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ORIGINAL ARTICLE

Nutrition

Prevention of refeeding syndrome: Evaluation of an enteral refeeding protocol for severely undernourished children

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Abstract

Objectives: Refeeding syndrome (RS) defines the deleterious clinical and metabolic changes occurring during nutritional support of severely malnourished patients. Pediatric guidelines to prevent and treat RS are scarce and highly variable. This study aimed to evaluate the effectiveness and safety of an enteral refeeding protocol in severely undernourished hospitalized children with anorexia nervosa (AN) or organic diseases (OD).

Methods: This ancillary study to the Preventing Malnutrition and Restoring Nutritional Status in Hospitalized Children (PREDIRE) trial (NCT01081587), included severely undernourished children hospitalized between January 2010 and June 2018 and treated with an enteral refeeding protocol drafted for the study. The effectiveness was assessed by weight gain and safety by clinical and laboratory abnormality occurrence over the initial 3-week refeeding period, which represents the most critical period for the development of RS.

Results: After 3 weeks of refeeding, the mean weight for height ratio increased from 72% to 82%, and half of the patients with severe undernutrition improved their nutritional status. The prevalence of RS was 10.4%. No clinical cardiac or neurological complication occurred. The most frequent laboratory complication was hypophosphatemia in 13.7% of patients; but symptomatic in only two patients (2.5%). Compared with patients with OD, patients with AN improved their weight-for-height ratio faster without significantly more frequent complications, except for hepatic cytolysis which was less prevalent in AN (8.3% vs. 36.8%).

Conclusions: The proposed enteral refeeding protocol appears safe for treating severely undernourished children of different etiologies, with a low prevalence of RS and half of the patients recovered from severe malnutrition within a 3-week period.

The study is registered on ClinicalTrials.gov (NCT01081587).

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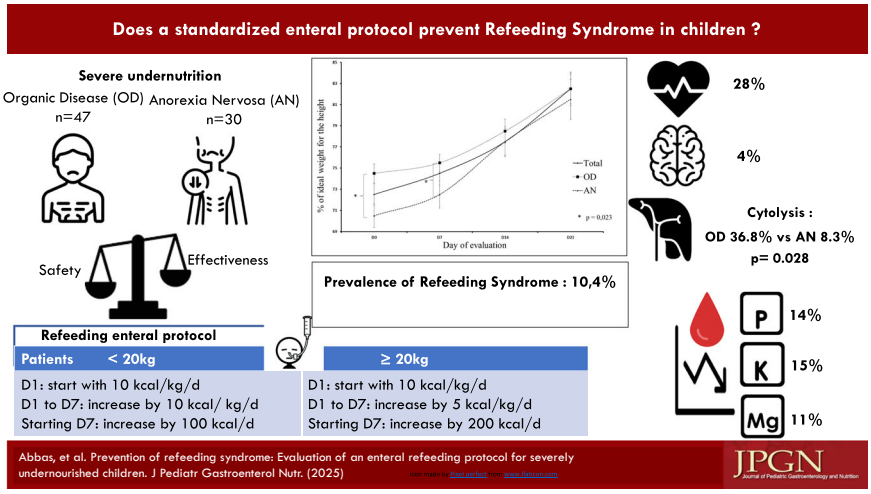

KEYWORDS
adolescent, anorexia nervosa, enteral nutrition, hypophosphatemia, malnutrition

1 | INTRODUCTION

Refeeding syndrome (RS) defines the deleterious clinical and metabolic changes that occur during a nutritional support of a severely malnourished patient. A rapid switch from an adaptive catabolic to an anabolic state underlies the physiopathology of RS,[1] which concerns around 6% of hospitalized adolescents with anorexia nervosa (AN) and 7.4% in pediatric intensive care unit patients.[2,3] The main complications of RS concern cardiac and neurological functions and are potentially life-threatening.

Guidelines to prevent and treat RS in children are rare and highly variable.[3-7] Most recommendations are based on expert opinion rather than evidence-based medicine or clinical studies which are very scare for children.[8,9] Then, methodological issues limit any recommendation in identifying the most effective refeeding approach. This highlights the importance of developing studies evaluating refeeding protocols in children.

