Refeeding syndrome, a critical condition in undernourished patients, is characterized by metabolic and electrolyte imbalances that occur upon reintroducing nutrition after a period of prolonged fasting. This syndrome, which includes hypophosphatemia, hypokalemia, hypomagnesemia, and thiamine deficiency, frequently affects critically ill pediatric patients who are often at risk of undernutrition due to various chronic or acute conditions. Despite its potential lethality, awareness and recognition of refeeding syndrome in this population remain low. This review addresses the clinical importance of refeeding syndrome in critically ill children and underscores the need for prevention and management strategies. Essential actions involve identifying patients at risk, reintroducing nutrition gradually, consistently monitoring serum electrolytes—especially phosphorus, potassium, and magnesium—and ensuring adequate supplementation, including thiamine. These recommendations are in line with the 2020 consensus guidelines from the American Society for Parenteral and Enteral Nutrition. The review calls attention to the frequently underestimated severity of refeeding syndrome in critically ill pediatric patients and urges the prompt development of comprehensive, evidence-based clinical protocols and educational strategies to enhance patient outcomes.

Keywords: Refeeding syndrome; Critical illness; Pediatrics; Child; Nutrition therapy

INTRODUCTION

Refeeding syndrome was first identified as a significant medical issue during World War II, when it affected severely malnourished individuals such as concentration camp detainees and prisoners of war [1]. This condition arises when individuals who have experienced prolonged periods of undernutrition are reintroduced to regular nutrition, which can lead to a sharp increase in morbidity and mortality rates following their release and the resumption of a normal diet. It is characterized by metabolic disturbances and electrolyte imbalances that can lead to severe complications, including death [2-4].

The occurrence of refeeding syndrome is well-documented in conditions such as anorexia nervosa [3,5]. However, its prevalence among critically ill pediatric patients remains unclear. These patients often suffer from undernutrition due to chronic conditions.
illnesses, various congenital and acquired diseases, malabsorption, or child abuse [6]. There is an increasing awareness of the unexpectedly high prevalence of undernutrition and refeeding syndrome in this population. Studies indicate that between 13% and 20% of patients admitted to pediatric critical care units are undernourished [7-10]. Furthermore, a study involving 1,261 children in a French pediatric intensive care unit (PICU) found that 7.4% developed refeeding syndrome. Notably, among the 15.8% of patients who were undernourished, the incidence of refeeding syndrome was much higher at 46.7%, and 58.1% of these patients experienced severe forms of refeeding syndrome [9].

The early initiation of enteral nutrition is often recommended for its overall benefits in critically ill children [11,12]. However, it may inadvertently increase the risk of refeeding syndrome. The difficulty in managing this patient population stems from the frequent occurrence of electrolyte imbalances and the nonspecific nature of the syndrome’s symptoms, which complicates diagnosis and treatment. Furthermore, the syndrome is likely underreported in the clinical setting due to a lack of awareness. A study revealed that only 14% of 281 surveyed physicians and medical students could accurately identify refeeding syndrome [13]. Consequently, it is imperative to enhance awareness of the potential complications associated with nutrition therapy, especially in undernourished critically ill children. This review aims to highlight these challenges and advocate for heightened awareness and proactive management strategies to better the outcomes for these high-risk pediatric patients.

**PATHOPHYSIOLOGY AND CLINICAL FEATURES**

Glucose is the body’s primary energy source, metabolized to provide immediate energy. Any excess glucose is stored as glycogen in the liver and muscles, or it is converted into fat for long-term storage. Additionally, fat constitutes an essential long-term energy reserve. It undergoes lipolysis to produce fatty acids and glycerol when needed. Fatty acids are an important energy source for muscles, while glycerol can be converted back into glucose. During prolonged fasting, the body efficiently prioritizes its energy sources. Initially, it depletes glycogen stores before shifting to the metabolism of proteins and fats. This metabolic shift leads to increased ketogenesis, which helps to mitigate muscle and protein breakdown. However, this adaptive response to limited energy resources can only sustain life for a limited time. Extended periods of starvation eventually result in the depletion of stored energy, along with a critical reduction in micronutrients and electrolytes, particularly phosphate, potassium, and magnesium [14].

