Refeeding syndrome in critically ill children

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Background
Refeeding syndrome (RFS) is a metabolic disturbance that occurs when nutrition is reintroduced to individuals who are severely malnourished or experiencing significant metabolic stress from a serious illness. It results from underfeeding for a period, followed by re-initiation of nutritional support. The syndrome is characterized by sudden shifts in electrolytes, including phosphorus, magnesium, and potassium, and can be potentially fatal.
Aim
This review aimed to study children with RFS to understand the incidence, risk factors, and clinical outcomes associated with this condition. Specifically, research often focuses on determining how common RFS is among malnourished or critically ill children; identifying which children are most at risk, such as those with severe malnutrition or specific medical conditions; understanding the symptoms and complications that arise from RFS, including electrolyte imbalances and metabolic disturbances; and managing and preventing children with RFS through developing guidelines for safely reintroducing nutrition to malnourished children to prevent RFS.
Conclusion
Refeeding should start with a small increase in energy intake, along with supplementation of vitamins and electrolytes. Identification of patients who are at risk and early diagnosis before treatment and initiation of feeding is a crucial step in reducing RFS. Nutrition teams can offer guidance and education on preventing, recognizing, and treating RFS. Establishing local treatment guidelines is essential to support this process.

Keywords:
children, in critically Ill, refeeding syndrome

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Introduction

Refeeding syndrome (RFS) is a potentially fatal illness if not recognized early and treated adequately. It can occur when nutrition is reintroduced following an extended period of starvation. It refers to the medical complications caused by fluid and electrolyte imbalances resulting from rapid or excessive nutritional replenishment. This syndrome is most commonly seen in individuals at high risk of malnutrition, including those with eating disorders and patients with renal failure undergoing hemodialysis [1].

RFS occurs in patients with severe malnutrition or metabolic stress due to critical catabolic conditions (such as sepsis or diabetic ketoacidosis) after the reintroduction of nutrition. It is characterized by an exaggerated physiological, metabolic cardiopulmonary, hematologic, neurological dysfunction, and biochemical response to glucose refeeding after a long period of malnutrition [2]. During the initial phase of nutritional therapy, RFS is associated with severe electrolyte deficiencies as result of a rapid dietary reintroduction whether orally, enterally, or parenterally in pediatric cases who are metabolically stressed because of severe illness or severely malnourished [3]. RFS is recognized by severe electrolytes and fluid disturbances secondary to the shift from catabolism to anabolism after the beginning of nutritional therapy [4].

The important biochemical feature of RFS is electrolyte disturbances, such as hypophosphatemia, hypokalaemia, hypomagnesemia, and decreased thiamine levels [5]. It is complicated by abnormal sodium retention and fluid balance with resulting impaired organ function; renal, respiratory failure, or heart failure and cardiac arrhythmias; peripheral oedema; increased serum hepatic enzymes, triglycerides, hyperglycemia, changes in protein, and fat metabolism; vitamin depletion (especially thiamine and folate) and trace element deficiencies [6].

The attention, awareness, and recognition of the doctors and nurses are usually clinically inefficient

and consequently miss the diagnosis of these complications with variable symptoms and signs. Scanty information is available as regards predisposition, occurrence, and management protocols. Moreover, both the clinical course and the outcome of RFS are unpredictable [7]. This review yields valuable information about the RFS and clinical guidance for the management of hospitalized cases.

Epidemiology of refeeding syndrome

The estimated incidence in pediatric ICU patients receiving nutritional support, either alone or as part of a combined treatment approach, has been reported to be as high as 7.4% [8]. A study by Christian *et al.* [9] reported that 35% of pediatric patients in the ICU exhibited symptoms and signs of RFS after nutrition was reintroduced.

In Egypt, studies were not conclusive about the prevalence of RFS in the pediatric population. A study conducted at the pediatric ICU of Cairo University reported 58% of malnourished children had hypophosphatemia during their PICU stay [10].

In neonates who are small for gestational age, the rates of hypophosphatemia have been significantly higher [11]. Additionally, neonates with a high umbilical artery resistance index were more likely to experience early hypophosphatemia [12].

