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An overview of Refeeding syndrome

Sphesihle Mthembu

Moderator: Luansha Naicker

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

School of Clinical Medicine
Discipline of Anaesthesiology and Critical Care

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INTRODUCTION

Malnutrition is frequent in chronically ill patients and is associated with several complications, refeeding syndrome is one of those complications.[1] Refeeding syndrome was first officially described after World War II in prisoners in the 1940s.[2] Schnitker et al. documented the course of Japanese prisoners following liberation. [3]These patients were noted to have neurological and cardiac abnormalities when feeding was commenced after prolonged periods of starvation, one fifth of these prisoners died unexpectedly despite refeeding and supplementation. [3, 4] The term was first coined by Weinsier and Krumdiek in 1981, they also described the fatal outcomes during parenteral feeding. [2]The first clinical description is sometimes attributed to older sources including Rodulfus Glaber in 1033 and Antonio Beniviene in 1507. [2]

Definitions

Refeeding syndrome (RFS) is defined as a severe, life-threatening, potentially fatal cluster of symptoms and signs caused by a switch from catabolic to anabolic metabolism resulting in metabolic abnormalities, electrolyte disturbances and fluid shifts in previously malnourished patients in whom feeding is reinitiated whether orally, enterally or parenterally. [1, 2, 5]The distinguishing characteristic is hypophosphataemia. It is associated other biochemical abnormalities including disorders of sodium and fluid balance, changes in glucose, abnormalities in protein and fat metabolism, thiamine deficiency, hypokalaemia and hypomagnesaemia. Using hypophosphataemia solely as a risk identification strategy can lead to false positives and false identification, because there are many other causes of hypophosphataemia. This entity is often not recognized in non-specialist wards.[2] The incidence of refeeding syndrome is largely unknown, because no universally accepted definition exists.

The National Institute for Health and Clinical Excellence (NICE) guidelines divide RFS into two categories, imminent RFS and manifest FRS. Imminent RFS which is defined as a phosphate decrease from baseline of >30% or a phosphate of <0.6 mmol/L or decrease in other electrolytes below baseline without clinical manifestations within 72 hours of nutritional reinitiation. Manifest RFS presents with electrolyte abnormalities as described above as well as clinical manifestations. [1]

The ASPEN criteria divides refeeding syndrome into mild, moderate and severe depending on the degree of electrolyte disturbance. It defines it as a decrease in one or more of the following electrolytes phosphorus, potassium and magnesium as described in table 1 within 5 days of reinitiating or significantly increasing nutritional intake. The grading or severity of the syndrome is dependent on the degree of electrolyte abnormalities.[1, 6]

RS Definition	Diagnostic Criteria
Refeeding hypophosphatemia	Various degrees of % phosphate reduction after refeeding or drop below predefined cut-offs [17]
NICE guidelines integrated by Friedli et al. [32,48]	Imminent RS: Decrease in phosphate from baseline >30% or <0.6 mmol/L OR any two other electrolytes decrease below normal range within 72 h after start of nutrition therapy without clinical manifestations Manifest RS: Clinical symptoms of RS associated with the previous phosphate or electrolyte shift within 72 h after start of nutrition therapy
King's College criteria [50]	Severely low electrolyte concentrations (potassium below <2.5 mmol/L, phosphate < 0.32 mmol/L, or magnesium < 0.5 mmol/L) associated with peripheral edema or acute circulatory fluid overload and organ dysfunction including respiratory failure, cardiac failure, and pulmonary oedema
ASPEN consensus criteria [1]	Mild RS: A decrease in any one, two, or three of the following: serum phosphorus, potassium, and/or magnesium levels by 10–20% within 5 days of reinitiating or substantially increasing energy provision Moderate RS: A decrease in any one, two, or three of the following: serum phosphorus, potassium, and/or magnesium levels by 20–30% within 5 days of reinitiating or substantially increasing energy provision Severe RS: A decrease in any one, two, or three of the following: serum phosphorus, potassium, and/or magnesium levels by >30% and/or organ dysfunction resulting from a decrease in any of these and/or due to thiamine deficiency within 5 days of reinitiating or substantially increasing energy provision

Table 1. *Refeeding syndrome definitions and diagnostic criteria. Krutkyte, G. et al. Refeeding Syndrome: A Critical Reality in Patients with Chronic Disease. Nutrients 2022, 14, 2859. https://doi.org/10.3390/nu14142859*

Clinical presentation

The clinic picture of these patients varies considerably the most common symptoms include tachycardia, tachypnea, delirium and peripheral edema. Other symptoms, such as impaired neuromuscular function, cardiac arrhythmia, congestive cardiac failure, encephalopathy, neuropathy and variable gastrointestinal, cardiac arrythmias are also possible due to the electrolyte disturbances as described above. Rapid deterioration of the clinical condition can be expected.[2, 5]

The suggested diagnostic criteria for refeeding syndrome varies across the literature. Certain sources suggest the use of a combination of severely low serum electrolytes, peripheral oedema or fluid overload, and a severe disturbance in organ function.[5, 7] The American Society of Parenteral and Enteral Nutrition suggests the use of combination of a decrease of at least 10% in at least one serum electrolyte and /or organ dysfunction resulting from these electrolyte abnormalities and/or secondary thiamine deficiency all developing within 5 days of initiation of nutritional support. [5] Using hypophosphataemia solely as a risk identification strategy can lead to false positives and false identification, because there are many other causes of hypophosphataemia.

