

Prevalence of Refeeding Syndrome in a Pediatric Intensive Care Unit

Prevalencia de Síndrome de Realimentación en una Unidad de Cuidados Intensivos Pediátricos

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What do we know about the subject matter of this study?

Refeeding syndrome (RFS) is a condition that generates morbidity and mortality if not recognized and managed appropriately. It occurs within 5 days after restarting or increasing feeding, in patients with risk factors.

What does this study contribute to what is already known?

This study reports the prevalence of RFS in a national referral unit, detecting that 41% of patients had risk factors for RFS and 44% of them presented it, considering only hypophosphatemia.

Abstract

Refeeding syndrome (RS) is defined as a decrease in serum levels of phosphate, potassium, or magnesium, and/or organ dysfunction due to thiamine deficiency, occurring within the first 5 days after restarting feeding. It is an underdiagnosed entity with high morbidity and mortality, and its true incidence is unknown. **Objective:** To estimate the prevalence of RS in a Pediatric Intensive Care Unit (ICU). **Patients and Method:** Observational, descriptive, prospective study with convenience sampling. Patients aged 1 month to 18 years, admitted from May to October 2023, were included and clinically monitored for 5 days after resuming feeding. The severity of RS was classified according to the decrease in serum levels of phosphate, potassium, and/or magnesium (10-20% mild; 20-30% moderate; and over 30% severe). Statistical analysis was performed using the Chi-square test and Student's T-test, with $p < 0.05$ considered significant. STATA v.15.0 software was used for the analysis. **Results:** Out of the 343 patients admitted, 41% had some risk factor for RS, mainly critically ill and malnourished patients, with the most frequent reasons for admission being respiratory failure followed by septic shock. 81% of those with risk factors developed RS, and 44% had hypophosphatemia. Half of the malnourished patients had hypophosphatemia, and when severe, it was associated with higher mortality ($p < 0.05$). **Conclusion:** A high percentage of patients developed RS, with 44% presenting hypophosphatemia, which agrees with international reports. Identifying patients at risk for RS allows for precautions in the initiation of feeding and avoiding this complication.

Keywords:

Refeeding Syndrome;
Pediatric Intensive
Care;
Nutritional Support;
Hypophosphatemia;
Malnutrition

Introduction

Nutrition is one of the core pillars in the treatment of the critically ill patient. The catabolic state of the critically ill child causes her/his needs to change considerably. In the latter, malnutrition may be pre-existing and manifest itself on admission, or develop later, favored by hypercatabolic and hypermetabolic states¹⁻³. Refeeding syndrome (RFS) is a potentially fatal entity associated with the onset of nutritional rehabilitation in malnourished or prolonged fasting patients³⁻⁵, described as a range of metabolic and electrolyte imbalances that occur because of the reintroduction and/or increase of caloric intake. Calories can come from any source: oral diet, enteral nutrition (EN), parenteral nutrition (PN), or intravenous (IV) dextrose.

It is an underdiagnosed entity; most reports are based on retrospective observational data and use very discordant definitions of it⁴.

The incidence of RFS in adults ranges from 15-30% in different studies⁶. Reporting incidence in the pediatric population is even more scarce. In 2003, in a report by Dunn et al⁷, 15 of 164 patients were considered at risk for RFS. Of those who developed hypophosphatemia, 3 developed cardiac abnormalities and lethargy.

In 2020, ASPEN developed consensus recommendations for the detection and management of patients who are at risk or have developed RFS, aimed at providing clinical guidance on the prevention and management of RFS for health centers and clinicians, unifying criteria so that research is uniform, and the incidence of its sequelae can be determined. It defines RFS according to the following criteria: Decrease in 1, 2, or 3 of serum levels of phosphate, potassium, and/or magnesium by 10%-20% (mild), 20%-30% (moderate), or higher than 30% and/or organ dysfunction due to a decrease in any of these and/or thiamine deficiency (severe); occurring within 5 days of restarting or substantially increasing energy supply⁸.