Upon refeeding, there is an immediate transition from a catabolic to an anabolic state, marked by a rapid increase in caloric intake and a subsequent rise in insulin secretion. This increase in insulin enhances glycolysis—the process of breaking down glucose for energy. The resulting spike in insulin levels can lead to hypoglycemia and promote the transfer of electrolytes from the extracellular to the intracellular space [3,15]. This movement can significantly reduce extracellular concentrations of potassium, phosphate, magnesium, and thiamine, which acts as a coenzyme. Given the pre-existing deficiencies in these electrolytes and micronutrients due to prolonged starvation, their levels can quickly fall as they are consumed during the metabolic response to refeeding. This abrupt change can precipitate severe complications associated with refeeding syndrome, which stem from imbalances and deficiencies in electrolyte and micronutrient levels [2-4].

The clinical presentations of refeeding syndrome, which typically manifest in the initial days of nutritional reintroduction, include disturbances in fluid balance, hypoglycemia, hypophosphatemia, hypomagnesemia, hypokalemia, and thiamine deficiency. This syndrome can lead to a range of symptoms that affect the neurological, cardiac, hematological, and gastrointestinal systems, primarily due to electrolyte imbalances. Despite the variety of symptoms, refeeding syndrome often goes undetected because its clinical manifestations are nonspecific [2-4,16].

Phosphorus plays a critical role in synthesizing adenosine triphosphate (ATP), a crucial molecule for energy storage. Moreover, during refeeding, the production of ATP can cause a marked decrease in phosphorus levels [14]. This phenomenon was exemplified in the case of a 28-year-old woman with chronic diarrhea and malabsorption. When she resumed nutritional intake, she developed severe hypophosphatemia, with her serum phosphorus level dropping to 0.4 mg/dL. This led to arrhythmia, hypotension, respiratory failure, and ultimately resulted in her death [17].

Potassium is essential for maintaining the sodium-potassium membrane gradient, and its deficiency, known as hypokalemia, disrupts the electrochemical balance and impairs the transmission of electrical impulses in the body. Magnesium, which is as crucial as potassium, serves as a cofactor in ATP phosphorylation and is vital for neuromuscular and enzymatic functions [14]. Deficiencies in either electrolyte can result in neuromuscular disorders, arrhythmias, and gastrointestinal symptoms [18,19].

Thiamine, an essential cofactor in glucose-dependent metabolic pathways, sees a significant increase in demand during the transition from starvation to refeeding [20]. A deficiency in thiamine can result in neurological abnormalities, including enceph-
alopecia, delirium, and coma [21,22]. Furthermore, thiamine plays a critical role in converting lactate to pyruvate, and its deficiency can cause lactic acidosis [23,24]. Thiamine deficiency may also lead to decreased ATP production in the myocardium, potentially resulting in congestive heart failure [24].

DEFINITIONS

A universally agreed-upon definition of refeeding syndrome was lacking until 2020, when the American Society for Parenteral and Enteral Nutrition (ASPEN) committee and clinical practice task force introduced diagnostic criteria [16]. The ASPEN consensus definitions for refeeding syndrome represent a significant shift from previous descriptions by broadening the scope of assessment to include three critical electrolytes: phosphorus, potassium, and magnesium. The diagnostic criteria and severity stratification are as follows. (1) Any decline in serum phosphorus, potassium, and/or magnesium levels: mild refeeding syndrome—a decrease ranging from 10% to 20%; moderate refeeding syndrome—a reduction between 20% and 30%; severe refeeding syndrome—a decrease of over 30% or the emergence of organ dysfunction due to these electrolyte imbalances or thiamine deficiency. (2) These alterations typically manifest within 5 days of reintroducing or substantially augmenting energy intake.

ASSESSING RISK FACTORS FOR REFEEDING SYNDROME

Refeeding syndrome, which often presents with nonspecific symptoms, may be overlooked because these signs are subtle and not overtly associated with nutritional issues, potentially delaying appropriate treatment. Identifying high-risk factors for refeeding syndrome is crucial in managing the nutritional needs of critically ill children. Table 1 lists conditions that are associated with an increased risk of this syndrome. The ASPEN consensus recommendations categorize the risk into three levels: mild, moderate, and significant, as shown in Table 2 [16]. These categories are determined based on multiple factors, including body mass index (BMI)-for-age z-scores (or weight-for-length z-scores for children under 2 years), history of weight loss, duration of inadequate energy intake, serum electrolyte levels, and the presence of comorbidities.