Higher rates of electrolyte abnormalities, particularly hypophosphatemia, have been observed in neonates with intrauterine growth retardation and very low birth weight [13]. Mizumoto *et al.* [14] have reported hypophosphatemia and hypokalaemia in neonates receiving total parenteral nutrition.

Daniel *et al.* [15] reported the occurrence of RFS in children with diabetic ketoacidosis in intensive care units. Additionally, a higher incidence of hypophosphatemia has been observed in children with eating disorders, such as anorexia nervosa, particularly those with body weights below 68% of their ideal body weight or BMIs under 15.1 [16]. It has been observed in nutritionally supported cancer patients, with an incidence of up to 25% [17]. In developing countries, children with severe malnutrition and celiac disease are at an increased risk of developing RFS [18].

Pathophysiology of refeeding syndrome

During starvation, glucose levels start to fall within 24–72 h in a catabolic state (due to decreased consumption or even starvation). As a result, the peptide hormone glucagon and catecholamine are released, and insulin secretion is reduced [19].

The body shifts from carbohydrate metabolism to fat and protein catabolism, providing fatty acids and ketones for energy. The breakdown of protein results in the loss of lean body mass, impacting vital organs like the lungs, heart, liver, kidneys, and intestines. Myocardial atrophy can impair cardiac contractility, reducing cardiac performance and output. The activity of enzymes involved in amino acid metabolism decreases, and hyperammonaemia may develop during refeeding [20].

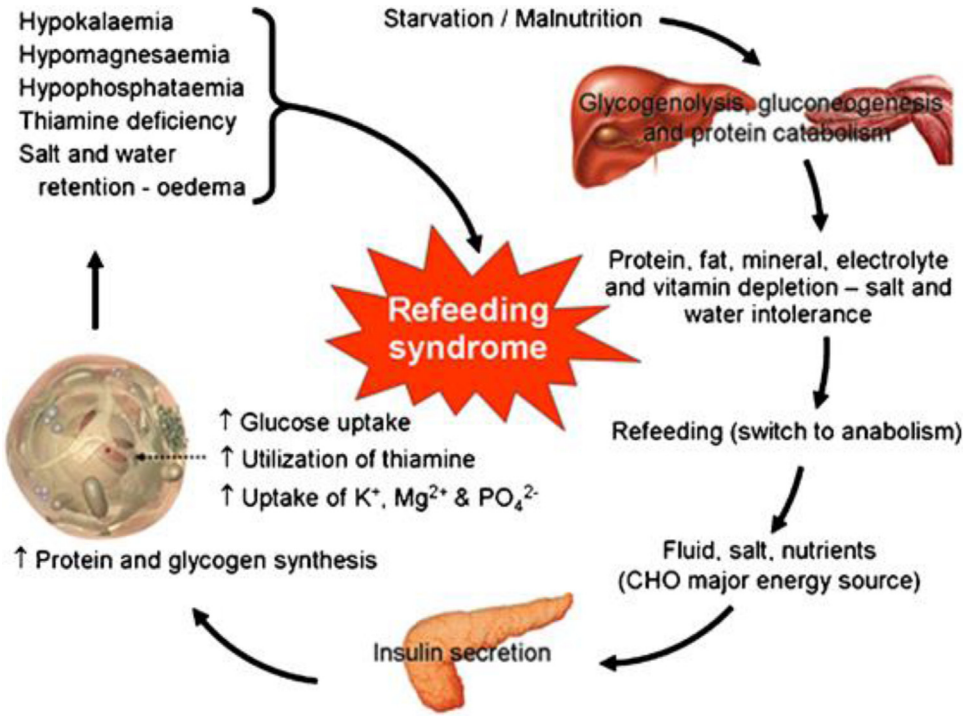
Liver wasting results in decreased synthesis of protein. Gastrointestinal atrophy is responsible for dysmotility and malabsorption, moreover aggravating malnutrition and increasing the infection risk. The kidneys also lose the ability to concentrate urine, which leads to increased diuresis. Consequently, the body becomes hypothermic, hypotensive, and bradycardic [21].