In western countries, clinical studies evaluating refeeding protocols in hospitalized children concern mainly AN and eating disorders,[8,10-13] but very few publications concern organic etiologies.[8] AN is often associated with a chronic and severe undernutrition, which is a well-known risk factor of RS,[14,15] while children with severe but acute undernutrition could be at lower risk of developing RS. Few data illustrate this difference.

The primary objective of the present study was to evaluate the refeeding effectiveness of an enteral nutrition protocol in severely undernourished children from a western university hospital. The secondary objective was to describe the type, frequency, and occurrence time of complications in order to evaluate the prevalence of RS during the initial 3 weeks of the refeeding protocol. The effectiveness and safety of the protocol were then analyzed according to etiology (AN vs. organic diseases, OD).

What is Known

- In children, guidelines to prevent refeeding syndrome (RS) are rare and variable.
- The prevalence of RS varies from 2% to 34%.
- Hypophosphatemia is the hallmark of the RS.
- The complications appear mainly during the first week.

What is New

- The proposed enteral refeeding protocol appears effective and safe.
- Children with AN improved their nutritional status faster than those with organic diseases (OD).
- During refeeding, the prevalence of cardiac, neurologic, or electrolytes complications are the same in OD and AN; only hepatic cytolysis is more frequent in OD (36.8% vs. 8.3%, $p = 0.028$).

2 | METHODS

2.1 | Study design and setting

This is an ancillary study of the Preventing Malnutrition and Restoring Nutritional Status in Hospitalized Children (PREDIRE) study, which evaluated the frequency

and treatment of children with undernutrition (NCT 01081587).[16,17] The present study evaluated and collected data of children (<18 years) severely undernourished, hospitalized in a pediatric university hospital between January 2010 and June 2018, and who benefited from a pediatric enteral refeeding protocol elaborated for the study, and detailed in Supporting Information S1.

Inclusion criteria were children (<18 years), with severe nutrition as defined below, starting enteral nutrition protocol. Exclusion criteria were missing medical record, parental refusal of inclusion, deviation from the enteral protocol (change in calories, premature stop).

Severe undernutrition in children was defined using at least one of the following criteria: (1) body mass index (BMI) less than –2 standard deviations (SD) of the national reference curves[18]; (2) weight for height ratio (WHR) inferior to 80%; (3) height for age ratio (HAR) inferior to 85%[19]; and/or (4) acute weight loss of at least 10% of their previous normal weight before hospital admission.[20] The children were then divided into two groups depending on the etiology of the undernutrition: children with OD and children with AN.

2.2 | Data collection

Clinical and laboratory data were extracted from the electronic medical records. Since the first 3 weeks of refeeding are the most critical in terms of RS, the present study focused on this period. Weight and height were recorded prior to inclusion in the protocol (Day 0), and the evolution was analyzed at Days 7, 14, and 21 after the inclusion using *Z*-scores to standardize according to age. The consequences and the severity of undernutrition and of the refeeding protocol were evaluated by clinical symptoms (cardiologic, digestive, and neurologic) and laboratory abnormalities (hepatic, ionic, and hematologic).

The nutritional medical team involved in the study detected and rigorously recorded the signs of RS using a computerized protocol.[16]

2.3 | Refeeding protocol and monitoring

The refeeding protocol was drafted based on current guidelines, the analysis of the international literature, and the experience of the pediatric nutritional team of our center. The protocol was incorporated into the medical prescription software to ensure its use in a standardized manner (protocol detailed in Supporting Information S1).[21]

Children were closely monitored by clinical examination and laboratory testing for the first 7 days; thereafter, the frequency was adapted to the evolution. The daily clinical examination included daily weighing, looking for signs of fluid and salt retention, heart failure, intolerance to the enteral feeding, and careful neurologic examination. Tachycardia was defined as a heart rate higher than the normal ranges as defined by the advanced pediatric life support (APLS) and the pre-hospital pediatric life support (PHPLS) groups (Supporting Information S2).

Laboratory testing included serum electrolytes with hepatic and renal function, creatinine phosphokinase (CPK), lipid profile, complete blood count (CBC), and coagulation. Anemia and lymphocytopenia were defined by a level inferior to the normal range according to age. The thresholds used to define hypophosphatemia was 0.8 mmol/L and to define hypomagnesemia was those used in the laboratory of the pediatric hospital, and the assessment of the severity of hypokalemia is described in Supporting Information S3.