ASPEN includes being a critically ill patient among the main risk factors for developing RFS, given that they often lack adequate nutrition for long periods. It also includes as risk patients those with malignant diseases, associated with prolonged starvation, electrolyte losses, and treatments that induce gastrointestinal toxicity and mucositis, as well as anorexia. Other risk factors are dysphagia and esophageal dysmotility; surgery without nutrition for prolonged periods; malabsorptive states (short bowel syndrome, Crohn's disease, cystic fibrosis, pyloric stenosis, pancreatic insufficiency); eating disorders; prolonged vomiting; mental health disorders; renal failure/hemodialysis, and child abuse victims. The impact force of each risk factor is not known. It occurs more frequently in patients with chronic diseases⁶. The risk of RFS, in general, is

thought to be closely related to the degree of malnutrition related to periods of fasting. Short periods of nutrient deprivation may have a more significant effect on children due to the additional metabolic demands of growth. Growth velocity, height, weight-for-height, or BMI-for-age z-score should be considered when assessing children at risk of RFS^{3,8}.

The exact pathophysiological mechanisms leading to RFS have not yet been definitively elucidated. The central aspect is the shift from catabolic to anabolic metabolism as a normal physiological reaction to the resumption of nutrition in an at-risk patient. Increased glucose secondary to caloric intake generates increased insulin, which drives phosphate and potassium intracellularly both by demand (glucose phosphorylation when glycolysis is initiated) and through the direct effects of insulin (stimulation of sodium-potassium-adenosine triphosphatase [ATPase]).

In the presence of a previous deficit of potassium, phosphate, or magnesium, a potassium-mediated drop in serum concentrations may occur. The mechanism of the decrease in magnesium levels in this context has not been well elucidated. The drop in serum electrolytes can be sudden, severe, and even fatal for an individual who has been in a catabolic state. Thiamine is a cofactor of glucose-dependent metabolic pathways so it may decrease in this context. The alteration in fluid homeostasis is mainly due to the antinatriuretic effect of insulin leading to water and sodium retention and consequent edema^{3,4,6,8-11}. The clinical manifestations of RFS are secondary to electrolyte imbalance and fluid overload.

The main objective of the study was to evaluate the prevalence of RFS in pediatric patients with risk factors for RFS in a Pediatric Intensive Care Unit (PICU) between May and October 2023. The secondary objectives were to identify patients with risk factors for developing RFS and to classify patients with a diagnosis of RFS according to severity.

Patients and Method

Observational, descriptive study detailing a specific clinical condition in a prospective cohort in a convenience sample. It includes patients aged 1 month to 18 years, admitted to ICU between May and October 2023, and who presented one or more risk factors for developing RFS at admission according to the ASPEN criteria⁸.

The main variable of the study was the presence or not of RFS according to the ASPEN criteria⁸, a complex variable that includes the presence of the following quantitative variables, of which at least one may be altered: serum potassium, magnesium, and/or phos-

phate values during the first five days of refeeding. The measurement of thiamine described in the definition was not included as it was unavailable in our hospital.

The severity of RFS was also determined according to the ASPEN criteria as an ordinal qualitative variable as follows: a reduction in serum levels of phosphate, potassium, and/or magnesium between 10-20% corresponds to mild RFS; between 20-30% to moderate RFS, and more than 30% to severe RFS.

Hospital readmissions and patients in whom it was not possible to collect at least one sample for the analysis were excluded.

Malnutrition was defined as a weight/height Z-score less than -2 in children under 5 years of age, and body mass index (BMI) for age in children over 5 years of age.

Clinical history and laboratory studies data were collected. The selected patients underwent clinical and blood electrolyte monitoring for up to 5 days after reinitiation or increased feeding. The risk of RFS was considered as presence or absence; it was not categorized into severity degrees. Treating physicians were notified when a patient met risk factors for RFS or when a diagnosis of RFS was made. In patients at risk of RFS, refeeding was initiated with a reduced caloric intake according to the ASPEN consensus.