Insulin, thyroid, and growth hormones secretions are decreased. These changes occur to preserve protein and the functioning of the organs that help in survival [22]. The basal metabolic rate decreases by up to 20% to conserve energy. Functional loss of vital organs occurs, with consequent depletion of intracellular electrolytes such as potassium, magnesium, and phosphate Pulcini *et al.* [23].

Once nutrition is reintroduced to a patient after a period of prolonged starvation, anabolic processes begin immediately. The body transitions from protein and fat catabolism to carbohydrate metabolism, with glucose becoming the primary energy source once again. The increased glucose intake, along with a rise in insulin secretion, drives electrolytes back into the cells, resulting in hypophosphatemia, hypokalemia, and hypomagnesemia. Additionally, insulin exerts an anti-natriuretic effect on the kidneys, encouraging sodium and fluid retention, which leads to an increase in extracellular fluid volume, as observed by Krleza *et al.* [24], as shown in Fig. 1.

Rapid correction of undernutrition can cause intravascular volume overload through fast fluid shifts, which can precipitate congestive heart failure in undernourished patients with myocardial atrophy [25]. Insulin also promotes the synthesis of protein, fat, and glycogen, processes that depend on minerals like phosphate and magnesium, as well as vitamins such as thiamine. It aids in the cellular uptake of potassium and glucose through the sodium-potassium ATPase

Figure 1



Pathophysiology of refeeding during starvation by Krleza *et al*.[24].

transporter. As magnesium and phosphate are absorbed into the cells, water follows via osmosis. These processes result in a reduction in serum levels of phosphate, potassium, and magnesium [26].

Clinical features of refeeding syndrome

RFS typically develops within the first 72 h of rapid feeding, characterized by a drop in serum phosphate levels, or when two out of the three electrolytes (phosphate, magnesium, and potassium) fall below normal levels [27–29]

The clinical presentations of RFS can differ, from mild cases with few signs and symptoms to severe forms that may lead to life-threatening complications (Table 1), as obtained by Mehanna *et al*. [30]. RFS may affect the function of multiple organs, leading to cardiac arrhythmia, heart, and renal failure [9].

Prevention of refeeding syndrome

RFS is a preventable disease despite being associated with fatal complications [31]. There are several ways to prevent and control the RFS [32].

Assessment

Anthropometrics

Anthropometrics provide measures of height, weight, body mass index, and skin-fold measurement. These measurements determine the amount of muscle and body fat percentage. It is used to assess weight loss or gain and compare growth rates in children. To estimate growth patterns during a nutrition assessment, dietitians take anthropometric measures such as weight, height, skull, and mid-upper arm circumferences, and compare them to standard values [33].

Biochemical studies

Results of laboratory studies may provide medical professionals with useful information about medical problems that may influence appetite or nutritional status. It was possible to collect biochemical data through samples of blood and urine [34]. Plasma and urinary electrolytes, particularly phosphate, sodium, potassium, magnesium, and blood glucose, should be closely monitored before and during refeeding. A urine sodium concentration below 10 mmol/l may indicate saline depletion in urinary electrolytes. Measuring urine magnesium, phosphate, and potassium levels can also be helpful in assessing the body's loss of these electrolytes [35].

Clinical data

Clinical data includes the medical history of any diseases, previous diagnostic procedures, or current medications of suffering children. The risk of developing a nutritional deficiency or malabsorption may be raised by certain disorders or treatment procedures. It is also necessary to determine whether a child is consuming any supplements of vitamins or

