Review Article

Refeeding syndrome and other related issues in the paediatric intensive care unit

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Abstract: The objectives of this review are to describe the pathophysiology of refeeding syndrome, to synthesis the available evidence in critically ill children, and to provide practical recommendations for its prevention and management in paediatric intensive care units (PICUs). The refeeding syndrome appears in patients who have had a reintroduced and/or increase caloric intake after a period of restricted or no caloric intake. It is manifested by a decrease in one or many electrolytes (potassium, magnesium and/or phosphorous), a thiamine deficiency and/or sodium retention. Despite the lack of evidence, the patients most at risk for refeeding syndrome seem to be malnourished children and those with restricted nutritional intake for more than 7 days. On admission to PICU, nutritional status should be assessed, this should include anthropometric measurements (weight and height z-score, mid upper arm circumference and head circumference in young children) and a diet history. Indeed, nutrient intakes of the child prior to admission to PICU should be collected to identify whether the child's intakes were decreased or inadequate in the weeks prior to hospitalization, including the number of meals and foods consumed per day. In children with low serum levels of potassium, magnesium and/or phosphorous, these imbalances should be corrected before nutrition support is commenced, along with supplement thiamine 100 mg per day. Current recommendations to avoid refeeding syndrome in critically ill children, are that energy intake should not exceed resting energy expenditure (REE) during the acute phase of critical illness and nutritional support must be increased progressively in a stepwise manner. Finally, the presence of a protocol to guide the timing and management of nutritional support in the PICU and the presence of a nutrition support team including a dedicated dietitian is recommended.

Keywords: Critically ill children; nutrition; paediatric intensive care; refeeding syndrome

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Introduction

Refeeding syndrome describes a potentially fatal physiological response to the increase in energy (carbohydrate) from any source including: intravenous (IV) dextrose (e.g., 5% dextrose solution), oral food, enteral nutrition (EN) or parenteral nutrition (PN) following a period of starvation or severely reduced energy intake (1), reflecting a change from catabolism to anabolism following the release of insulin (2). The most common symptoms

attributed to refeeding syndrome include electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypophosphatemia), cardiac and respiratory failure. In hospitalised children, refeeding syndrome is commonly reported to occur following a period of inadequate nutrition of 7–10 days duration (3).

Definition of refeeding syndrome

Until recently, there has been no consensus based definitions for refeeding syndrome. The American Society for Parenteral and Enteral Nutrition (ASPEN) committee and clinical practice task force comprising of dietitians, pharmacists, clinicians and nurses developed consensus based recommendations for screening and managing patients at risk of, or who have developed, refeeding syndrome (4). ASPEN's definition of refeeding syndrome is "*a measurable reduction in levels of one or any combination of phosphorus*, *potassium*, *and/or magnesium*, *or the manifestation of thiamine deficiency*, *developing shortly (hours or days) after the initiation of calorie provision to an individual who has been exposed to a substantial period of undernourishment*". ASPEN proposed the following diagnostic criteria for refeeding syndrome as being (4):

(I) A reduction in serum levels in one or any of the electrolytes, phosphorus, potassium or magnesium by 10–20% (mild refeeding syndrome), 20–30% (moderate refeeding syndrome), or >30% (severe refeeding syndrome), or organ dysfunction results from a decrease in any of these and/or as a result of thiamine deficiency (severe refeeding syndrome).

(II) Combined with this occurrence within 5 days of recommencing or significantly increasing energy provision.

Pathophysiology

Refeeding syndrome is a response to rapidly changing hormonal pattern and downstream effects on metabolic pathways. During starvation, the basal metabolic rate may be reduced by 20–25%, in addition to metabolic conservation strategies involving switching from using glucose as the primary fuel to that of ketone bodies and the downregulation of pathways including gluconeogenesis (5). During periods of starvation, homeostatic mechanisms ensure serum concentrations of electrolytes such as magnesium, potassium and phosphorous are maintained by depleting intracellular ion stores, as well as mechanisms to reduce renal excretion of electrolytes (2,5).