Pathophysiology

The pathophysiology of refeeding syndrome (RFS) is not completely understood. The proposed mechanism is centered around the switch from catabolic to anabolic metabolism causing overwhelming transcellular shifts of electrolytes when feeding is initiated. The resultant clinical consequences are water retention and electrolyte deficiencies.[1, 3]

Prolonged fasting

Early in starvation the blood glucose levels fall, resulting in a decrease in insulin and an increase in glucagon levels. Glycogenolysis is then stimulated in the liver. Lipolysis of triacetylglycerol also ensues producing fatty acids and glycerol which are then converted to ketone bodies to be used by tissues for energy. [2]As the glycogen stores dwindle (within 24 hours), gluconeogenesis is stimulated using amino acids (from muscle breakdown), lactate and glycerol. This glucose is used by the brain and red blood cells. Therefore, the energy source is switched from carbohydrates to protein and fat. During this period the basal metabolic rate decreases by 20% to 25%.[2]

In the later stages of fasting the human body adapts to the depletion of nutrients by prioritizing the conservation of energy and essential functions as well as muscle and protein. [8]The use of ketone bodies as an energy source decreases in the peripheral tissues in exchange for the use of fatty acids. This results in an increase in intravenous ketone bodies which promotes a switch from glucose to ketone bodies as the main source of energy in the brain. [2]Due to this reduced need for glucose, the liver reduces the rate of gluconeogenesis which preserves muscle protein. In this process several intracellular minerals become severely depleted. Despite the intracellular deficiency the serum levels of potassium, calcium, magnesium and phosphate are maintained within normal limits. [2, 3] This can make the diagnosis of this syndrome difficult prior to refeeding.[3]

Re-feeding

When feeding is commenced the serum glucose will rapidly increase, stimulating an increase in insulin and decrease in glucagon secretion. Glycogen, fat and protein synthesis is increased. This anabolic state causes an immediate shift in metabolism from lipid oxidation back to glycolysis and requires a large amount of minerals including phosphate and important cofactors such as thiamine.[1, 8] Additionally, insulin stimulates the absorption of potassium along with magnesium and phosphate into the cells. This decreases the serum levels of these minerals even further, resulting in the clinical features of refeeding syndrome[2]. Water is drawn into the intracellular compartment by osmosis causing the clinical feature of fluid overload and oedema.