Table 1 Clinical features of the Refeeding Syndrome

Hypophosphatemia (Normal range 0.8–1.45 mmol/l)	Hypokalemia (Normal range 3.5–5.1 mmol/l)
Presents as	Presents as
1-Cardiovascular: heart failure, arrhythmia, decreased stroke volume, cardiomyopathy, shock, and death	1-Cardiovascular: Hypotension, ventricular arrhythmias, cardiac arrest, bradycardia, or tachycardia.
2-Respiratory: reduced contractility of the diaphragm, dyspnea.	2-Respiratory: Hypoventilation, shortness of breath, and respiratory failure.
3-Skeleton: rhabdomyolysis, weakness, myalgia, weakness of the diaphragm	3-Musculoskeletal: Fatigue, weakness, tiredness, muscle twitching, rhabdomyolysis, and muscle necrosis.
4-Neurology: delirium, coma, epilepsy, tetany, Paresthesia, weakness, Confusion, Disorientation, lethargy, areflexic paralysis, coma.	4-Gastrointestinal: Anorexia, nausea, vomiting, paralytic ileus, and constipation.
5-Endocrine: hyperglycemia, insulin resistance, osteomalacia	5-Renal: Metabolic alkalosis.
6-Hematology: hemolysis, thrombocytopenia, and leukocyte dysfunction.	
7-Renal: acute tubular necrosis, and metabolic acidosis.	
Hypomagnesaemia	Hyponatremia
(Normal range 0.77–1.33 mmol/l)	(Normal range 136–145 mmol/l)
1-Cardiovascular: paroxysmal atrial or ventricular arrhythmias.	1-Cardiovascular: heart failure and arrhythmia
2-Respiratory: hypoventilation, and respiratory failure.	2-Respiratory failure, and pulmonary oedema.
3-Neuromuscular: fatigue, weakness, muscle cramps (Trousseau and Chvostek), tremor, tetany, ataxia, vertigo, paresthesia, hallucinations, depression, convulsions, and coma	3-Renal failure
4-Gastrointestinal: abdominal pain, diarrhea, or constipation, vomiting, and appetite loss.	4-Skeleton: muscle cramps, fatigue, and oedema.
5- Anemia.	
6- Refractory hypocalcemia and hypokalemia	
7-Death	
Vitamin/Thiamine Deficiency	Hyperglycemia
Deficiency of thiamine presents as	1-Cardiac: Hypotension
1-Neurology:Wernicke–Korsakoff syndrome, and psychosis,	2-Respiratory Failure, Hypercapnia
2-Cardiovascular: congestive heart failure and lactic acidosis, beriberi, disease, and encephalopathy.	3-Ketoacidosis, and coma
3-Skeleton: muscle weakness	4-Dehydration
4-Death	5-Impaired immune function

Cited from Mehanna *et al*. [30].

minerals that may influence their nutritional status. Oedema, heart, or respiratory failure may exist because of fluid overload, electrolyte abnormalities, and vitamin deficiencies [33].

Dietary data

The dietitian obtains information about any known food allergies and food intolerances. The dietitian asks the patient about the last 24 h before the nutrition assessment. Alternatively, the dietitian may record each food or drink consumed for 3 days to a week. A food frequency questionnaire may be included in the dietary data component. It may be used to collect information about how much a particular food group is consumed [32].

Identification of high-risk patients

Identification of patients who are at risk and early diagnosis before treatment and initiation of feeding is a crucial step in reducing RFS. Those at risk include patients with chronic malnutrition, marasmus, or kwashiorkor; prolonged starvation for a period of 10 to 14 days; diabetic ketoacidosis; chronic renal failure; prolonged intravenous hydration; pathological obesity; significant weight loss; and patients who have recently lost 5–10% in the last 2 months [34], as shown in Table 2 by Friedli *et al*. [36].

Risk assessment (ASPEN Criteria for Identifying Pediatric Patients at Risk for RFS,2020) [32]

The ASPEN Criteria includes

(a) Anthropometry (Weight-for-length, or BMI-for-age *z*-score).
(b) Bad energy intake.
(c) Comorbidities.
(d) Decreased S.C fat and muscle mass.
(e) Electrolytes disturbances.

Before initiating nutritional therapy, it is advised to identify patients at risk of RFS to adjust the nutritional treatment plan accordingly as shown in Table 3 by Joshua *et al*. [32]. There are some differences between adult and pediatric populations in terms of RFS risk.