On refeeding, with increased amount of carbohydrate, hormone levels of glucagon rapidly decrease with glycaemia and subsequent release of the anabolic hormone insulin. Increasing insulin levels drive phosphorus and potassium intracellularly to meet increased demand (e.g., phosphorylation of glucose as a result of glycolysis) and also as a result of stimulation of the sodium-potassium adenosine triphosphate (ATP)ase transporter promoting active transport of glucose and potassium and phosphorus into the cell, where phosphorus is also required for phosphorylation of glucose as glycolysis is stimulated. Phosphate is an essential component of ATP, malnutrition may lead to phosphate depletion leading to increased risk of respiratory failure (4). Thiamine deficiency may also occur as a result of malnutrition. Thiamine requirements are significantly increased during the transition from starvation to feeding, as it is involved (co-factor) for glucose dependent metabolic pathways (6). These concomitant metabolic processes result in a precipitous drop in serum levels of these electrolytes (4). Refeeding syndrome occurs as a result of functional serum deficits of these minerals in addition to a rapid change in basal metabolic rate (2,5). Fluid overload arising from hyperinsulinemic decrease in renal excretion of sodium and water leading to pulmonary oedema and congestive cardiac failure (*Figure 1*) (7).

Signs and symptoms of refeeding syndrome

Although the clinical signs of varied hallmark characteristics are (I) electrolyte abnormalities (hypokalaemia, hypomagnesaemia, hypophosphatemia and sodium retention) and thiamine deficiency (II) hyperglycaemia, (III) cardiac—arrhythmias, heart failure, (IV) respiratory—respiratory failure, intercostal and diaphragm muscle failure, failure to wean from the ventilatory, (V) haematology—anaemia, (VI) immunological—immune dysfunction, (VII) neurological—Wernicke's encephalopathy, and (VIII) musculoskeletal—weakness and rhabdomyolysis (4,7).

Consensus criteria for identifying paediatric patients at risk of refeeding syndrome

Those most at risk for refeeding syndrome are severely malnourished children with starvation physiology (8), as well as children with inflammatory bowel disease (9,10), anorexia nervosa (11), preterm infants (12), and haematological cancers (13). Yet despite refeeding syndrome

