 kcal/kg/d in less stable patients. Calories should be given slowly and calories increased in a stepwise manner to 15–20 kcal/kg/d from days 4 to 10 [26]. An infusion rate as low as 10 ml/h in enteral feeding is recommended [30]. Note that case 5 illustrates the fact that even slow and careful administration of a hypocaloric diet does not eliminate the risk for developing RFS. We recommend advancing calories by 200–300 kcal every 3-4 d; however, slower calorie advancement may be necessary in those who fail to improve clinically [14].

Refeeding complications

Hyperglycemia during refeeding may cause hyperosmotic coma and death [40,45]. Thus glucose levels should be monitored during the initial phases of nutritional repletion to avoid drastic changes. Infections are common in RFS, as shown in case 3. Neutrophilic function can be compromised by both hyperglycemia [66] and the generalized lack of ATP [67] in hypophosphatemic patients. Respiratory complications are common in RFS, as illustrated in cases 3 and 5 [3,30].

Indices to monitor

Cardiac complications occur within the first week of refeeding [68]. During the first week, heart rate [69], ECG [44,70], and fluid balance must be monitored to prevent cardiac decompensation [25]. Abnormal values in hepatic enzymes (alanine transaminase and aspartate transaminase) have been associated with refeeding complications, which justifies their monitoring [71,72]. Malnourished children in developing countries are particularly susceptible to fluid overload due to both their chronic protein deficiency and the rapid administration of nutrition. Assessing heart rate, respiratory rate, hepatomegaly, and jugular venous pressure may be beneficial in such children [62]. Pretreatment leukocyte values can predict which malnourished children are at risk for sudden death when refeeding is started [62]. RFS may occur in the outpatient setting during oral feeding; therefore, the caretaker must discourage binging in severely starved patients [44,73]. Binging tendencies, especially in anorexics, may be prevented with periodic restraints [74]. Mild starvation, even for as little as 48 h, can precipitate RFS and may be indicated by low serum pre-albumin levels [20,63]. As previously mentioned, monitoring tends to be limited to electrolytes, but we suggest routine use of the above indices in very sick and malnourished patients undergoing nutritional support. The recommendations are summarized in Table 3.

Conclusion

RFS remains an important cause of morbidity and mortality in the severely malnourished or cachectic patient and

deserves clinical attention. It affects all age groups and the symptoms occur early during refeeding especially with TPN. Despite all the available case reports and adequate advancements in understanding the pathophysiology, symptoms and death from RFS remain high. These symptoms can be successfully prevented and treated easily when recognized in a timely manner. Patients at risk must be suspected and recognized, corrected for vitamin and electrolyte deficiencies, and supplemented slowly with adequate energy requirements, while monitoring for key life-threatening laboratory abnormalities.

Some hospitals have their adapted recommendations for managing the malnourished patient [25]. Guidelines for managing patients at risk for developing RFS are available for practice in the United Kingdom and may not apply to other countries [26]. In an effort to make these guidelines more comprehensive and for broader utilization, we have reviewed the vast majority of clinical case reports on RFS and compiled recommendations based on the derived sum of knowledge from these patients. Our report has focused on the details of nutritional support, circulatory volume restoration, and micronutrient, vitamin, and electrolyte supplementation in the patient at increased risk for developing RFS. In addition, we have demonstrated the evolution of treatment modalities and efficiency over the past 40 y and derived recommendations from both positive and negative patient outcomes, not provided by preceding guidelines. Drawbacks of this method lie in the fact that management in one case may differ substantially from another, making their comparison difficult. Studying cases and drawing conclusions from them serves as a practical tool to contribute to the growing knowledge on this topic. We have demonstrated the evolution in management of RFS over time and the needed efforts toward optimal management.

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