Table 2 Pediatric patients at high risk of RFS

1-Patients with anorexia nervosa.
2-Individuals with body weight less than 80% of their ideal body weight.
3-Patients who have been malnourished or not fed for 10–14 days (including those receiving extended intravenous fluids without sufficient calories or protein) or have experienced rapid, significant weight loss.
4-Postoperative patients.
5-Individuals with chronic conditions that lead to malnutrition, such as uncontrolled diabetes mellitus, cancer, congenital heart disease, chronic liver disease, and cirrhosis.
6-Patients with uncontrolled diabetes mellitus, which leads to electrolyte depletion and diuresis.
7-Individuals with chronic malnutrition, such as marasmus and kwashiorkor.
8-Those on a low-energy diet or who have undergone prolonged fasting.
9-Morbidly obese patients with significant weight loss.
10-High-stress patients who have been unfed for more than 7 days.
11-Patients with gastrointestinal diseases, such as chronic liver disease, dysphagia/dysmotility (e.g. eosinophilic esophagitis), severe gastroesophageal reflux disease (GERD), cyclic vomiting syndrome, or intestinal failure.
12-Malabsorptive syndrome as inflammatory bowel disease, chronic pancreatitis, cystic fibrosis, short bowel syndrome
13- Long term users of antacids (magnesium and aluminum salts bind phosphate) and diuretics (loss of electrolytes)
14-Patients with hemodialysis or chemotherapy
15-Cerebral palsy and other conditions cause dysphagia.
16-Children of neglect.

Cited from Friedli *et al*. [36].

The risk of RFS is closely tied to the degree of malnutrition, but adults are generally more tolerant of prolonged periods of starvation. In children, even short periods of nutritional deficiency can have more significant effects due to the additional metabolic demands of growth and development [32].

Monitoring at baseline of patients at risk of developing RFS:

Close monitoring may aid in the prevention or reduction of RFS complications. In the initial phase of nutritional support, a patient should be placed on a cardiorespiratory monitor. Neuromuscular and mental status should be routinely assessed. To avoid fluids overload and their possible cardio-respiratory sequalae, fluid intake, and urine output should be carefully monitored. Checking daily weight also ensures proper fluid balance to prevent volume overload. The weight gain goal should be no more than 1 kg per week, as shown in Table 4 by Friedli *et al*. [37].

Management of refeeding syndrome

The initiation of feeding should start on day 3 of hospitalization, at which time the patient's phosphorous, potassium, and magnesium levels are within the normal reference ranges [32]. However the management of RFS should include:

Table 3 ASPEN Consensus Criteria for Identifying Pediatric Patients at Risk for RFS

Variables	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 from baseline	–2 to –2.9 *z*-score from baseline	–3 *z*-score from baseline
Weight loss	Below 75% of the normal expected rate of weight gain.	Below 50% of the normal expected weight gain	Below 25% of the normal expected weight gain
Energy intake	3–5 consecutive days of protein or energy intake less than 75% of the estimated needs.	5–7 consecutive days of protein or energy intake below 75% of the estimated need.	Over 7 consecutive days of protein or energy intake below 75% of the estimated requirement.
Serum potassium, phosphorus, or magnesium concentrations	Mildly decreasedto 25% below lower limit of normal	Moderately/significantlydecreased to 25%–50% below lower limit of normal	Significantly decreased to 25%–50% below lower limit of normal
Higher-risk comorbidities	Mild diseases	Moderate diseases	Severe diseases
Loss of subcutaneous fat	Mild loss of s.c fatOR *z*-score of mid-upper arm circumference of –1 to –1.9	Moderate loss of s.c fat OR *z*-score of mid-upper arm circumference of –2 to –2.9	Severe loss of s.c fat OR *z*-score of mid-upper arm circumference of –3 or greater
Loss of muscle mass	No changes	Mild or moderate muscle mass loss OR *z*-score of mid-upper arm circumference of –2 to –2.9	Severe muscle mass loss OR *z*-score of mid-upper arm circumference *z*-score of –3 or greater

Cited from Joshua *et al*. [32]

Table 4 Monitoring at baseline of patients at risk of developing RFS

Clinical monitoring	Biochemical monitoring
• Identify high-risk patients early and regularly monitor blood pressure and heart rate. • Track fluid intake and output. • Observe for neurological signs and symptoms. • Monitor changes in body weight, and the rate of feeding. • Provide patient education.	• Track blood glucose and electrolytes levels. • Perform ECG monitoring in severe cases.