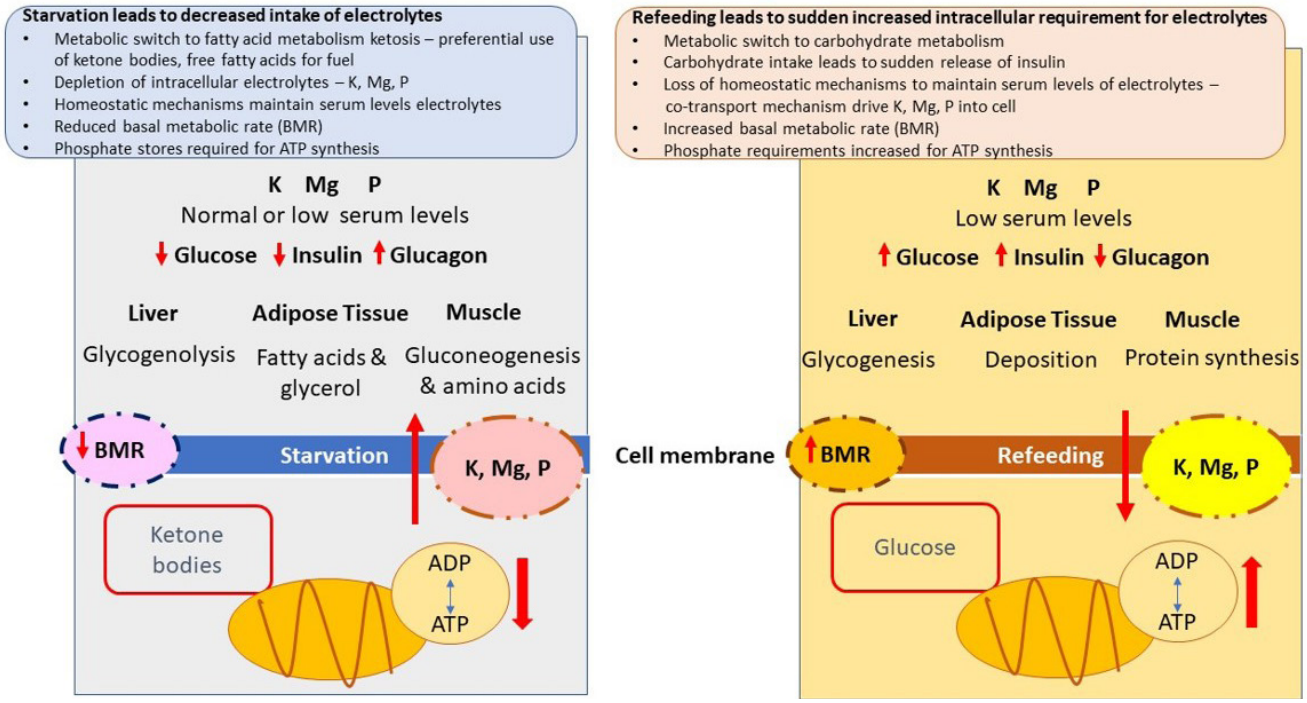

Figure 1 Pathophysiology in starvation and refeeding phase.

being considered an issue for critically ill children, there is an absence of evidence to guide medical management. ASPEN has proposed characteristics and associated diagnosis for children at risk of refeeding syndrome (4) (*Tables 1*,*2*).

Incidence of refeeding syndrome in critical illness

Paediatric critical illness

There are no studies considering the management of refeeding syndrome in children during critical illness. Only one study showed that the incidence of refeeding syndrome in critically ill children on PN was of about 9%, according to the criteria used in the institution (14). ASPEN provides management and treatment strategies for paediatric patients, however, they are not age specific and arguably may result in significant overfeeding of older children e.g., starting at a glucose infusion rate of 4–6 mg/kg/min (5.8–8.6 g/kg/day) and advancing by 1–2 mg/kg/min/per day aiming for a maximum glucose rate of 14–18 mg/kg/min (20.1–25.9 g/kg/day) (4). These starting and goal rates are significantly higher than those recommenced for critically ill children by the European Society of Paediatric and Neonatal Intensive Care (ESPNIC) (15) and the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) (16). For critically ill children, recent guidelines recommend energy intake should not exceed resting energy expenditure (REE) during the acute phase of critical illness (15-17). As this recommended amount is significantly lower than those for children in a normal ward setting, the incidence of refeeding syndrome in critically ill children may also be reduced. Prospective studies are needed to confirm this.

Neonatal critical illness

Neonates were excluded from the ASPEN consensus based recommendations for the avoidance and treatment of refeeding syndrome (4). However, the committee did recognise that neonates at risk of refeeding syndrome include those who are small for gestational age; including those inter uterine growth restriction arising from maternal complications, elevated uterine artery resistance index, extreme prematurity e.g., <28 weeks gestational age, very low birth weight and weight for age or length for age of <–2 z-scores (4). As infants arguably comprise of up to 50%

Table 1 Characteristics and associated diagnosis for refeeding syndrome, adapted from ASPEN consensus recommendations for refeeding syndrome: section 1 (4)

Section 1: paediatric diagnosis requiring PICU admission associated with an increased risk of refeeding syndrome
1. Major stressors or surgery without nutrition for prolonged periods of time
2. Oncology—solid tumours/haematological cancers
3. Post-operative patients with complications
4. Malabsorption e.g., short bowel syndrome, pancreatitis, pyloric stenosis
5. Refugees or patients from disadvantaged countries—including those with late diagnosis of chronic medical conditions e.g., congenital heart disease
6. Premature infant or small for gestational age/intrauterine growth retardation
7. Anorexia nervosa

ASPEN, American Society for Parenteral and Enteral Nutrition; PICU, paediatric intensive care unit.

Table 2 Characteristics and associated diagnosis for refeeding syndrome, adapted from ASPEN consensus recommendations for refeeding syndrome: section 2 (4)

Section 2	Mild risk—3 risk criteria required	Moderate risk—2 risk criteria required	Severe risk—1 risk criteria required
Weight for length z-scores (<24 months)	–1 to –1.9 z-scores—change from baseline	–2 to –2.9 z-scores—change from baseline	>–3 z-scores—change from baseline
Body mass index for age z-scores >2 years	<75% of normal for expected weight gain	<50% of normal for expected weight gain	<25% of normal for expected weight gain
Weight loss	3–5 consecutive days of protein or energy intake <75% of estimated requirements	5–7 consecutive days of protein or energy intake <75% of estimated requirements	>7 consecutive days of protein or energy intake <75% of estimated requirements
Energy intake	Mildly abnormal or decreased to 25% below lower limit of normal	Moderate/significantly abnormal or decreased to 25–50% below lower limit of normal	–
Abnormal prefeeding serum potassium, phosphorus, magnesium	Mild disease	Moderate disease	Severe disease
Diagnosis—section 1	Evidence of mild loss	Evidence of moderate loss	Evidence of severe loss
Loss of subcutaneous fat	–1 to –1.9 z-scores	–2 to –2.9 z-scores	>–3 z-scores