2.4 | Outcomes

The refeeding effectiveness of the protocol was assessed using the absolute weight gain (kg) and the percentage of ideal weight for the height gain between the inclusion (starting of refeeding protocol) and the end of the study (3 weeks later). The safety of the protocol was assessed by recording the type, frequency, and occurrence time of complications during the 3-week study period. RS was determined according to the American Society for Parenteral and Enteral Nutrition (ASPEN) definition.[22] The impact of etiology (AN vs. OD) was evaluated by comparing efficacy and complications in both groups.

2.5 | Statistical analyses

Quantitative variables are presented with their mean and associated SD, and qualitative variables are presented as the number of patients and associated percentage (*n*, %). Wilcoxon rank sum test for quantitative variables and χ^2 test or Fisher's exact test for qualitative variables were used for the comparison between groups. For the modeling of the effectiveness of the protocol, we used a mixed linear model with a random effect on each subject on the intercept. We explained the WHR by the time, the AN status, and an interaction of the AN and time. Statistical significance for the *p* value was arbitrarily set at 0.05. Statistical analyses were performed using R software V 3.6.3 and the package nlme.

2.6 | Ethical considerations

For the initial PREDIRE study, parents provided written informed consent for participation in the study and the

use of the data for research purposes. The study was approved by the institutional review board (n°2008-A010-55) and the National Advisory Committee on Information Processing in Material Research in the Field of Health (CCTIRS). The study is registered on clinicaltrials.gov (NCT01081587). This ancillary study was approved by the ethics committee of the *Hospices Civils de Lyon* on September 2020 (n°20-5196).

3 | RESULTS

3.1 | Population description

A total of 77 patients from the PREDIRE study were included (Figure 1); their mean ± SD age was 8.52 ± 6.3 years and 46 (59.7%) were girls (Table 1). As expected, the mean age was significantly younger in the OD than in the AN group (5.0 *vs.* 14.0 years, respectively, $p < 0.001$; Table 1). Undernutrition was of organic etiology in the majority of patients (61.1%), mainly due to neurological (11.7%) and gastrointestinal (10.4%) diseases (Table S1).

3.2 | Effectiveness of the refeeding protocol

The median duration of the enteral refeeding protocol was not significantly different according to the etiology (17 and 21 days in the OD vs. AN group). Of note, at the end of the 3-week study period, 54 (70.1%) children were still under the enteral refeeding protocol.

The mean ± SD weight at inclusion was –2.85 ± 1.34 SD, and was significantly lower in the OD (–3.23 ± 1.14 SD) than in the AN group (–2.24 ± 1.43 SD, $p < 0.001$). For the height, despite a statistically lower *Z*-score in the OD group, both groups were inside the normal range (–2 SD to +2 SD). The OD group was more heterogeneous regarding age, weight, and height. The BMI was below the –3 SD in both groups, but there was no significant difference between both groups (Table 1).

The mean weekly weight gain at Days 7, 14, and 21 was 0.67, 0.85, and 0.49 kg, respectively. The mean WHR from the beginning of refeeding protocol and the end of the study 3 weeks later increased from 72% to 82%. WHR was significantly lower in children with AN than in children with OD at admission ($p = 0.023$) and at Day 7 ($p = 0.023$). At Days 14 and 21, there was no significant difference between both groups, and the improvement in WHR was higher in children with AN (Figure 2). At the end of the study (Week 3), 50% of the children with OD and 47% of those with AN recovered a nutritional status with a WHR over 80% (severe undernutrition remaining in 50% and 53% of children with OD and AN, respectively; Figure S1).

To explain the impact of etiology (AN vs. OD) on the effectiveness of the protocol, we used a mixed linear model with a random effect on each subject on the intercept (Supporting Information S4). Before refeeding, AN had a WHR 8.3% lower than OD. During refeeding, WHR gain each week was significantly higher for AN with a difference of 0.49% of WHR gain higher each week for AN compared to OD ($p = 0.033$).

3.3 | RS: Type, frequency, and delay of complications

The complications related to the undernutrition were analyzed before and during the refeeding period.