According to Friedli *et al., 2017* [37]

Nutritional support

The NICE and ASPEN guidelines suggest that refeeding is initiated in patients who consumed little foods for more than 5 days. It is beneficial to control dietary and fluid consumption deficits. Nutritional repletion should be initiated gradually and customized to meet everyone's needs for patients at high risk of RFS. The intake can then be progressively increased to meet or exceed full requirements over the course of 4–7 days as reported in Table 5 by Joshua *et al.* [32].

Correction of electrolyte abnormalities

The management principles aim at correcting biochemical abnormalities and fluid imbalances. Correction of electrolyte abnormalities should be done before the start of feeding according to the [38]. Serum electrolyte levels should be checked daily during the first week and at least three times in the subsequent week, until stability is achieved. Also, urinary electrolytes can be tested to determine body losses and to guide replacement. Hypophosphatemia, hypokalemia, and hypomagnesemia are treated with intravenous supplementation in hospitalized patients, as reported in Table 6 by Pantoja *et al.* [39].

Potassium, phosphate, calcium, and magnesium supplements should be given orally, enterally, or intravenously. Further infusions may be necessary with careful monitoring of serum electrolyte levels [38]. Patients with confirmed renal dysfunction, hypocalcemia, or hypercalcemia should take necessary precautions [40].

Correction of fluid balance and sodium intake

A fluid intake of 25–35 ml/kg/day is typically sufficient to maintain proper hydration. Fluid intake should account for both artificial feeding and infusions. Fluid balance should be assessed and corrected daily. Abnormal losses, such as those caused by fever, vomiting, or diarrhea, should be identified when the replenishment phase begins. Balanced solutions are the preferred option. Fluid intake should cover routine daily maintenance needs, along with the replacement of any water and electrolytes lost. Diuretics may be helpful in managing excess fluid by regulating sodium transport in the kidneys [41].

During the initial period of refeeding, sodium should be restricted to avoid fluid overload, particularly in

Table 5 ASPEN consensus recommendations for prevention and treatment of pediatric patients at high-risk of RFS

Aspect of Care	Recommendations
Initiation of nutrition	1- Start with a maximum of 10 kcal/kg/day and gradually increase over 4–7 days to meet full nutritional needs. 2-Begin the glucose infusion at a rate of 4–6 mg/kg/min, increasing by 1–2 mg/kg/min daily until reaching a maximum of 14–18 mg/kg/min. 3-A minimal amount (2 cc/h) of Pediasure isindicated continuously by nasogastric infusion
Protein restriction	No recommendation
Electrolytes	1- Check serum levels of potassium, magnesium, and phosphorus before initiating feeding. 2-Monitor high-risk patients every 12 h for the first 3 days, then once daily for 1 week, and at least three times during the following week until stability is reached. 3-Correct any electrolyte deficiencies. 4-No recommendation can be made for prophylactic electrolyte dosing if refeeding electrolyte levels are normal. 5-If electrolytes are difficult to correct during the initiation of nutrition, decrease calories/grams of dextrose by 50% and advance the dextrose/calories by 33% of the target every 1–2 days depending on clinical presentation.
Thiamin and multivitamins	1-Administer Thiamine 2 mg/kg, up to a maximum of 200–300 mg/day, before feeding or starting IV fluids with dextrose inhigh-risk patients. Maintain thiamine supplementation for 5–7 days, or longer, in patientswith severe starvation, other risks for deficiency, and/or symptoms of thiamine deficiency. 3- Multivitamins are recommended.
Monitoring and long-term care	1- Check vital signs every 4 h during the first 24 h after initiating nutrition. 2- Cardiorespiratory monitoring is advised for patients who are unstable or have severe deficiencies. 3-Weigh patients daily and monitor intake and output. 4-Estimate energy requirements as necessary for patients receiving oral feeding.