ASPEN, American Society for Parenteral and Enteral Nutrition.

of the paediatric intensive care unit (PICU) population (18,19), recognising those at risk and implementing appropriate management strategies is important and may differ from those of older children. In 2014, approximately 15 million preterm babies were born, equating to 11% of all live births worldwide, with a range of 9% in European and more than 80% in Asia and sub-Saharan Africa, where 45% of all global live births occur (20). More recently, refeeding syndrome has been described in inter uterine growth retarded term infants and preterm infants (21-28), with a number of hypothesis including a mechanism termed, placental interrupted feeding syndrome of the preterm infant (27). Medical advances, including the use of early aggressive PN with up to 3.5 g/kg per day of amino acids in infants <32 weeks gestational age (29), have significantly improved nutritional outcomes conserving intrauterine growth patterns (30). However, the unintended consequences associated with high early amino acid and glucose use (following sudden abrupt cessation of maternal nutrient supply) are hypophosphatemia, hyperkalaemia

(27,31), zinc deficiency (32), and dysregulated acid-base homeostasis during the first week of life (27,31). This has been likened to refeeding syndrome with similar physiological mechanisms as those occurring in other conditions where there is nutritional deprivation e.g., severe oedematous malnutrition (21-28). Management strategies to ameliorate this have included an increased amount of phosphorus (27) and zinc (32) when providing early aggressive nutrition support.

Studies describing electrolyte imbalance in critically ill children

Electrolyte imbalances in critically ill children are common and the presence of hypophosphatemia, hypomagnesaemia and hypokalaemia, alone does not necessarily mean refeeding syndrome is present. There are many other causes, which is of particular relevance to critically ill children, as in multiple pharmacopeia that are used to provide organ support such as e.g., inotropes, diuretics, insulin (1,2) (*Table 3*). Potassium plays an essential role in the excitability of skeletal, cardiac and smooth muscle (33). Hypokalaemia affects 40% of critically ill children with 16% experiencing moderate to severe hypokalaemia (<3.0 mmol/L), with severity associated with increased risk of mortality (34). Magnesium is an essential co-factor for over 300 enzymes, including ones associated ATP activity (35). In children, hypomagnesemia was associated with higher mortality rate and duration of PICU length of stay compared to those with normal serum levels (36), although other studies have not found a similar association with serum levels influenced by diuretic use (37). There are a number of studies considering the incidence of hypophosphatemia in critically ill children (38-42), affecting up to 42% of children on PICU admission and was associated with an increased risk of length of stay. Risk factors associated with hypophosphatemia were malnutrition and the use of furosemide, dopamine, steroids and β2 agonist (43).

The prevalence of thiamine deficiency in critically ill children

Thiamine is involved in a number of intermediate metabolic pathways associated with energy production including converting pyruvate from glucose into acetyl co-enzyme A for entry into the Krebs cycle, during thiamine deficiency alters intermediate metabolism resulting in lactic acidosis (44). Serum studies of thiamine in critical illness report 12.5–32% of patients have low thiamine levels, associated factors is the magnitude of acute phase inflammatory response (44), malnutrition (45), but not diuretic use (46) and was associated with reduced mortality risk in malnourished patients (47) but no effect was demonstrated in well-nourished patients (45,48). Four of the case studies focused on thiamine deficiency and lactic acidosis, reporting cases of symptom resolution following the supplementation of thiamine, limiting lactate production by limiting pyruvate dehydrogenase activity in septic shock (48), extracorporeal membrane oxygenation (49), haematological malignancies (50), and following cardiac surgery (51).

Screening, assessment and management of critically ill children at risk of refeeding syndrome

Assessing risk

Despite the lack of scientific data, the patients most at risk for refeeding syndrome seem to be malnourished children and those with reduced or restricted intake for more than 7–10 days (7). Prior to commencing nutrition support it may be useful for clinicians to consider the following screening questions:

- Is the children at risk of refeeding syndrome e.g., malnutrition <–2 weight-of-length z-scores or history of poor intake for 7–10 days?
- Are serum electrolytes low or on the lower end of the normal range before nutrition support has been commenced?
- Is the child on multiple pharmacopeia including diuretics and inotropic support?