Endorsed by the Society of Critical Care Medicine (SCCM) and ASPEN in 2017 [11], and subsequently by the European Society of Pediatric and Neonatal Intensive Care (ESPNIC) in 2020 [12], these nutritional support guidelines for critically ill children underscore the importance of assessing nutritional status through z-scores of anthropometric measurements upon admission to the PICU. The BMI-for-age z-score, in particular, is a quick and effective method for evaluating the nutritional status of these patients. For instance, a child presenting with a BMI-for-age z-score of −3 or lower is considered to be at high risk for refeeding syndrome based on this criterion alone.

PREVENTION AND MANAGEMENT OF REFEEDING SYNDROME

To prevent and manage refeeding syndrome in at-risk patients, a gradual and cautious reintroduction of nutrition is advised. The cornerstone of reintroducing nutrition is to incrementally increase caloric intake over a period of several days. It is crucial to monitor serum electrolytes, particularly phosphorus, potassium, and magnesium, and provide supplementation as necessary. The shifts in these electrolytes during refeeding are closely associated

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**Table 1. Conditions that place critically ill children at high risk for refeeding syndrome [3,6,16]**

<table>
<thead>
<tr>
<th>Clinical conditions</th>
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</thead>
<tbody>
<tr>
<td>Chronic critical illness (e.g., congenital heart disease)</td>
</tr>
<tr>
<td>Advanced neurologic impairment</td>
</tr>
<tr>
<td>Eating disorders (e.g., anorexia nervosa)</td>
</tr>
<tr>
<td>Dysphagia</td>
</tr>
<tr>
<td>Gastrointestinal dysmotility</td>
</tr>
<tr>
<td>Malabsorption (e.g., short bowel syndrome, inflammatory bowel disease, chronic pancreatitis, cystic fibrosis)</td>
</tr>
<tr>
<td>Malignancy</td>
</tr>
<tr>
<td>Child abuse</td>
</tr>
<tr>
<td>Significant vomiting and diarrhea</td>
</tr>
<tr>
<td>Unintentional weight loss of &gt;5%–10% of body weight in 1–6 months</td>
</tr>
<tr>
<td>Prolonged fasting &gt;7–10 days</td>
</tr>
<tr>
<td>Inadequate nutritional intake for &gt;10 days</td>
</tr>
</tbody>
</table>
Refeeding syndrome in critically ill children

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Mild risk: 3 risk criteria needed</th>
<th>Moderate risk: 2 risk criteria needed</th>
<th>Significant risk: 1 risk criterion needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight-for-length z-score (1–24 months) or BMI-for-age z-score (2–20 years)</td>
<td>z-score of −1 to −1.9 that is a change from baseline</td>
<td>z-score of −2 to −2.9 that is a change from baseline</td>
<td>z-score of ≤−3 that is a change from baseline</td>
</tr>
<tr>
<td>Weight loss</td>
<td>&lt;75% Of norm for expected weight gain</td>
<td>&lt;50% Of norm for expected weight gain</td>
<td>&lt;25% Of norm for expected weight gain</td>
</tr>
<tr>
<td>Energy intake</td>
<td>3–5 Consecutive days of protein or energy intake &lt;75% of estimated need</td>
<td>5–7 Consecutive days of protein or energy intake &lt;75% of estimated need</td>
<td>&gt;7 Consecutive days of protein or energy intake &lt;75% of estimated need</td>
</tr>
<tr>
<td>Abnormal pre-feeding serum potassium, phosphorus, or magnesium concentrations</td>
<td>Mildly abnormal or decreased to 25% below the lower limit of normal</td>
<td>Moderately/significantly abnormal or decreased to 25%–50% below the lower limit of normal</td>
<td>-</td>
</tr>
<tr>
<td>Higher-risk comorbidities</td>
<td>Mild disease</td>
<td>Moderate disease</td>
<td>Severe disease</td>
</tr>
<tr>
<td>Loss of subcutaneous fat</td>
<td>Evidence of mild loss or mid-upper arm circumference z-score of −1 to −1.9 z-score</td>
<td>Evidence of moderate loss or mid-upper arm circumference z-score of −2 to −2.9</td>
<td>Evidence of severe loss or mid-upper arm circumference z-score of −3 or greater</td>
</tr>
<tr>
<td>Loss of muscle mass</td>
<td>-</td>
<td>Evidence of mild or moderate loss or mid-upper arm circumference z-score of −2 to −2.9</td>
<td>Evidence of severe loss or mid-upper arm circumference z-score of −3 or greater</td>
</tr>
</tbody>
</table>