Before the start of the refeeding protocol, the most frequent clinical abnormalities were cardiologic (bradycardia in 34.3% and hypotension in 29.9% of

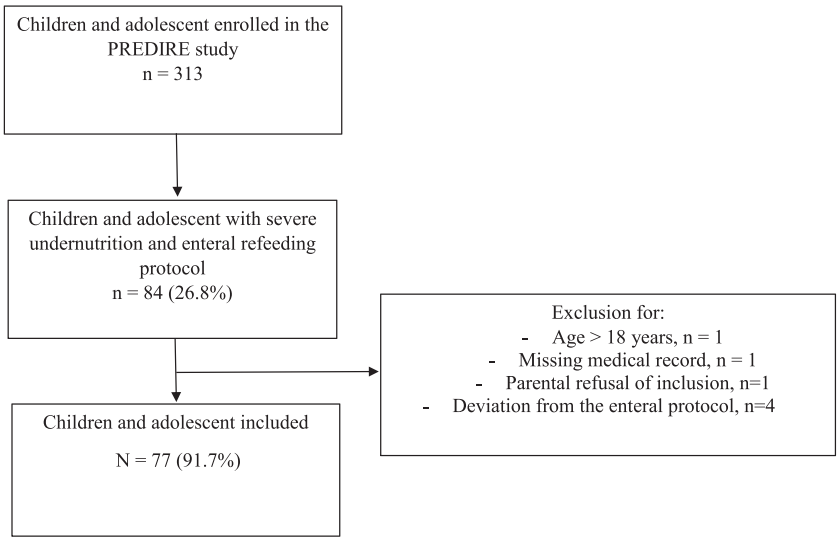

FIGURE 1 Flowchart. PREDIRE, Preventing Malnutrition and Restoring Nutritional Status in Hospitalized Children.

TABLE 1 Characteristics at inclusion of children hospitalized according to the etiology of the undernutrition.

	Total ($n = 77$)	Organic disease ($n = 47$)	Anorexia nervosa ($n = 30$)	p Value OD vs. AN
Anthropometry				
Sex, female	46/77 (59.7%)	19/46 (41.3%)	27/30 (90%)	**$p < 0.001$**
Age (years)				
Mean (SD)	8.52 (6.30)	5.02 (5.44)	14.00 (2.49)	**$p < 0.001$**
Weight				
kg	20.99 (13.81)	12.87 (10.19)	33.70 (7.81)	**$p < 0.001$**
SD	–2.85 (1.34)	–3.23 (1.14)	–2.24 (1.43)	**$p < 0.001$**
Height				
cm	119.73 (41.36)	95.24 (34)	158.10 (12.38)	**$p < 0.001$**
SD	–0.61 (1.83)	–1.36 (1.64)	0.59 (1.51)	**$p < 0.001$**
BMI				
kg/cm2	12.98 (1.81)	12.76 (1.72)	13.32 (1.92)	$p = 0.242$
SD	–3.49 (1.17)	–3.63 (1.20)	–3.28 (1.10)	$p = 0.197$
Percentage of weight loss (mean)	24%	24%	28%	$p = 0.503$
Clinical abnormalities *n* (%)				
Bradycardia	24/70 (34.3%)	1/40 (2.5%)	23/30 (76.7%)	**$p < 0.001$**
Hypotension	20/67 (29.9%)	4/37 (10.8%)	16/30 (53.3%)	**$p < 0.001$**
Hypothermia	12/67 (17.6%)	1/38 (2.6%)	11/29 (37.9%)	**$p = 0.001$**
Laboratory abnormalities *n* (%)				
Hepatic cytolysis	25/77 (32.5%)	19/47 (40.4%)	6/30 (20.0%)	$p = 0.12$
Hypophosphatemia (normal range >0.8 mmol/L)	10/77 (12.9%)	5/47 (10.6%)	5/30 (16.6%)	$p = 0.8$
Hypokalemia (2.60–3.40 mmol/L)	7/77 (9.0%)	7/47 (14.8%)	0/30 (0%)	ND
Hypomagnesemia (normal range for age: 0.59–0.71 mmol/L)	2/77 (2.5%)	2/47 (4.2%)	0/30 (0%)	ND
Hypoglycemia (<3.3 mmol/L)	16/72 (22.2%)	5/43(11.6%)	11/29 (37.9%)	**$p = 0.005$**
Hyperglycemia (>7 mmol/L if fasting, or >11 mmol/L if postprandial)	7/72 (9.7%)	7/43 (16.3%)	0/29 (0.0%)	ND
Anemia (normal range for age)	26/74 (35.1%)	25/45 (55.6%)	1/29 (3.4%)	**$p < 0.001$**
Lymphocytopenia (normal range for age)	3/73 (4.1%)	2/45(4.4%)	1/28 (3.6%)	$p = 1$