The Ethics Committee, the hospital management, and the head of the ICU have approved this study.

Statistical analysis: Qualitative variables were described with absolute (n) and relative (%) frequencies. Continuous variables were expressed as mean and standard deviation (SD) after a study of normality with

the Kolmogorov-Smirnov test. The study of the association between qualitative variables was performed with the Chi-square test or Fisher's exact test in the case of expected values less than 5. If the association was confirmed, the strength of the association was calculated with the measure of relative risk (RR) and its corresponding 95% confidence interval (CI). For the study of differences between groups of continuous variables, Student's t-test was used for independent samples. A $p < 0.05$ value was considered significant. The statistical software STATA v.15.0 was used for the analysis.

Results

During the study period, 347 patients were admitted to the ICU, of whom 141 had risk factors for RFS, estimating a prevalence of 41 patients per 100 at risk. Four patients were excluded because they did not have the basic data for analysis; therefore, data from the remaining 137 patients are presented.

Table 1 shows the characteristics of the population. Two groups were established as patients with and without hypophosphatemia (44% and 56%, respectively). The proportion of patients with postoperative admission was significantly higher in this group ($p = 0.028$), estimating that a patient with this type of pathology is at high risk of suffering hypophosphatemia (RR = 8.4; CI 95% 0.98-72.1).

Table 2 shows the risk factors for RFS most frequently observed in the total number of patients. The main risk factors were belonging to the critical popula-

Table 1. Characterization of the sample and reason for admission according to the presence of hypophosphatemia

	Total (n = 137)	Without hypophosphatemia (n = 77)	With hypophosphatemia (n = 60)	p
Age (month)*	37,5 +/- 4,9	33,7 +/- 6,5	42,3 +/- 7,3	ns
Gender Female	53 (38,7)	30 (39,0)	23 (38,3)	ns
Male	84 (61,3)	47 (61,0)	37 (61,7)	
Diagnosis				
- Respiratorio	93 (67,9)	57 (74,0)	36 (60,0)	ns
- Neurológico	15 (10,9)	6 (7,8)	9 (15,0)	ns
- Shock séptico	17 (12,4)	6 (7,8)	11 (18,3)	0,063
- Oncológico	11 (8,0)	6 (7,8)	5 (8,3)	ns
- Posoperatorio	7 (5,1)	1 (1,3)	6 (10,0)	0,028
- Cardiológico	5 (3,6)	5 (6,5)	-----	0,053
- Metabólico	1 (0,7)	-----	1 (1,7)	ns
PIM2 (%)	3,5 +/- 0,4	3,7 +/- 0,7	3,3 +/- 0,4	ns
Días en UCI**	7 (5 - 12)	7 (5 - 11)	7 (5 - 13)	ns

PIM2: Índice de Mortalidad Pediátrica 2. UCI: Unidad de cuidados intensivos. *Valores en media y desvío estándar (DS). **Mediana y rango intercuartílico (RIQ). Todos los restantes valores se expresan en n (%).

Table 2. Association between hypophosphatemia and risk factors for Refeeding Syndrome

	Total (n = 137)	Without hypophosphatemia (n = 77)	With hypophosphatemia (n = 60)	p
Malnutrition	31 (22.6)	15 (19.5)	15 (25.0)	ns
Oncological	11 (8)	6 (7.7)	5 (8.3)	ns
Malabsorption	1 (0.7)	-----	1 (1.6)	ns
Post-surgical	7 (5.1)	1 (1.3)	6 (10)	ns
Critical	126 (91.9)	55 (71.4)	33 (55)	ns

All values are expressed as n (%).