ASPEN, American Society for Parenteral and Enteral Nutrition; BMI, body mass index.

Table 2. Identification of pediatric patients at risk for refeeding syndrome, adapted from the ASPEN Consensus Recommendations on Refeeding Syndrome [16]

with the patient's tolerance to the increased caloric load, underscoring the importance of their management. If patients exhibit signs of intolerance to the calories despite these precautions, it is advisable to temporarily reduce or maintain the caloric intake at its current level. Once the patient’s condition has stabilized, a careful and gradual increase in caloric intake may be continued. Additionally, thiamine supplementation is important due to its essential role in carbohydrate metabolism [2–4,16]. The information that follows, as well as that in Table 3, is derived from the ASPEN 2020 consensus recommendations on refeeding syndrome.

Energy Intake

In pediatric patients at risk for refeeding syndrome, the ASPEN guidelines suggest starting critically ill pediatric patients at 40%–50% of their energy goal, or with a glucose infusion rate of 4–6 mg/kg/min (equivalent to 23–35 kcal/kg/day), and then increasing the rate by 1–2 mg/kg/min each day. This recommendation applies to both enteral and parenteral glucose administration. If difficulties in correcting electrolyte levels occur, or if there is a sharp decline in electrolyte levels at the onset of nutritional therapy, it may be necessary to reduce the caloric intake or dextrose content by 50%. Subsequently, the dextrose or caloric intake should be gradually increased by approximately 33% of the target every 1–2 days, guided by the patient's clinical response [16].

The ASPEN guidelines notably do not advocate for a specific, universal energy target for nutritional support. Additionally, the SCCM/ASPEN and ESPNIC nutrition guidelines for critically ill pediatric patients advise that nutritional intake, especially during the acute phase of catabolism, should be limited to the patient's resting energy expenditure (REE) and should not exceed it [11,12]. This approach is particularly prudent for critically ill children who are at an increased risk of developing refeeding syndrome. While indirect calorimetry is recognized as the most accurate method for determining REE [25], its lack of practicality often leads to the recommendation of the Schofield equation as an alternative. This equation provides an estimate of nutritional needs based on a patient's weight and height [12,26].

The guidelines [11,12] recommend initiating enteral nutrition within the first 24 hours of hospitalization [12], unless contraindicated. Reaching up to two-thirds of the nutritional goal during the first week of critical illness is associated with improved clinical outcomes [11]. For critically ill children, enteral nutrition is the preferred method over parenteral nutrition when feasible [11,12]. This approach includes active feeding methods such as oral, nasogastric tube, or trans-pyloric feeding techniques.

Ultimately, for critically ill children at risk of refeeding syndrome, the recommendation is to initiate early enteral nutrition. A suggested strategy involves starting with an initial energy intake that is lower than what the ASPEN guidelines recommend, such as 20%–30% of the target based on the REE. This should be gradually increased over the course of a week, with close moni-
Before starting nutrition, serum levels of potassium, magnesium, and phosphorus should be checked. In high-risk patients, these electrolytes should be monitored every 12 hours during the first 3 days [16], with more frequent monitoring as required. Any deficiencies identified should be corrected in accordance with established standards of care. The use of prophylactic electrolyte supplementation is still a matter of debate when pre-feeding levels are within the normal range [16].