Note: Bold values indicate statistical significant results.

Abbreviations: AN, anorexia nervosa; BMI, body mass index; ND, not done; OD, organic disease; SD, standard deviation.

children), and hypothermia (<36°C in 17.6% children). The most frequent laboratory abnormality was hepatic cytolysis in 32.5% of patients; the range of liver enzymes varied from 1.5 to 10 times the normal values. Decreased phosphatemia was present in 26.0%, but real hypophosphatemia (<0.8 mmol/L) was found only in 12.9% of patients, hypoglycemia in 22.2%, and hyperglycemia in 9.7%. Anemia and lymphocytopenia affected 5.1% and 4.1% children, respectively. Compared with children with OD, those with AN presented significantly more bradycardia, hypotension, hypothermia, hypoglycemia, and significantly lower level, but in the normal range, of white blood cells (WBC) and lymphocytes (5.163 (2.008) vs. 10.836 (5424) $p<0.001$ and 2267 (1049) vs. 4.360 (2796) $p = 0.001$, respectively). Conversely in children with OD, anemia was significantly more frequent, and hyperglycemia was only present in this group. Initially, hepatic cytolysis was similar between both groups (Table 1).

During the 3-week refeeding study period, gastrointestinal symptoms occurred in 28.5% of children, with a similar frequency for the three main symptoms