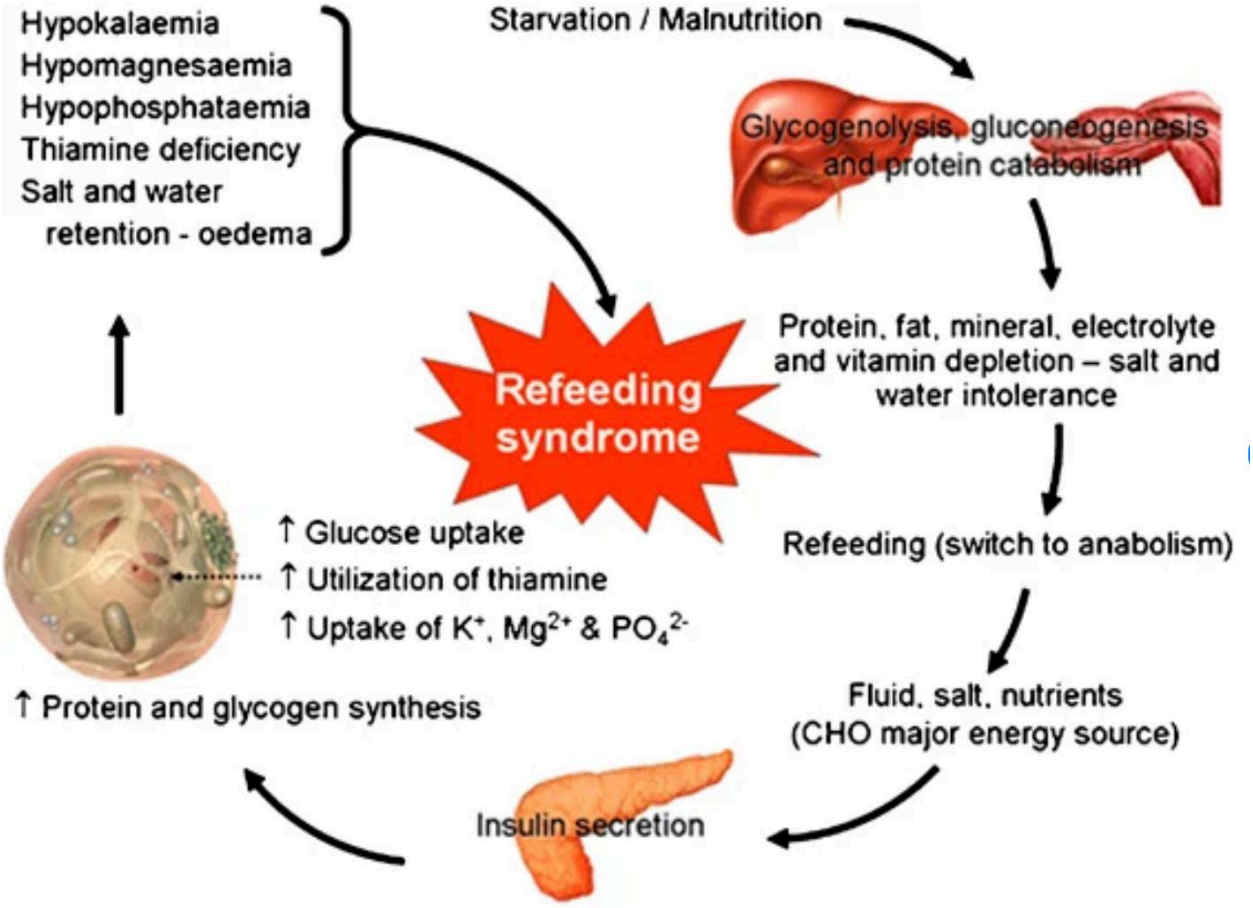

Figure 1. *Pathogenesis and features of the refeeding syndrome. Nutrition in clinical practice - The refeeding syndrome: Illustrative cases and guidelines for prevention and treatment. July 2008European Journal of Clinical Nutrition 62(6):687-94*

Phosphorus

Phosphorous is a predominantly intracellular mineral, that is essential for almost all intracellular processes. It is important for energy storage in the form of adenosine triphosphate (ATP), for enzyme and second messenger activation by phosphate binding, for control of the affinity of the oxygen binding to haemoglobin (via 2,3-diphosphoglycerate(2,3 DPG), ATP). [2]It is also important in the regulation of PH by acid-base buffering.

In RFS the long-term depletion of the phosphorous mineral in conjunction with the increase in use caused by the insulin surge, leads to a great intracellular and extracellular deficit. Even a small decline in serum phosphorus may lead dysfunction of the cellular functions noted above. [2]

Potassium

Potassium is the main intracellular cation, which can also be depleted in under-nutrition but remain within the normal range in the serum. Like phosphorus upon refeeding the

insulin surge causes potassium to shift intracellularly, causing significant hypokalaemia. This can cause derangements in the electrochemical membrane potential, causing arrythmias or even cardiac arrest. [2]

Magnesium

Magnesium is an intracellular ion that is an important cofactor for enzyme systems including production of ATP. It is also important for the structural integrity of RNA, DNA and ribosomes. [2]Because it also affects membrane potential, deficiency can lead to cardiac dysfunction and neuromuscular abnormalities. Potassium and Magnesium levels are connected; this means that severe hypomagnesaemia will lead to hypokalaemia. This necessitates the correction of both potassium and magnesium concurrently, because a potassium only replacement will be inadequate for the correction of hypokalaemia.

Vitamin deficiency

Prolonged starvation causes several vitamin deficiencies, the most important with regards to refeeding is thiamine. Thiamine is an important co-enzyme in carbohydrates metabolism which is critical in glycolysis and in the Krebs cycle. Thiamine deficiency occurs due to the sudden increase in glucose-dependent metabolic pathways, which place a high demand on enzymes requiring thiamine as a cofactor.[1, 2] This may affect glucose metabolism and result in the production of lactate leading to lactic acidosis. This deficiency can lead to Wernicke's encephalopathy (ataxia, confusional state, ophthalmoplegia and coma). This can lead to Korsakoff's syndrome, which is characterized by retrograde and anterograde amnesia and confabulation. Another complication related to thiamine deficiency is beriberi, which results from impaired ATP production due to oxidative metabolism. Beriberi can manifest as wet beriberi (congestive heart failure with tachycardia, peripheral vasodilation and oedema) or dry beriberi (nervous impairment leading to peripheral neuropathy with muscle weakness, paresthesia and hyporeflexia).[1, 2]

Glucose

After feeding has been initiated, the glucose intake leads to the release of insulin and therefore suppression of gluconeogenesis and glycogen. If glucose is taken in large quantities, it can cause hyperglycaemia as well as osmotic diuresis, dehydration, metabolic acidosis and ketoacidosis. Excess glucose also leads to lipogenesis, this may cause fatty liver, increased CO2 production, hypercapnoea and respiratory failure.

Sodium and fluid

The intake of carbohydrates leads to a sudden decrease in renal excretion of sodium and water. These patients are at risk for fluid overload if excessive fluids to maintain normal urine output. This is often made worse by loss of cardiac muscle during starvation, placing patients at risk for cardiomyopathy, reduced contractility and even cardiac failure.

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		Constipation		
Pulmonary				
Diaphragmatic weakness				
Respiratory failure				
Dyspnea				
Hematologic				
Hemolysis				
Thrombocytopenia				
Leukocyte dysfunction				

Table 2. *Clinical features of refeeding syndrome. Nutrition in Clinical Practice, Volume35 Number2, April 2020 178–195*

Risk factors and Risk stratification

The onset of RFS can be very rapid, within hours after initiating refeeding. Because of this there is a heavy emphasis on prevention and therefore early identification and detection of at-risk patients.

The primary risk factors identified include pre-existing malnutrition, poor nutritional intake of more than 5 days, malignancies, severe malnutrition, overaggressive in initiation of nutritional support without adequate supplementation of electrolytes and thiamine and associated conditions that exacerbate electrolyte and micronutrient deficiencies, such as chronic alcoholism, gastrointestinal disorders, and poor or eccentric diets. This risk is significantly higher in the geriatric population. The first step in assessing RFS risk relies on malnutrition screening tools and recognition of these comorbidities.