**Thiamine and Multivitamins**

Administering thiamine before refeeding is crucial, particularly in high-risk patients. The recommended dosage is 2 mg/kg, with a maximum of 100–200 mg per day, to be given before nutrition is reintroduced. It is advised to continue supplementation for at least 5–7 days, or longer, in patients at high risk of deficiency. Patients on parenteral nutrition should receive a daily multivitamin infusion. For those on enteral nutrition, a daily multivitamin is recommended for at least 10 days, depending on the patient’s clinical status [16].

**Monitoring and Long-term Care**

For patients at risk, it is recommended to monitor vital signs every 4 hours during the first 24 hours after initiation. For unstable patients or those with severe deficiencies, cardiorespiratory monitoring should be performed in accordance with established standards of care. It is advisable to assess weight daily and to carefully monitor fluid intake and output. For patients on oral feeding, energy requirements should be estimated as needed. Additionally, short- and long-term nutrition care goals should be evaluated daily during the initial days until the patient stabilizes, which is indicated by the absence of a need for electrolyte supplementation for two consecutive days. Subsequent evaluations should be carried out in accordance with institutional standards of care [16].

### Table 3. Prevention and management of refeeding syndrome in at-risk pediatric patients, modified from the ASPEN Consensus Recommendations on Refeeding Syndrome [16]

<table>
<thead>
<tr>
<th>Aspect of care</th>
<th>ASPEN Consensus Recommendations</th>
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</table>
| Identification of patients at risk | • Consider higher-risk comorbidities  
  • Obtain a careful history of weight loss and energy intake  
  • Measure anthropometrics: weight, length  
  • Calculate the weight-for-length z-score for ages 1–24 months, or BMI-for-age z-score for ages 2–20 years  
  • Conduct examinations for subcutaneous fat and muscle mass |
| Energy intake | • Initiate nutrition at a maximum of 40%–50% of the goal  
  • Start the glucose infusion rate at approximately 4–6 mg/kg/min, increasing it by 1–2 mg/kg/min daily, up to a maximum of 14–18 mg/kg/min  
  • In cases of uncontrolled electrolyte drops, decrease calories/g of dextrose by 50%, and then advance by approximately 33% of the goal every 1–2 days  
  • Note on energy goal for critically ill children: measure resting energy expenditure via indirect calorimetry or calculate it using the Schofield equation[^11][12] |
| Electrolytes |  
  | Phosphorus | • Check serum electrolytes before initiation of nutrition |
  | Potassium | • Monitor every 12 hours for the first 3 days in high-risk patients |
  | Magnesium | • Replete low electrolytes as needed |
| Thiamine | • Administer thiamine at a dose of 2 mg/kg, up to a maximum of 100–200 mg/day, before initiating nutrition  
  • Continue thiamine supplementation for 5–7 days or longer in patients at high risk for deficiency |
| Multivitamins | • For parenteral nutrition: add a daily injectable multivitamin  
  • For enteral nutrition: administer a multivitamin once daily for at least 10 days |
| Monitoring and long-term care | • Vital signs every 4 hours in the first 24 hours after initiation of calories in patients at risk  
  • Daily weights with monitored intake and output  
  • Daily assessment of short-term and long-term nutritional goals during the initial days until the patient stabilizes  
  • Patient stabilization is indicated by no requirement for electrolyte supplementation over 2 days |

ASPEN, American Society for Parenteral and Enteral Nutrition; BMI, body mass index.  
[^11]: The ASPEN consensus recommendations on refeeding syndrome does not include a specific recommendation for energy goals.
Acute Care Concerns

Recent case reports highlight the effectiveness of extracorporeal life support (ECLS) in treating severe left ventricular dysfunction and heart failure resulting from refeeding syndrome in adults [27, 28]. These examples suggest that ECLS could be a viable treatment option for life-threatening cardiac complications related to refeeding syndrome in critically ill children.

CONCLUSION

The review focuses on refeeding syndrome in critically ill children, a severe and potentially lethal condition that is frequently overlooked in clinical practice. Establishing comprehensive, evidence-based clinical protocols and educational initiatives is essential for improving care and reducing the morbidity and mortality related to refeeding syndrome.

CONFLICT OF INTEREST

Younga Kim is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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