Table 3. Association between the presence of hypophosphatemia, need for support, complications, and mortality

	Total (n = 137)	Without hypophosphatemia (n = 78)	With hypophosphatemia (n = 59)	p
MV	123 (89.8)	71 (92.2)	52 (86.7)	ns
Inotropics	24 (17.5)	11 (14.3)	13 (21.7)	ns
Diuretics	117 (85.4)	69 (89.6)	48 (80.0)	ns
Salbutamol	90 (65.7)	56 (72.7)	34 (56.7)	0.051
Renal failure	20 (14.6)	9 (11.7)	11 (18.3)	ns
Mortality	8 (5.8)	3 (3.8)	5 (8.5)	ns

MV: Mechanical ventilation. Values expressed as n (%).

tion (requiring respiratory and/or hemodynamic support) and malnutrition before admission (72% critical patients, 22% with malnutrition). In any case, no statistically different proportions were found between the two groups studied with or without hypophosphatemia.

In relation to the treatments and complications presented (Table 3), no statistically significant relationship was found between the treatments administered and the presence of hypophosphatemia.

Most of the patients presented RFS (81%), defined as a decrease in potassium, magnesium, and/or phosphate in the first 5 days after starting or increasing feeding; 44% of the patients presented hypophosphatemia, which could be isolated or combined with other electrolyte imbalances (Table 4).

The presence of combined electrolyte imbalances was more frequent than the isolated one, and the most frequent combination was hypophosphatemia with hypokalemia. A statistically significant association could be observed between the presence of hypophosphatemia and hypokalemia ($p = 0.002$; RR 3.7; CI 95% 1.54-8.93). Of the patients with hypophosphatemia, 86.7% also presented hypokalemia, decreasing to 63.6% in the group without hypophosphatemia.

When analyzing the results according to RFS severity, most patients had mild RFS (41%), one-third of the subjects had severe RFS (33%), and only 26% had moderate RFS, values that did not change significantly if we consider only the cases with hypophosphatemia (Table 5). When analyzing the group of patients with hypophosphatemia in severity ranges (Table 5), a statistically significant association was observed between mortality and the presence of severe hypophosphatemia ($p = 0.031$; OR 10.6; CI 95% 1.10-13.2). This relationship could be affected by the underlying morbid

Table 4. Isolated and combined electrolyte disturbances

	Total n = 137 (%)
Isolated hypophosphatemia	6 (4.4)
Isolated hypokalemia	39 (28.5)
Isolated hypomagnesemia	2 (1.5)
Hypophosphatemia + hypokalemia	38 (27.7)
Hypophosphatemia + hypomagnesemia	2 (1.5)
Hypokalemia + hypomagnesemia	10 (7.3)
Hypophosphatemia + hypokalemia + hypomagnesemia	14 (10.2)
No electrolyte disturbances	26 (19.0)

Table 5. Mortality, PIM2 and days of hospitalization in relation to the severity of hypophosphatemia

	Total (n = 60)	Severe Hypophosphatemia (n = 19)	Not severe Hypophosphatemia (n = 41)	p value
Mortality	5 (8.3)	4 (21.1)	1 (2.4)	0.031
PIM2 (%)	3.3 +/- 0.4	2.8 +/- 0.5	3.5 +/- 0.5	0.029
Length of stay (days)	7 (5 - 13)	7 (5 - 15)	7 (6 - 12)	ns

PIM2: Pediatric Mortality Index 2.

condition, systemic and functional involvement, and the implementation of general or specific therapeutic measures to prevent RFS.

In relation to the feeding route, 90.5% received enteral feeding and the rest parenteral. In 3 children, nutritional support was not started, and they only received intravenous dextrose solution.

Electrolyte alterations were corrected by intravenous formulas when they were considered severe or, in mild to moderate cases, with increased electrolyte intake via enteral or parenteral route. Thiamine was not administered because it was not available for intravenous use in our setting. A description of the clinical manifestations of RFS was not provided because of the wide variability of its presentation and because it is not possible to differentiate when organic failures are the cause of the electrolyte imbalances or the manifestation of the pathology that led to admission to intensive care. The main therapeutic difficulty was the lack of an institutional protocol to guide the nutritional support of patients diagnosed with RFS and the low caloric intake worsened malnutrition in all patients with previous malnutrition.