In 2006 the National Institute for Health and Clinical Excellence (NICE) introduced the first dedicated screening criteria and published guidelines about nutrition support in critically ill patients, including criteria for identification of patients who are at high risk for RFS.[1] This criteria includes parameters such as a low body mass index (BMI), unintentional weight loss, minimal or absent caloric intake in the preceding days, pre-existing serum electrolyte abnormalities and the presence of the above-mentioned high-risk comorbidities. [8] Another risk stratification tool that has been validated is the Short Nutritional Assessment Questionnaire (SNAQ). The value of these tools in predicting hypophosphatasemia is poor, they score poorly for specificity and sensitivity. In a 2011

review of 321 hospitalizations, only about 25% of 92 patients deemed at risk by NICE criteria developed severe hypophosphatemia during refeeding (sensitivity= 50% and specificity= 76% for parenteral feeds , and sensitivity= 38% and specificity= 73% for nasogastric(NG)feeds).[6]

There have been subsequent frameworks that have proposed similar risk parameters, this includes those proposed by Freidli et al. in 2018 as well as the ASPEN criteria in 2020. The ASPEN criteria stratifies patients into moderate or high-risk categories based on the severity of weight loss, BMI, duration of fasting, severity of pre-existing electrolyte derangements, presence of high-risk comorbidities as well as the proportion of muscle or subcutaneous fat loss.[8]

Due to the severity of its manifestations, refeeding syndrome has long been associated with life-threatening outcomes and mortality since its earliest descriptions. However, its actual prognostic impact in ICU patients remains unclear. Several studies have reported conflicting results, with significant variability depending on the definition of RFS used and the specific ICU subpopulations examined.

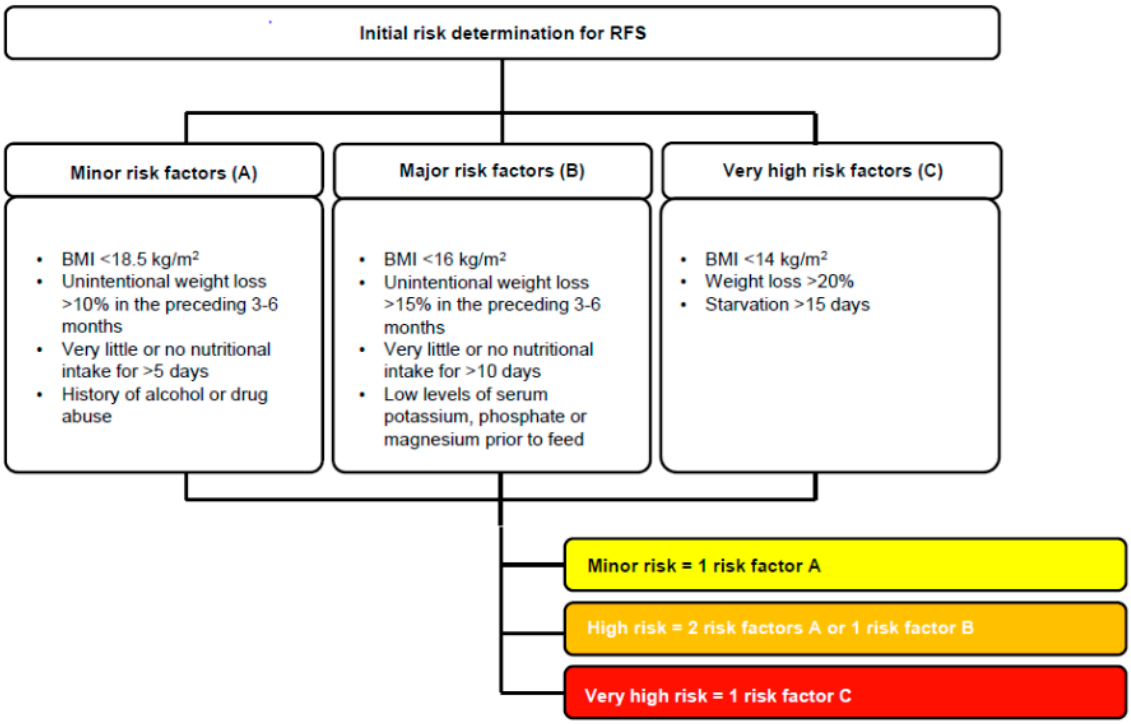

Figure 2. *Risk stratification of refeeding syndrome. Krutkyte, G. et al. Refeeding Syndrome: A Critical Reality in Patients with Chronic Disease. Nutrients 2022, 14, 2859. https://doi.org/10.3390/nu14142859*

	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 3. *ASPEN consensus criteria for identifying adult patients at risk for refeeding Syndrome. Nutrition in Clinical Practice, Volume35 Number2, April 2020 178–195*

Monitoring

The first 10 days of refeeding pose the highest risk of RFS, close clinical monitoring is required in these patients. Vital signs, hydration status, body weight or fluid balance and analysis of laboratory parameters is required to identify early signs of refeeding syndrome, these are required daily in at risk patients for the first 3 days and less frequently in the subsequent days as depicted in Figure 4. ECG monitoring is essential in the first 3 days for very high-risk patients as patients may exhibit severe and fatal arrythmias. [1, 5]

Management

To ensure prevention the NICE guidelines recommend an adequate assessment of nutrition prior to initiation of feeding. The risk factors should be ascertained. Baseline plasma electrolytes especially phosphate, sodium, potassium, magnesium and glucose should be measured and deficiencies corrected prior to refeeding. These electrolytes need to be closely monitored during feeding. There is a huge overlap between the avoidance of RFS and prevention of worsening of RFS since there is no aetiologic therapy for it. The overall management of RFS relies on early detection and supportive measures as well as cautious management of feeding.