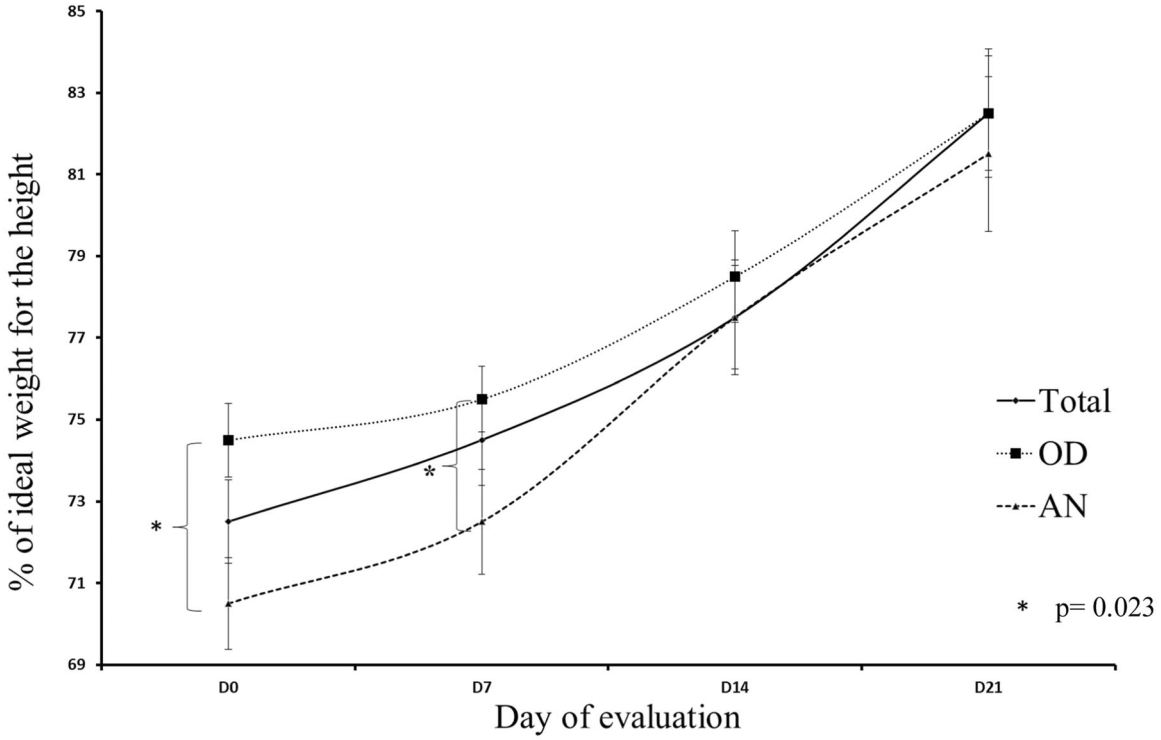

FIGURE 2 Evolution of the weight for height ratio during the refeeding protocol. WHR was significantly lower in children with AN than in children with OD at admission ($p = 0.023$) and at Day 7 ($p = 0.023$). At Days 14 and 21, there was no significant difference between both groups. During the 3-week refeeding protocol, the improvement in WHR was higher in children with AN than in children with OD. AN, anorexia nervosa; OD, organic disease; WHR, weight for height ratio.

(abdominal pain, vomiting, and diarrhea). The diarrhea appeared during the first week, while abdominal pain and vomiting appeared during the second and third weeks. The most frequent cardiac sign during refeeding was tachycardia in 27.7% of children, occurring between Days 4 and 17. Peripheral edema occurred in 6.7% of children, between Days 2 and 21. Neurological signs and symptoms were observed in only 4% of children: 1 AN presented auditory and visual hallucination on Day 3 associated with a severe hypophosphatemia (0.42 mmol/L), and 2 OD presented with decreased or abolished deep tendon reflexes without electrolyte abnormalities. There was no significant difference between children with OD and those with AN in terms of the frequency of the clinical abnormalities nor their time of occurrence (Table 2).

During the 3-week refeeding study period, the most frequent laboratory abnormality recorded was decreased of phosphatemia (<1.2 mmol/L) in 46.6% of children, but real hypophosphatemia (<0.8 mmol/L) in 13.7% of children, with only 2.5% of them presented with symptoms; there was no significant difference between the OD and AN groups. Hypokalemia was observed in 14.7% of children, mainly between Days 1 and 7; but only one patient presented moderate but symptomatic hypokalemia (2.6 mEq/L) with electrical signs on the electrocardiogram. Hypomagnesemia concerned in 11% of the children and appeared between Days 1 and 9. Liver biological abnormalities occurred in 25.8% of children: cholestasis in one child and cytolysis in 15 (24.2%) children. Abnormal liver function tests were significantly more frequent in OD children (Table 2).

As suggested by ASPEN experts,[22] the occurrence of RS is defined according to the number of electrolyte abnormalities present (phosphoremia, kalemia, and magnesemia). Overall, 19 (24.1%) children had only one abnormality, six (7.8%) had two, and none had three. According to the ASPEN definition, during the 3-weeks refeeding period, the prevalence of RS in the total cohort was 10.4% (8/77 children). No significant differences in terms of sex, age, WHR, and percentage of weight loss before refeeding were observed between children with RS and those without (Table S2). Among the eight patients who developed RS, two had AN, representing a 6.6% prevalence of RS in the AN group. There was no significant difference in terms of risk of RS between patients with OD and those with AN (Fischer test, $p = 1$).

Over the 3-week study period, a premature interruption or suspension of the protocol occurred in 14 (18.2%) children, between Days 1 and 16. The most frequent cause of suspension was digestive intolerance in 7 (58.3%) children, excessive weight gain in 3 (25%), and RS in 2 (16.7%).

TABLE 2 Clinical and laboratory abnormalities occurring during the 3-week enteral refeeding protocol according to etiology.