Joshua *et al*. [32]

Table 6 Guidelines for phosphate, magnesium, potassium replacement in children

	Intravenous potassium Replacement Dose (Administer over 6–12 h)	Intravenous magnesium Replacement Dose (Administer over 4 h)	Intravenous phosphate Replacement Dose (Administer over at least 1 h)
Mild deficiency	For potassium levels between 3.1–3.5 mmol/l,administer oral replacement with 20 mmol (as KCl or other salts) or IV replacement with 20 mmol of KCl over 4–8 h. Check levels the following day.	Oral replacement with 10–15 mmol of $MgCl_2$, Mg-citrate, or Mg-L-aspartate. Oral magnesium should be administered in divided doses to minimize diarrhea, as the absorption process is saturated at ~5–10 mmol ofmagnesium.	Oral replacement with 0.3 mmol/kg/day of phosphate (divided doses to minimize diarrhea) OR IV replacement with 0.3 mmol/kg/day of phosphate (as K_3PO_4or Na_3PO_4) over 8–12 h. Check levels the following day.
Moderate deficiency	For potassium levels between 2.5–3.0 mmol/l,administer IV replacement with 20–40 mmol of KCl over 4–8 h. Check levels after 8 h; if they remain abnormal, administer an additional 20 mmol of KCl.		For phosphate levels between 0.3–0.6 mmol/l, IVreplacement with 0.6 mmol/kg/day of phosphate (as K_3PO_4or Na_3PO_4) over 8–12 h isrecommended. Check levels after 8–12 h and repeat the infusion if necessary, with a maximum of 50 mmol ofphosphate in 24 h.
Severe deficiency	For potassium levels <2.5 mmol/l, administer IV replacement with 40 mmol of KCl over 4–8 h. Check levels after 8 hours; if they remain abnormal, administer an additional 40 mmol of KCl.	For magnesium levels <0.5 mmol/l, administer IV replacement with 20–24 mmol of $MgSO_4$(4–6 g) over 4–8 h. Reassess levels every 8–12 h	<0.3 mmol/l Same replacement therapy as for moderate deficiency.

Pantoja *et al*. [39]

patients with cardiac dysfunction. Friedli *et al*. [37] recommend restricting sodium intake to 20 mEq/day and total fluid intake to 1000 ml/day or less during the first few days of nutritional therapy to prevent fluid overload. The central venous pressure and heart rhythm monitoring should be considered in patients at high risk of heart decompensation [40].

Correction of micronutrient deficiency

Oral iron supplementation should be given after the first week of the beginning of the nutritional therapy. In malnourished catabolic patients, parenteral iron supplementation must be considered with caution, as it may cause and/or prolong hypophosphatemia [42].

Multivitamin and thiamine supplementations are recommended before and for the first 10 days of refeeding by all guidelines [39]. It is recommended to administer a prophylactic high dose of oral thiamine (200–300 mg) at least 30 min before starting refeeding to reduce the risk of Korsakoff's syndrome or Wernicke's encephalopathy. Multivitamins and trace element supplements should be given once daily [43].

Wernicke's encephalopathy is a neurological disorder caused by a lack of thiamine (vitamin B1). It is defined by a set of three symptoms: confusion, ataxia (lack of muscle coordination), and ophthalmoplegia. This condition is often seen in individuals with malnutrition, alcoholism, or those with certain medical conditions that impair thiamine absorption [44].

Korsakoff's syndrome is a long-term complication that can develop after Wernicke's encephalopathy. It is primarily characterized by memory problems, especially difficulty forming new memories (anterograde amnesia), and confabulation (the fabrication of stories to fill in memory gaps). Korsakoff's syndrome is also associated with a thiamine deficiency and is often seen in individuals with chronic alcohol use or severe malnutrition [45].

Monitoring and long-term care

Monitoring vital signs, such as blood pressure, heart and respiratory rates, oxygen saturation, hydration levels, and fluid balance, is essential for identifying early signs of RFS, including fluid overload and organ failure, especially renal failure, during the vulnerable phase (up to 10 days) [40]. Daily tracking of body weight and hydration status is recommended, as an increase of 0.3–0.5 kg/day in body weight may signal the early stages of fluid overload [37].