Nutrition

RFS was initially associated with parenteral refeeding, however current evidence indicates that RFS can develop following any form of nutritional reintroduction, including oral diet, enteral nutrition (EN), parenteral nutrition (PN), or intravenous dextrose. Therefore, no specific route of nutrient delivery is currently recommended for RS prevention.

The normal energy requirements can be calculated using various feeding equations such as the Harris-Benedict and the Schofield equations. These equations use sex, weight, height, age, and level of activity. Alternatively in the absence of such equations patients should receive approximately 25 kcal/kg /day nutritional intake as estimated energy requirements. [9]This rate can be increased over the course of 5 to 10 days if there are no clinical and biochemical markers of RFS. [1, 10]

An important feature in the management of RFS is the approach to the initiation of nutritional intake. Both the ASPEN and the NICE guidelines recommend cautious initiation of feeds to reduce the risk of RFS. [8]The NICE guidelines recommend that in patients who have had inadequate nutritional intake for 5 days or more, refeeding should be started at no more than 50% of the patients' energy requirements or no more than 10kcal/kg/day or 5kcal/kg/day in very high-risk patients on the first day. These guidelines are more restrictive than the ASPEN guidelines which recommend reinitiation at 10-20kcal/kg/day. [6] The NICE guidelines also suggest that nutritional intake be started and should be tailored to each individual patient. [10] The intake can then be increased to meet or exceed the nutritional target/energy requirements over 5 to 10 days. In patients who are very malnourished (BMI <14 or negligible intake for 2 weeks or more), the recommendation is to start at a maximum of 5kcal/kg/day as mentioned above and cardiac monitoring is required in these patients due to the risk of cardiac arrythmias. Caution is required when excessive restrictive protocols are used, because they may heighten the risk of malnutrition-related complications.

In addition to the importance of the caloric regimen, a potential key factor influencing the risk of RFS may also be represented by the qualitative composition of the macronutrients delivered. A prospective cohort study in critically ill patients with coronavirus disease 2019 (COVID-19) reported that a higher protein intake during the refeeding phase was associated with a lower incidence of RFS, suggesting a potential benefit of protein supplementation in this population. Unfortunately, the opposite was found in a retrospective study in mechanically ventilated patients with established RFS found that high protein nutritional support was associated with increased six-month mortality, although no association was observed with short-term outcomes. The authors hypothesized the existence of a time- and dose-dependent effect of protein intake on RFS risk during specific phases of refeeding in critically ill patients [81]. These findings underscore the need for further research into the role of macronutrient composition in RFS prevention and outcomes.

After the diagnosis of RFS the recommendation from the Australasian Society of Parenteral and Enteral Nutrition is to wait until the electrolytes levels stabilize before progressing feeds, therefore feeds can be continued at the same rate.[5] The NICE guidelines however recommend that the energy intake should be reduced significantly. None of the guidelines suggested a complete caseation of nutritional intake. A few studies have demonstrated improved 60 day and overall survival rates in patients who received caloric restriction(20kcal/hr for 48 hours) that those who continued standard caloric intake.[5, 8]This confirms caloric restriction as the mainstay in RFS management.

Electrolytes and Vitamin supplementation

Daily monitoring of serum electrolytes is required in the first 72 hours of refeeding. [1] The ASPEN guidelines suggest that initiation of nutritional support be delayed until electrolyte abnormalities are corrected in moderate to high-risk patients. [6, 8]The NICE guidelines however suggest that the correcting electrolytes and fluid imbalances is not necessary prior to refeeding as this can be done along with feeding. This is significant shift from the previous guidelines as this potentially avoids prolonged malnourishment and its effects.[4] Oral, enteral or intravenous supplementation of potassium, phosphate, calcium and magnesium should be given as indicated in table 3 unless there are high serum levels. Electrolyte replacement is advised if serum levels are lower than the normal range (Mg <0.70-0.75 mmol/L, PO4 <0.80 mmol/L, K <3.5 mmol/L) as per local protocol. The daily dose of electrolyte replacement is given to according to the serum electrolyte values at these ranges:1-1.5mmol/kg/day of potassium, 0.2-0.4 mmol/kg/day of magnesium, 0.3-0.6mmol/kg/day of phosphate as demonstrated in table 4. [4]

The best method for electrolyte replacement is still to be determined. [8]The preferred method of electrolyte replacement is intravenous in hospitalized patients, in a High-care dependency unit or ICU. Although the preference of most clinicians is to administer phosphate via central venous access, safety and efficacy has been demonstrated when 50mmol was given via peripheral line over 24 hors in 30 patients. [1]Caution should be exercised in patients with existing renal impairment and hypocalceamia as it can worsen these parameters. [10]

There is no evidence of prophylactic electrolyte supplementation in patients who are at risk of refeeding syndrome. This can only be considered at the discretion of the treating physician.[5]

The recommendation is for vitamin supplementation to be started immediately before feeding recommencement and be continued for the first 10 days of refeeding. These are only level D recommendations. Serum electrolyte levels should be measured daily for a week, then 3 times weekly once the serum levels are normal.[5, 10]

Fluid repletion should be managed carefully to avoid fluid overload and losses replaced. Sodium administration should be limited to replacement and losses only.