	Total *n*/total (%)	Organic diseases *n*/total (%)	Anorexia nervosa *n*/total (%)	*p* Value OD vs. AN	Day of occurrence of abnormality Mean (SD)
Clinical abnormalities					
Tachycardia	18/65 (27.7%)	13/39 (33.3%)	5/26 (19.2%)	$p = 0.336$	9.67 (4.16)
Diarrhea	8/72 (11.1%)	7/44 (15.9%)	1/28 (3.6%)	$p = 0.139$	2.80 (2.95)
Abdominal pain	8/73 (11%)	3/44 (6.8)	5/29 (17.2%)	$p = 0.252$	6.60 (5.41)
Vomiting	7/67 (10.4%)	5/40 (12.5%)	2/27 (7.4%)	$p = 0.693$	7.25 (9.50)
Edema	5/75 (6.7%)	2/46 (4.3%)	3/29 (10.3%)	$p = 0.369$	9.25 (8.18)
Neurologic symptoms	3/75 (4%)	2/46 (4.3)	1/29 (3.4%)	$p = 1$	6.33 (7.57)
Laboratory abnormalities (normal values)					
Abnormal LFT	16/62 (25.8%)	14/38 (36.8%)	2/24 (8.3%)	**$p = 0.028$**	6.50 (5.16)
Hypophosphatemia (<0.8 mmol/L)	10/73 (13.7%)	7/43 (16.3%)	3/30 (10.0%)	$p = 0.51$	4.90 (3.90)
Hypokalemia (2.60–3.40 mmol/L)	11/75 (14.7%)	7/45 (15.6%)	4/30 (13.3%)	$p = 1$	4.73 (5.06)
Hypomagnesemia (0.59–0.71 mmol/L)	8/73 (11.0%)	4/43 (9.3%)	4/30 (13.3%)	$p = 0.709$	4.88 (2.59)
Premature interruption of protocol	14/77 (18.2%)	10/48 (20.8%)	4/30 (13.3%)	$p = 0.34$	7.17 (3.74)

Note: Bold value indicates statistical significant results.

Abbreviations: AN, anorexia nervosa; LFT, liver function test; OD, organic disease.

4 | DISCUSSION

The present study shows that the proposed enteral refeeding protocol for severely undernourished children enabled to restore a nutritional status in nearly half of the children within a 3-week period, with a low prevalence of RS. Hypophosphoremia was the main laboratory abnormality but was rarely symptomatic and no serious clinical complications appeared during the refeeding period. The weight gain was significantly faster in children with AN than in those with OD.

The effectiveness of the proposed refeeding protocol was determined by measuring the mean weight gain, which was twice as low than the 1 to 2.6 kg/week previously reported in some pediatric studies.[23-26] This discrepancy may be explained by the younger age of our cohort (8 years vs. 14.2–15 years) and the three times lower initial caloric intake of our protocol compared with the previous studies (10 vs. 30–40 kcal/kg/day, or 1860–1900 kcal/day). While some authors recommend to start refeeding with 25%–50% of the total energy requirement (TER), with a progressive increase toward 100% of the TER in the first week,[27,28] others advise starting lower with around 10% of the TER for the younger children (10 kcal/kg/day or even less).[15,29] The classical cautious approach (initial low intake and slow increase) has been questioned by some authors because higher caloric intake (>1400 kcal/day) were not associated with a higher risk of RS but only in non-severely undernourished AN patients.[30-33] In the current protocol, we chose to start with this lower caloric intake to minimize the risk of RS, even if the time to reach an optimal nutritional status could be longer. Despite this lower initial caloric intake, the nutritional status of the children improved significantly, with only half of the children being still classified as severely undernourished after 3 weeks of refeeding. However, it appears challenging to accurately assess the true effectiveness of renutrition associated with this protocol during the initial 3-week period; is this a commendable outcome, or at least average? To our knowledge, precise data regarding the percentage of children who are no longer classified as severely malnourished after 3 weeks of enteral nutrition is not available in any of the pediatric studies we reviewed. We can only juxtapose the average weight gain observed in our study with that reported by other researchers. After 3 weeks, our patients exhibited an average weight gain of 2 kg, which aligns with findings from studies with comparable caloric intake, indicating weight gains ranging from 1.5 to 2.5 kg.[34-36] However, this gain is lower than that observed in high-caloric refeeding (HCR) protocols, which reported weight increases between 2.46 and 8.1 kg over the same 3-week period.[37-38] Consequently, comparing the precise percentage of individuals who are no longer severely malnourished after 3 weeks is not feasible with the available data and is contingent upon the initial nutritional status and etiology.