Discussion

41% of the patients admitted during the study period had risk factors for developing RFS and 44% of them presented the syndrome if we consider only hypophosphatemia. In one-third of the cases, the decrease in serum phosphate was in severe range. This value coincides with that reported in other international studies⁶⁻⁷. Recently a study conducted in Switzerland using the ASPEN criteria found an incidence of RFS of 46.7%, mostly severe. The length of stay in the ICU and acquired infections were higher in children who developed RFS than in those at risk who did not¹².

Hypophosphatemia is often considered the hallmark of this syndrome. However, this may result from a definition bias or the relatively few causes of hypophosphatemia compared to hypokalemia, making it a more significant cause of hypophosphatemia than

hypokalemia^{4,8,9}. 81% of our patients presented with RFS. The prevalence of hypokalemia was high (74%) in our sample, which may be related to the treatments used for respiratory and renal support (bronchodilators and diuretics). The ASPEN consensus definition could then be very sensitive and not very specific for use in pediatric critical care, where hypokalemia is frequent and multifactorial. It would be good to perform another study to assess the sensitivity and specificity of the definition for diagnosis in this context.

The most frequent risk factors in our sample coincide with those reported in other studies (72% critical patients, 22% with malnutrition). Of the malnourished patients, 50% presented hypophosphatemia.

A study in France this year showed a prevalence of hypophosphatemia of 46% in infants with severe bronchiolitis admitted to a PICU and was associated with longer mechanical ventilation (MV) ⁽¹³⁾. Another paper found a similar prevalence, and malnutrition was present in 24% of patients, serum phosphate level was significantly lower in malnourished than in well-nourished children ($p = 0.018$) and was associated with prolonged PICU stay ($p < 0.001$), but was not associated with increased mortality ($p = 0.13$). Hypophosphatemia was associated with the use of furosemide, dopamine, steroids, and beta-2 agonists¹⁴.

Phosphate is the main intracellular anion essential for numerous biological processes. Its depletion can lead to muscle dysfunction and acute respiratory failure in severe cases. It can also cause decreased cardiac contractility. Since phosphate is important in the conduction of electrical impulses, its deficiency can lead to cardiac arrhythmias. Phosphate depletion also decreases the production of 2,3-diphosphoglycerate, leading to an increase in the affinity of hemoglobin for oxygen, with reduced oxygen release to tissues and tissue hypoxia¹⁵.

Symptoms of hypophosphatemia are not specific but can be life-threatening¹⁶. In our sample, there was evidence of higher associated mortality in the group with hypophosphatemia in severity ranges. This finding is consistent with the literature. According to a review published in 2021, several studies report that hypophos-

phatemia is associated with worse outcomes (prolonged hospital stay, need for respiratory support, higher mortality). However, there was insufficient evidence on the optimal threshold at which hypophosphatemia becomes critical and requires treatment, nor on the time window to correct it¹⁶. This is an observational study and further studies are needed to assess whether or not the treatment decreases mortality in our patients.

Some studies report that since it is a physiological metabolic alteration due to transmembrane ion movement, asymptomatic patients may not be treated¹⁷. It would be beneficial to reach a consensus on the indication and treatment of patients with symptomatic hypophosphatemia. It is important to remember that nutrient restriction in addition to phosphate replacement in patients with RFS may improve survival, although the evidence is weak, and more studies are required to reach a consensus.

On the other hand, the key to preventing the syndrome is to minimize the risk of its occurrence. In clinical practice, RFS is probably underreported due to a lack of knowledge about this condition. In a recent study among 281 physicians, only 14% were able to diagnose RFS correctly¹⁸, so it is important to raise awareness of this potential complication of nutritional therapy. The 3 basic pillars for adequate nutrition are: screening of the patient's previous nutritional status, calculation of nutritional needs¹⁹, and, finally, monitoring of the nutritional situation during admission.