Mineral	Dose
Phosphate	
Maintenance requirement	0.3-0.6 mmol/kg/day orally
Mild hypophosphataemia (0.6-0.85 mmol/l)	0.3-0.6 mmol/kg/day orally
Moderate hypophosphataemia (0.3-0.6 mmol/l)	9 mmol infused into peripheral vein over 12 hours
Severe hypophosphataemia (<0.3 mmol/l)	18 mmol infused into peripheral vein over 12 hours
Magnesium	
Maintenance requirement	0.2 mmol/kg/day intravenously (or 0.4 mmol/kg/day orally)
Mild to moderate hypomagnesaemia (0.5-0.7 mmol/l)	Initially 0.5 mmol/kg/day over 24 hours intravenously, then 0.25 mmol/kg/day for 5 days intravenously
Severe hypomagnesaemia (<0.5 mmol/l)	24 mmol over 6 hours intravenously, then as for mild to moderate hypomagnesaemia (above)

***Table 4**. Recommendation for phosphate and magnesium supplementation*

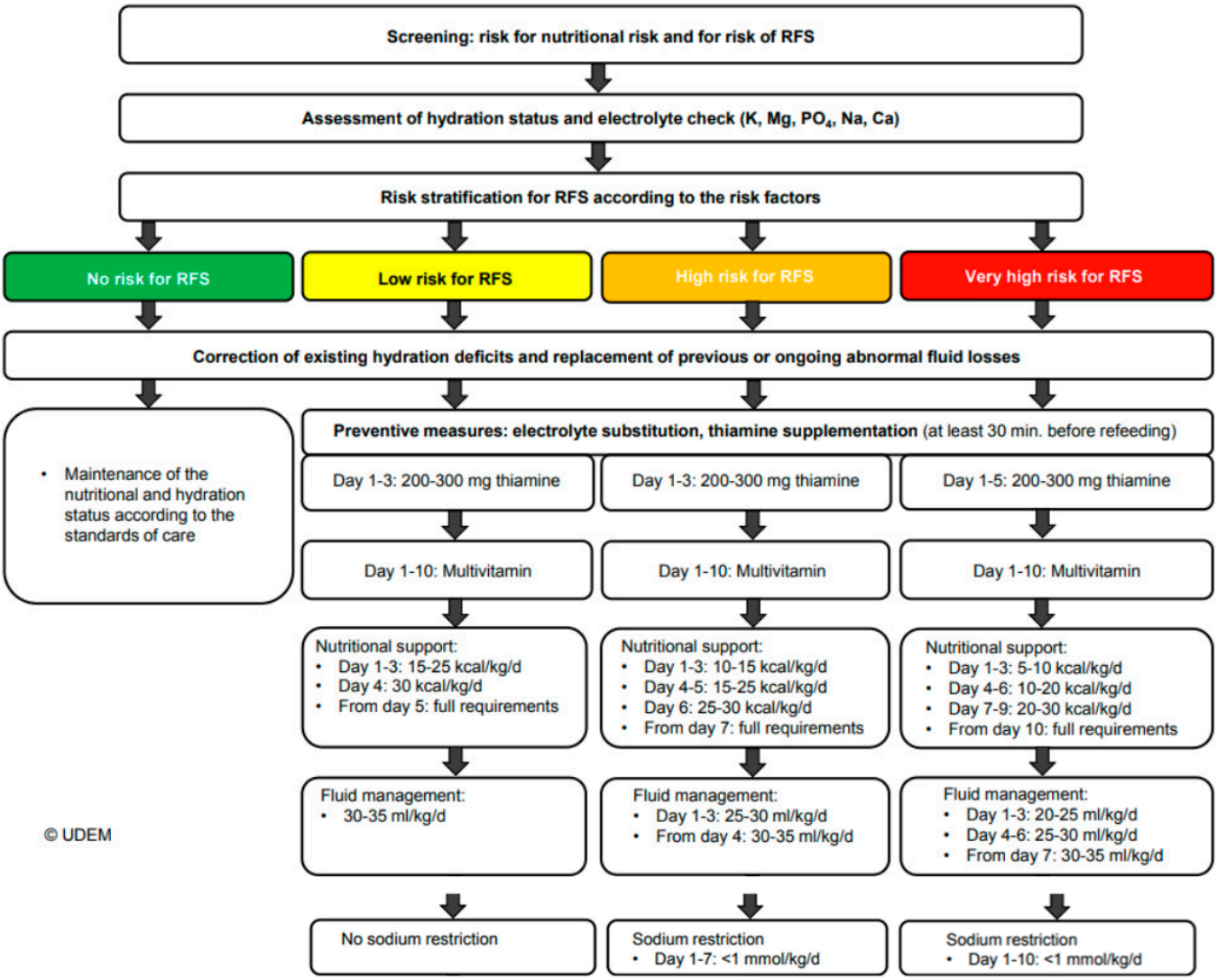

***Figure 4**. Screening and prevention algorithm. Krutkyte, G. et al. Refeeding Syndrome: A Critical Reality in Patients with Chronic Disease. Nutrients 2022, 14, 2859. https://doi.org/10.3390/nu14142859*