Nutrition assessment

Careful screening of these patients through routine nutritional assessment on admission to PICU is essential (15), using weight-for-length z-score, body mass index-for-age, mid upper arm circumference for age using established malnutrition cut-off criteria e.g., <–2 weight-for-length z-score as those with moderate malnutrition. Recent weight loss should be documented, (if this is not possible asking caregivers for a visual assessment) along with a recent diet history are all essential to assess refeeding syndrome risk before commencing any nutrition support.

Table 3 Other causes of electrolyte abnormalities in critically ill children (2)

Hypophosphatemia	Hypomagnesaemia	Hypokalaemia
Cellular phosphate redistribution	Cellular magnesium redistribution	Cellular potassium redistribution
Insulin administration	Inotropes	Inotropes
Metabolic or respiratory alkalosis	"Hungry" bone syndrome	Glucose and insulin
Intravenous (IV) glucose	Drugs	Vitamin B12 therapy
Increased losses or poor intake	Aminoglycosides	Rapidly growing tumours
Inappropriate feed or inadequate intake	b2-adrenergic agonists	Gastrointestinal loss of potassium
High output stoma	Cyclosporin and tacrolimus	Inappropriate feed or inadequate intake
Diarrhoea	Cytotoxic	High output stoma
Phosphate binding medications e.g., proton pump inhibitors	Diuretics	Diarrhoea
Prematurity	Pamidronate, pentamidine, amphotericin B, foscarnet	Pyloric stenosis
Renal tubular phosphate loss	Proton pump inhibitors	Vomiting
Post-trauma	Increased renal loss of magnesium	Renal potassium loss
Fanconi syndrome	Postrenal transplantation	Mineralocorticoid excess conditions
Hypophosphatemic osteopenia of prematurity	Cardiac surgery	Cushing's syndrome
Chronic diuretic use	Continuous renal replacement therapy	Renal tubule mechanisms
Oncogenic hypophosphatemia	Prematurity	Alkalemia
Others	Poor magnesium intake	Carbonic dehydratase inhibitors
Hyperparathyroidism or parathyroid hormone-related peptide release	Inappropriate feed or inadequate intake	Fanconi syndrome
Liver disease	High output stoma	Severe hypomagnesemia
Septicaemia	Diarrhoea	Diuretics
	Miscellaneous	Renal tubular acidosis
	Diabetes mellitus	
	Hyperaldosteronism	
	Hypercalcemia	
	Hyperthyroidism	

Nutrition considerations for critically ill children at risk of refeeding syndrome

During the last decades, there has been increasing recognition that during the early acute phase of critical illness cautious nutrition support should be provided, with energy intake not exceeding REE, as measured by indirect calorimetry or estimated using Schofield equation (15,52), which is then increased accordingly during the stable and rehabilitative phases of critical illness (53,54). The World Health Organization (WHO) management of feeding of severe acute malnutrition follows very similar principles (8) to those recommended by Critical Care Societies (15,17,55,56) with cautious feeding with slow graded increase over a number of days (15,17,55,56) (*Figure 2*) (8). Particularly as mortality and morbidity are reportedly reduced with lower energy and protein intake