Only during the first three days is electrocardiogram monitoring recommended in highly exposed candidates to RFS and in those having significant electrolyte abnormalities before refeeding, as they may display severe arrhythmia with prolongation of the QT interval [34,37].

Signs like oedema, tachycardia, or tachypnoea should be treated as soon as possible, and correction of malnutrition must be maintained in accordance with the guidelines for the most critical patients. Weekly assessments of serum prealbumin and albumin levels have also been recommended. Electrolytes should be carefully monitored and supplemented throughout the refeeding process [37].

Table 7 Important symptoms and clinical complications of RFS

Cardiovascular	Gastrointestinal	Respiratory	Neurologic	Metabolic
Arrhythmias Tachycardia Hypotension Congestive heart failure Shock Sudden death	Vomiting Abdominal pain Maldigestion malabsorption Constipation	Dyspnea Respiratory failure Ventilator's dependency Diaphragm muscle weakness	Anorexia Paresthesia Tremor Wernicke encephalopathy Korsakoff syndrome Ataxia Tetany Coma	Hyperglycemia Metabolic acidosis Metabolic alkalosis Respiratory alkalosis Insulin resistance
Musculoskeletal	Hepatological	Hematologic	Renal	
Weaknesses Myalgia Rhabdomyolysis Osteomalacia	Acute liver failure	Anemia Hemolysis, Thrombocytopenia Leukocyte dysfunction	Acute tubular necrosis	

According to Friedli *et al*. 2020 [29].

Important clinical sequalae of refeeding syndrome in critically ill children and management of complications

Malnutrition can result from decreased food intake, reduced nutrient absorption as in celiac disease, inflammatory bowel disease, pancreatitis, or critical illness, surgery, and cancer. The most often observed clinical signs of patients suffering from RFS are peripheral oedema, tachypnoea, and tachycardia. When such signs arise, it is important to treat them and to rule out a potential lung embolism, as reported in Table 7 by Friedli *et al*. [29].

Patients with RFS are usually dehydrated and need to address existing hydration deficits, as well as replace abnormal fluid losses. Nutritional recovery should be started gradually and individualized for each patient. The introduction of carbohydrates during the refeeding phase results in a rapid reduction in renal sodium and water excretion [35].

Patients require close fluid balance monitoring to prevent fluid overload, pulmonary and brain oedema, congestive cardiac failure, and cardiac arrhythmia [46]. During this vulnerable phase, an excessive amount of glucose delivery causes hyperglycemia, osmotic diuresis, dehydration, metabolic acidosis, hyperosmotic coma, ketoacidosis, hypercapnia, and respiratory failure [47].

Severe malnutrition may cause hepatic injury and hematological disorders as hypoplasia of the bone marrow [48]. An excessive rise of hepatic enzymes occurs in association with poor perfusion of the liver and oxidative injury with reduced glutathione [49].

Conclusion

RFS is a potentially fatal condition that occurs when nutrition is rapidly reintroduced after a period of undernutrition lasting more than 10 days. Despite being potentially preventable, it is associated with high morbidity and mortality. Patients with RFS clinically present with a wide variety of signs and symptoms that range from minor illness up to critical and even fatal one. The patients manifest with hyperglycemia, low levels of phosphate, K, and Mg, and hypovitaminosis, mostly of vitamin B1, in addition to failure of volume and Na homeostasis leading to an arrhythmogenic effect and multisystem dysfunction. Nutrition assessments are used to assess the nutritional status and growth patterns of the affected cases to plan a nutritional intervention that helps an individual to achieve the desired health status. Refeeding should begin with a low level of energy replacement. Electrolyte replacement and vitamin supplementation are also necessary and should continue for at least 10 days. Identification of patients who are at risk and early diagnosis before treatment and initiation of feeding is a crucial step in reducing RFS. Nutrition teams can offer guidance and education on preventing, recognizing, and treating RFS. Local treatment protocols should be established to support this process.

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There are no conflicts of interest.

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