Anaesthetic implications

Malnutrition and long-term starvation can affect multiple body systems which can have serious sequalae as described in table 5. The most significant of these is the cardiovascular system which can present as reduction in cardiac output, blood pressure and bradycardia. These patients can also have loss of cardiac muscle with associated impaired left ventricular function and ejection fraction. [11] They can also present with reduced respiratory muscle strength and function which could predispose them to post operative pulmonary complications and need for post operative ventilation. Dehydration, renal impairment and electrolyte disturbances can also be expected in the acutely or chronically malnourished patients.[6, 11]

Preoperative assessment

The history may be difficult to elicit in these patients, especially those with chronic illnesses and psychiatric disorders. This means that we may require collateral history from caregivers and from the primary physicians. [11] The aim in this population who are either at risk or have already existing refeeding syndrome is to quantify their overall daily calorie intake and if they have any symptoms of electrolyte abnormalities.

Examination

A full examination is required; special attention should be given to the following features:

- Signs of malnutrition- thin, cachectic and wasted appearance
- Features of dehydration- dry mucous membranes, decreased skin turgor
- Features of fluid overload- peripheral oedema and abdominal swelling
- Hypotension, cardiac murmurs and arrythmias
- Evidence of vitamin deficiencies- nail changes, mouth ulcers, blindness

The European Society for Clinical Nutrition and Metabolism (ESPEN) suggests that severe undernutrition is present if one of the following is present:

- weight loss >10–15% within the past 6 months
- body mass index < 18.5
- subjective global assessment grade C (severely malnourished)
- serum albumin <3 g/dL/ 30 g/L (in the absence of hepatic or renal dysfunction).

Plasma albumin has low reliability as a marker of severe malnutrition, because it is also a “negative acute phase reactant”, meaning that it’s levels can be reduced in response to inflammation. [11]

Investigations

- Bloods- full blood count (FBC), creatinine, electrolytes, liver function tests, calcium, phosphate, magnesium, glucose, albumin.
- Urinalysis for ketonuria and proteinuria.
- ECG for cardiovascular complications such and features of electrolyte imbalance.
- Echocardiogram should be considered in patients with cardiac failure or murmurs[11]

System	Features
Central nervous system	Impaired mental ability
	Mental depression
	Depressed cognitive function
	Fatigue and generalised weakness
Musculoskeletal	Muscle mass and strength reduced
	Histologically confirmed myopathy in severe anorexia nervosa patients
	Reduced bone mass, osteopenia and osteoporosis with secondary fractures
	Impaired thermoregulation
	Impaired wound healing
Cardiovascular	Reduction in cardiac output and blood pressure and bradycardia
	Increased risk of arrhythmia due to vitamin and electrolyte disturbance
	Mitral valve prolapse (poorly understood? due to weak and thin ventricular wall)
	Loss of cardiac muscle mass with associated reduced left ventricular function and ejection fraction (consider echocardiography in anorexic patients)
	Increased vagal tone
	Peripheral vasoconstriction
	Sinus arrest and wandering atrial pacemakers
	ECG changes
	Prolonged QTc
	ST depression and T-wave inversion[14]
Respiratory	Reduced respiratory muscle strength and function
	Spontaneous pneumothorax
	Pneumomediastinum from persistent vomiting
	Decreased respiratory compliance (due to decreased elasticity of lung tissues)
Renal	Reduced glomerular filtration rate
	Total body water proportionally higher
	Proteinuria
	High urea due to dehydration
Gastrointestinal	Decreased enteral feeding leading to gut atrophy, bacterial translocation and impaired immune function (due to larger gaps between enterocytes)
	Oesophagitis and Mallory–Weiss tear from purging
	Gastric dilatation
	Paradoxical decrease in gastric emptying time
Micronutrient disturbances	Vitamin A insufficiency – blindness (xerophthalmia due to corneal ulceration is the leading cause of childhood blindness worldwide), immunosuppression[12]
	Reduced iron, ferritin and iron deficiency anaemia
	Folic acid and zinc levels may also be low
Electrolyte disturbances	Hypokalaemia (due to repeated purging and vomiting)
	Hypocalcaemia = prolonged non-depolarising muscle relaxation action. Can lead to tetany but low K^+ prevents this (rapid K^+ replacement can precipitate it though)
	Hypoglycaemia and hypoglycaemic coma
	Metabolic alkalosis (less common in malnutrition, more likely in patients who purge)
	Increased cortisol and corticotrophin-releaseing hormone levels with blunted response

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System	Features
Haematological	Leucopenia. Can be graded using Common Terminology Criteria for Adverse Events: < 1.2 = grade 3 < 2.8 = grade 2 < 3.0 = grade 1 Further drop due to stress response can occur due to inability to produce leucocytes Often normal immune function until 50% drop in normal expected body weight. Elevated liver transaminases Anaemia (often mild, due to bone marrow hypoplasia) Pancytopenia
Pharmacological	Delayed or reduced absorption of drugs Hypoalbuminaemia increases free fraction of drugs, decreased protein binding occurs[15] Prolonged treatment with non-depolarising muscle relaxants Lower total body mass means reduced drug doses required and lowered thresholds for toxicity Neostigmine, edrophinium and catecholamines can cause life-threatening arrhythmias[14]

Preoperative optimization

In the preoperative setting patients should be adequately rehydrated and renal as well as electrolyte disturbances should be corrected.