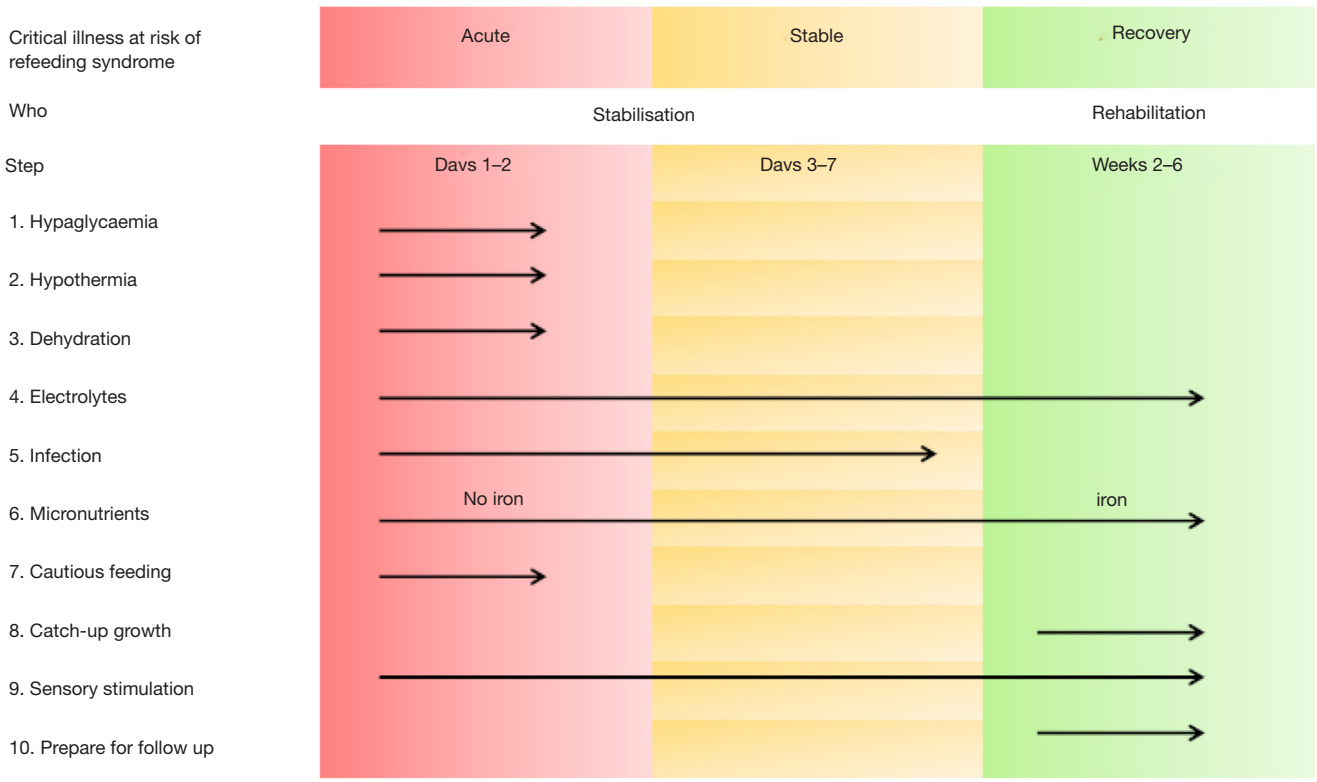

Figure 2 Schematic of World Health Organization (WHO) recommendations for the management of severe malnutrition. Adapted with permission WHO (8).

during the acute phase (57,58). For energy, the intake should not exceed the REE and for protein an intake of 1.5 g/kg/day is recommended during the acute phase (15).

In the acute phase of disease, excessive use of glucose should be avoided [maximum 5 mg/kg/min (7.2 g/kg/day)] because of the risk of hyperglycaemia due to the presence of insulin resistance in critically ill children (59), in addition to recommendations for energy (i.e., <REE) (16), amino acid (60) and protein (i.e., 1.5 g/kg/day) (58) requirements should also not be exceeded. If PN is required, it should be done so in line with ESPGHAN recommendations for energy, glucose and lipids to be administered parenterally according to age, weight and stage of disease in critically ill children (16,59,61). Micronutrient requirements during critical illness are poorly described with current recommendations suggesting they should be provided in sufficient amounts to meet reference nutrient intakes for age (62,63). However, in the context of refeeding syndrome, in those at-risk children, additional thiamine may be required with a recommended dose of 2 mg/kg (up to a maximum of 100–200 mg/day), for up to 5–7 days in addition to a multivitamin (4).

Management of children at risk of refeeding syndrome

The ESPNIC Metabolism, Endocrinology and Nutrition section provides recommendations with regards to assessment, use of nutritional algorithms, macronutrient requirements and feeding mode and type during guidance on nutritional support during critical illness, which can be adapted for children at risk of refeeding syndrome (*Table 4*) (15). To guide the timing and management of nutritional support in the PICU, the presence of a nutrition team including a dedicated dietitian is recommended. Before starting nutritional support, nutrition assessment should be completed, in addition to the monitoring and correction of any electrolytes, particularly potassium, phosphorus and magnesium is essential, along with multivitamin and thiamine supplementation. For children where serum electrolyte levels are difficult to correct or drop precipitously, where no other cause can be attributed, a reduction in energy (including dextrose containing fluid)