RS represents an illness spectrum occurring in high-risk populations. It is defined as any severe clinical

deterioration,[1] or as a symptomatic hypophosphatemia during nutritional support of malnourished patients.[39] As such, hypophosphatemia remains the hallmark of RS.[40] Although almost half of the present cohort presented a hypophosphatemia, none was severe, and only two patients presented with other clinical symptoms (neurologic symptoms and edema). In literature, the evidence of prophylactic effect of oral phosphate supplementation is still debated.[41] The proposed protocol, which includes a 1 mmol/kg/day phosphorus supplementation, thus seems effective in preventing severe hypophosphatemia. Moreover, when using the ASPEN definition,[22] the prevalence of RS observed herein was in the lower range of the 2%–34% reported in previous publications.[22,42]

According to the literature, the delay in complication occurrence after the start of refeeding is as follows: hypophosphatemia within 4 days, followed by cardiac complications within the first week, and neurologic complications, which are the last to occur.[1,27] The present findings however suggest that both clinical and laboratory abnormalities can also occur at later times, with several complications occurring during the third week. This highlights the need for physicians to pay special attention throughout the entire refeeding period.

Until now, the electrolyte and glycemic abnormalities during severe undernutrition have mainly been described in hospitalized children with AN.[41-45] To minimize the risk of developing refeeding complications, experts recommend correcting severe electrolyte abnormalities before starting to feed,[46] and supplement with phosphate, thiamine (vitamin B1), and other vitamins (B6, B9, and B12). Suggested doses of thiamine range from 1 to 2 mg/kg (or 200–300 mg/day), which are to be started 30 min before refeeding.[1,29] Some authors suggest vitamins should be supplemented to 200% and trace elements to 100% of the recommended daily intakes. Herein, all patients received oral thiamine (100–300 mg/day for 3 days depending on age), and no severe neurological or cardiac complications were recorded. Similarly, only one patient developed a severe and symptomatic hypokalemia. Thus, the thiamine, electrolyte, and vitamin supplementation provided in the present protocol appears sufficient to prevent major laboratory abnormalities.

To evaluate the evolution and complications depending on the etiology of undernutrition, children with an organic etiology were compared with children suffering from AN. The children with AN showed a lower initial WHR and more symptoms of chronic evolution of the undernutrition: higher rate of bradycardia, hypotension, hypothermia, and hypoglycemia. The AN group was more responsive to refeeding, and improved their WHR faster than the OD group. Since the undernutrition of AN patients, unlike patients with OD, results only from a decrease in oral caloric intake without any underlying disease (intestinal malabsorption, inflammation …), when caloric intake is restored, weight gain is certain. No major differences in the occurrence of complications were observed herein between children with OD and those with AN, except for hepatic cytolysis which was more prevalent in the OD group, probably due to underlying comorbidities or medication. The assessment of the risk of RS according to the category of patient (OD *vs.* AN) did not find any significant difference in this cohort of severely malnourished children. However, this result must be taken with caution given the small number of patients affected by RS ($n = 8$).

This study has several limitations. First, its single-center nature may limit the generalizability of the findings, we excluded patients from neonatal and pediatric intensive care which are at high RS risk. However, the standardization of the protocol and its integration into the prescription software limited the risk of variability during treatment administration and may facilitate its generalization to other centers. Second, this is a retrospective study, entailing a higher risk of loss to follow-up; the use of computerized medical records however limits the risk of missing data. Third, the lack of follow-up after 3 weeks for children discharged with enteral nutrition prevents a long-term evaluation of the protocol; the aim, however, was to focus on the initial refeeding period, during which the risk of RS is higher. This study provides new information about the specificities of children with AN and OD, which is currently lacking in the literature, and needed in order to move toward more personalized care.

In conclusion, the enteral refeeding protocol evaluated herein seems safe for refeeding severely undernourished children with different etiologies. Even if, half of the patients are no longer classified as severely malnourished after 3 weeks, we need studies more comparable in terms of initial nutritional status and similar etiologies to conclude on the true effectiveness of renutrition. The findings of the present study also provide new information about RS in the pediatric population. To improve care management of severely undernourished children, clinical pediatric studies are in need of more robust methodology, notably by comparing protocols in randomized controlled settings. Validation of the algorithm of RS prevention[9] and education of pediatric teams is a priority.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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