In elective cases an albumin <34g/L should be corrected with dietary supplementation to reduce the likelihood of refeeding syndrome as well as improve chances of post operative recovery. 7-10 days of preoperative parenteral nutrition was shown to improve post operative outcomes in critically ill and malnourished patients.

Perioperative management

This patient group may be at high risk for intraoperative hypothermia; therefore intraoperative monitoring of temperature is crucial. Maintain normothermia by using warm IV fluids, forced air warmer blankets and use of HME filters.

Due to wasting and loss of cushioning, these patients are also at risk for nerve compression injuries. Careful positioning is important, paying special attention to pressure points.

The potential for reduced total body mass is high which combined with low albumin concentration and volume of distribution, places these patients at high risk of drug toxicity. Smaller doses should be considered with most agents in particular non-depolarizing muscle relaxants. These should be administered with the use of a nerve stimulator, because electrolyte abnormalities can potentiate their action and prolong their duration of action. If possible, reversal agents such as neostigmine should be avoided and neuromuscular blocking agents be allowed to wear off because the reversal agents increase the risk of arrythmias. [11]

Hyperventilation should be avoided as this can further lower potassium levels, therefore lowering the threshold for life-threatening arrythmias. Halothane should be avoided for the same reason given its increased potential to cause arrhythmias. Given the potential

for cardiovascular instability and reduced cardiac output state the anaesthetist should have a low threshold for invasive cardiac monitoring.

Post operative

There is a possibility of experiencing difficulty with extubation due to impaired respiratory muscle function and impaired upper airway reflexes in the severely malnourished patient. Aim to extubate when the patient is fully awake and responding to commands, if feasible.

Refeeding syndrome in Critically ill patients

A systematic review and metanalysis was done by Schneider at al. in 2026 to ascertain the incidence of refeeding syndrome in the critically ill population as well as the mortality rates. 28 trials were included in this analysis with a total of 10412 patients of which approximately 60% were adults. In this systematic review only one RCT was included. They found a wide range of incidents across the different studies with a pooled incidence of 23%[12]. The incidence seemed to be much higher in the adult population (29%) than in the paediatric population (5%). However, these differences should be interpreted cautiously, as they may reflect variations in diagnostic criteria, surveillance intensity, and underlying disease severity rather than true differences in biological susceptibility. Neonates however were found to have a pooled incidence similar to that of adults. No statistically significant association was found between mortality and refeeding syndrome.[12]

Across all included studies, hypophosphatemia was a core diagnostic component, although biochemical thresholds, timing, and additional criteria varied considerably. In critically ill patients, electrolyte disturbances (particularly hypophosphatemia) are common and may arise from mechanisms unrelated to refeeding, including inflammation, renal dysfunction, circulatory failure, and metabolic stress. Consequently, reliance on biochemical abnormalities alone has potential to lead to misclassification and overestimation of refeeding syndrome incidence. These diagnostic limitations reduce specificity and complicate interpretation of associations with clinical outcomes, contributing to heterogeneity and limiting causal inference.[12]
In many studies, phosphate levels alone were used to define refeeding syndrome, with thresholds ranging from <1.4 mmol/L to ≤0.77 mmol/L or based on relative declines after nutritional initiation. Considerable variability was also observed in the timing of assessment, ranging from the first 72 hours to up to 8 days. Additional criteria, including potassium and magnesium disturbances, thiamine deficiency, glycemic alterations, and fluid imbalance, were variably applied. Some studies adopted ASPEN Consensus criteria, while others incorporated neonatal-specific markers such as hypercalcemia.[12]

Although associations with longer ICU stay and duration of mechanical ventilation were observed, these findings should be interpreted as observational and exploratory. They may reflect greater baseline severity, metabolic vulnerability, or clinical complexity rather than an independent effect of refeeding syndrome.[12]

CONCLUSION

Refeeding syndrome is a serious life-threatening metabolic complication arising from rapid reinitiation of nutritional support in at risk patients. This includes malnourished, critically ill patients, alcoholics or patients with inadequate nutrition. If not correctly diagnosed or if appropriate measures are not being taken, RFS can lead to increased morbidity and mortality.[4] In addition, patients with chronic disease are more exposed to this complication due to catabolic metabolism and reduced nutritional intake. That is why special attention should be devoted to preventing and managing RFS in this vulnerable population. Nonetheless, the inconclusive evidence poses a challenge to developing universal, evidence-based guidelines for the diagnosis, prevention and treatment of this disorder.

Evidence from randomized controlled trials is still lacking, this means that a bulk of the clinical management is based on expert consensus statements only. A few key aspects have been defined: Risk assessment before nutritional therapy is crucial to prevent RFS; patients at higher risk of RFS should receive a restricted energy and fluid intake as well as vitamin and electrolyte supplementation; monitoring and management of electrolyte levels and clinical symptoms is advised for patients at risk during the first 72 hours of refeeding.

Future research is needed to gain in-depth knowledge about this syndrome. A widely accepted definition of RFS needs to be defined, this will assist in developing standardized treatment protocols.

An in depth understanding on the physiological changes caused by malnutrition is required, because it can affect our anaesthetic management.

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