ASPEN criteria suggest classifying patients at admission into mild, moderate, or severe RFS risk levels, according to factors such as anthropometry, previous weight loss, decreased energy expenditure, electrolyte imbalance before feeding, comorbidities, and loss of subcutaneous fat or muscle mass (Table 6).

Patients considered at risk of RFS should receive calorie-conservative treatment. Recent guidelines for feeding in the critically ill patient recommend that intake should not exceed basal energy expenditure during the acute phase of illness^{11,20}. Other studies revealed that the lack of consensus on precise refeeding recommendations may lead to excessive intake and promote RFS¹².

The consensus recommends starting refeeding with an intake of 40-50% of the calculated caloric goal, with an initial glucose intake of 4-6 mg/k/min, increasing by 1-2 mg/k/min up to a maximum of 14 mg/k/min. This intake includes enteral and parenteral glucose intake, and the glucose intake included in the infused solutions and medications should be considered. In case of worsening electrolyte imbalance after refeeding, it is recommended to decrease the caloric intake/grams of dextrose by 50%, progressively increasing the percentage of calories and glucose by 33% every 1-2 days. Cessation of nutritional support may be considered when electrolyte levels may be life-threatening or the decrease in electrolyte levels is too quick.

We highlight as limitations of this study the difficulty in the follow-up and data collection. It was not

Table 6. ASPEN Consensus Criteria for Identifying Pediatric Patients at Risk for Refeeding Syndrome^a

	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 a -1,9 z-score	-2 a -2,9 z-score	-3 z-score or greater
Weight loss	< 75% of norm for expected weight gain	< 50% of norm for expected weight gain	< 25% of norm for expected weight gain
Energy intake	3-5 consecutive days of protein or energy intake < 75% of estimated need	5-7 consecutive days of protein or energy intake < 75% of estimated need	> 7 consecutive days of protein or energy intake < 75% of estimated need
Abnormal prefeeding serum potassium, phosphorus, or magnesium concentrations	Mildly abnormal or decreased to 25% below lower limit of normal	Moderately/significantly abnormal or down to 25%-50% below lower limit of normal	Moderately/significantly abnormal or down to 25%-50% below lower limit of normal
Higher-risk comorbidities	Mild disease	Moderate	Severe disease
Loss of subcutaneous fat or muscle mass	Evidence of mild loss OR Mid-upper arm circumference z-score of -1 to -1.9 z-score	Evidence of moderate loss OR Mid-upper arm circumference z-score of -2 to -2.9	Evidence of severe loss OR Mid-upper arm circumference z-score of -3 or greater

ASPEN: American Society for Parenteral and Enteral Nutrition; BMI: body mass index. *Table extracted from ASPEN Consensus Recommendations for Refeeding Syndrome. Nutr Clin Pract. 2020. doi: 10.1002/ncp.10474.

possible to completely rule out the existence or not of the electrolyte imbalances studied in patients who died or were transferred from the hospital or discharged to another area before the fifth day of hospitalization, which could influence the final results. Other limitations were that the risk of RFS was not stratified or correlated with its severity and that the type of nutritional support provided was not made explicit, nor was the clinical presentation.

Finally, it is important to remember the multiple causes of hypophosphatemia in pediatrics and especially in critical patients (either by phosphate shift from the extracellular into the intracellular space, decreased intestinal absorption, and/or increased renal excretion)²¹ that may determine that the hypophosphatemia found are of multifactorial cause or perhaps RFS has been overdiagnosed in patients with another cause of it, being equally important the detection of this dyselectrolytemia and its eventual treatment.

In conclusion, the prevalence of RFS in our sample was 81%, with 44% of the patients presenting isolated or combined hypophosphatemia. 33% presented RFS classified as severe due to electrolyte imbalances, with a statistically significant association with mortality in this group. The development of nutritional support protocols in the ICU that include the section on the management of RFS, the recognition of patients at risk of RFS, its stratification, and awareness of its definition is necessary to systematize its prevention and treatment.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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