Table 4 Summary of nutrition requirements during acute, stable and recovery phase of paediatric critical illness—including considerations for avoidance and management of refeeding syndrome in at risk children (4,8,15,54,56)

Aspect of care	Acute phase	Stable phase	Recovery phase
Energy—using Schofield equation for weight	<REE	1.3–1.5× REE	2× REE
Protein (g/kg/day)	1–2	2–3	3–4
Carbohydrates mg/kg/min (g/kg/day)			
Newborn	2.5–5 (3.6–7.2)	5–10 (7.2–14)	5–10 (7.2–14)
28 d–10 kg	2–4 (2.9 –5.8)	4–6 (5.8–8.6)	6–10 (8.6–14)
11–30 kg	1.5–2.5 (1.4–2.2)	2–4 (2.8–5.8)	3–6 (4.3–8.6)
31–45 kg	1–1.5 (1.4–2.2)	1.5–3 (2.2–4.3)	3–4 (4.3–5.8)
>45 kg	0.5–1 (0.7–1.4)	1–2 (1.4–2.9)	2–3 (2.9–4.3)
Electrolytes			
Monitor—serum magnesium, phosphate, potassium	12 hourly	Daily	As required
Replace—electrolytes	Replace and replete low levels of electrolytes based on standards of care		Replace and replete low levels of electrolytes based on standards of care
	If electrolytes are difficult to correct or precipitously drop after nutrition support is commenced, reduce calorie/protein intake by 50% for 24 hours and then advance dextrose/calories by approximately 33% of goal every 24–48 hours		Aim to increase nutrition support to meet requirements including sufficient calories and protein to support recovery and rehabilitation
	Cessation of nutrition support may be considered for 24–48 hours if electrolyte levels are severely/life threateningly low or continuing to drop precipitously low despite replacement		
Thiamine and micronutrients	In at risk children, before feeding or IV fluids containing dextrose, is commenced provide 2 mg/kg to a maximum of 100–200 mg/day		For children receiving oral nutrition provide age appropriate oral/enteral multivitamin supplements once daily for 10 days or longer based on nutritional deficit
	Continue thiamine supplementation for 5–7 days or longer in children who are severely malnourished		
	Routine serum thiamine levels are unlikely to be useful		
	For children receiving oral nutrition provide age appropriate oral/enteral multivitamin supplements once daily for 10 days or longer based on nutritional deficit		
	Withholding PN should be considered for up to 1 week in critically ill children. However micronutrient injectables including thiamine, may be given intravenously during this time if oral enteral nutritional supplementation is not possible		
Monitoring and long term care	Establish nutrition goals for long term nutrition recovery and rehabilitation considering short terms energy and protein goals		Establish nutrition goals for long term nutrition recovery and rehabilitation considering energy and protein goals
	Monitor vital signs are per unit standard including cardiorespiratory monitoring for children who are unstable or those with severe electrolyte disturbances		Energy from protein should be given at 10–15% to support lean body mass acquisition
	Daily weights or monitoring of fluid balance should be completed		Micronutrient supplementation particularly zinc may be required to support catch up weight gain and growth

REE, resting energy expenditure; PN, parenteral nutrition.

and protein intake of up to 50% may be required for 24–48 hours. In children where serum electrolyte levels are severely or life threateningly low, nutrition support may need to be withheld for 24–48 hours in order to replete these serum levels and restore homoeostasis (4). Once nutrition support is able to be established, increasing nutrition support towards nutrition goals should be possible and increased in a stepwise manner, according to the phase of critical illness (15,52,54). Depending on nutritional status prior to admission in PICU, nutrition support may need to be continued for longer into the recovery phase until sufficient oral intake is consistently achieved to support physical and nutritional rehabilitation (54).

Conclusions

There is a paucity of evidence on the management of refeeding syndrome in critically ill children. On admission in PICU, nutrition status should be assessed, including classifying anthropometrical status and taking a diet history. For children with low serum levels of electrolytes, imbalances should be corrected to near normal levels before nutrition support is commenced, along with micronutrient supplementation of multivitamins and thiamine. However, as recent guidelines recommend energy intake should not exceed REE during the acute phase of critical illness, it is likely there is a significantly lower incidence of refeeding syndrome amongst critically ill children hospitalised in the PICU than children in a normal ward setting, although prospective studies would be needed to confirm this.

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Footnote

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