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Identification and prevention of refeeding syndrome in pediatric intensive care

Идентификације и превенција синдрома дохране у педијатријској јединици интензивног лечења

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Identification and prevention of refeeding syndrome in pediatric intensive care

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SUMMARY
"Refeeding syndrome" is described in the literature as a range of metabolic and electrolyte disorders that result from starting nutritional rehabilitation in malnourished patients. Without a universally accepted definition, data on "refeeding syndrome" incidence are heterogeneous. In most cases, a clinician will subjectively identify "refeeding syndrome," many authors have developed their purposes and criteria for it in their studies. Using the PubMed database and the appropriate filters (refeeding syndrome-related terms: refeeding syndrome, pediatrics, child, nutrition support, nutrition assessment, malnutrition), a search of the published literature was conducted. The American Society for Parenteral and Enteral Nutrition's 2020 recommendations are the only guidelines for identifying children with or at risk for "refeeding syndrome". High-quality scientific evidence regarding the clinical syndrome is absent, so we need further research in all "refeeding syndrome"-related areas, from validation to better identification of risk factors, definitions of "refeeding syndrome," and standardization of treatment protocols. For now, clinicians must remain vigilant to protect patients from the potentially devastating consequences of "refeeding syndrome."
Keywords: refeeding syndrome; child; nutrition support; nutrition assessment; malnutrition

САЖЕТАК
Синдром дохране је описан у литератури као спектар метаболичких и електролитних поремећаја који настају као последица започињања исхране код потхрањеног пацијента. Не постоји универзално прихваћена дефиниција, а подаци о инциденци су хетерогени. У највећем броју случајева клиничари ће субјективном проценом идентификовати синдром дохране, а многи аутори су у студијама развили сопствене критеријуме за постављање дијагнозе. Користећи *PubMed* базу података и одговарајуће филтере (појмови повезани са синдромом дохране: синдром дохране, педијатрија, деца, нутритивна подршка, нутритивна процена, неухрањеност), претражили смо публиковану литературу. Препоруке америчког друштва за парентералну и ентералну исхрану из 2020. године су једине препоруке које омогућавају идентификацију деце са синдромом дохране или деце која су у ризику. Високо квалитетни научни докази о овом клиничком синдрому недостају, што указује на потребу за даљим истраживањима у области синдрома дохране, од валидације до боље идентификације фактора ризика, дефиниције синдрома дохране и стандардизације протокола за лечење ових пацијената. За сада клиничари морају да остану опрезни како би заштитили пацијенте од потенцијално разарајућих последица синдрома дохране.
Кључне речи: синдром дохране; деца; нутритивна подршка; нутритивна процена; неухрањеност

INTRODUCTION

"Refeeding syndrome" (RFS) is defined in the literature as a group of metabolic and electrolyte disorders that occur in response to nutritional rehabilitation in malnourished patients [1, 2]. It was first mentioned in the journals of starving Asian prisoners during World War II, Keys et al. 1994 reported on a prospective randomized control trial examining the physiologic consequences of protracted malnourishment [3]. Even though RFS is written most often in the adult population, it can also occur in childhood [4]. The physiology and pathophysiology of

RFS are well known, while clinical signs, symptoms, and treatment are less known. When risk factors are not identified promptly, negative consequences such as hydroelectrolyte imbalances, metabolic disorders, respiratory failure, cardiac arrhythmias, encephalopathy, coma, and death can occur [5, 6]. The consequences of a rapid refeeding scheme in the presence of malnutrition include disturbances in potassium, magnesium, thiamin, and phosphate levels; vitamin deficiencies; glucose and fluid intolerance; and cardiac, pulmonary, hematologic, and neuromuscular dysfunction [7]. This condition is frequently undiagnosed, particularly in the pediatric population, so becoming familiar with the pathophysiology, clinical manifestations, and treatment models will help clinicians avoid unnecessary life-threatening conditions. The criteria developed for predicting RFS have been published in previous years but scored poorly for sensitivity or specificity [8]. The American Society for Parenteral and Enteral Nutrition (ASPEN) Consensus in 2020 advocated for new rules for defining RFS and screening procedures that entail stratification of criteria in response to the challenges brought up by the individual definition of RFS. The authors suggest that the diagnostic criteria for RFS should be as follows: a decrease of serum phosphorus, potassium, and/or magnesium levels by 10%-20% (mild), 20%-30% (moderate), or >30% and/or organ dysfunction caused by a decrease in any of these and/or thiamin deficiency (severe) within five days of reintroducing calories [9]. Novel criteria sets such as those proposed by the ASPEN may be predictive for RFS in pediatric patients [10]. The crucial point in preventing the occurrence of RFS is to be aware of its existence.

EPIDEMIOLOGY OF REFEEDING SYNDROME IN PEDIATRICS

The epidemiological data on RFS are heterogeneous due to a lack of universally accepted defining criteria; a clinician usually identifies RFS subjectively, and many authors have created their definitions and standards in their studies, often using hypophosphatemia as the single

diagnostic criteria [11]. Consequently, the data on RFS incidence in the pediatric population is challenging. The overall prevalence of RFS in various hospital populations has been cited with a wide range of estimations, from 0.43% to 34% [12,13].

The cohort study made by Dunn et al. reported that within 72 hours of the beginning, the incidence of "electrolyte shifts" in the whole population was 27% (8 of 15) in the population at risk of those patients who developed hypophosphatemia, three developed lethargy, and cardiac dysfunction [14]. Two neonatal studies found that rates of hypophosphatemia were significantly higher in patients of early gestational age [15, 16]. In two other studies, hypophosphatemia and hypokalemia were discovered in neonates receiving parenteral nutrition [17, 18, 19].

PATHOPHYSIOLOGY

Understanding the pathophysiology of malnutrition is crucial for comprehending what occurs during refeeding [20]. Starvation can be defined as a catabolic state where the body shifts from carbohydrate utilization to fat and protein metabolism. With this shift, the pancreas' production of insulin declines in the absence of available carbohydrates [21]. The following change in the metabolic pathway is that ketone bodies and free fatty acids will replace glucose as the primary energy fuel. Further catabolism leads to a continuing and progressive wasting of cellular and muscle mass, resulting in hypotrophy, atrophy of vital organs, and, consequently, dysfunction. As a result, lower renal concentration capacity, hydroelectrolytic disbalances, a decline in metabolic rate and hemoglobin level, and reductions in respiratory and cardiac function may all result in serious complications.

When we start refeeding, increased glucose levels increase insulin secretion, stimulating glycogen, fat, and protein synthesis. This increment in insulin release and its anabolic activity are the keys to the pathophysiology [22]. This anabolic process requires electrolytes, primarily

phosphorus, magnesium, and potassium, and cofactors, such as thiamine, to be taken into cells. The consequence of this alteration in metabolism can be a life-compromising extracellular depletion of these electrolytes. Phosphate is essential for all intracellular processes, cell membranes' structural integrity, adenosine triphosphate (ATP) production, DNA, RNA, and 2,3-diphosphoglycerate. Hypokalemia (below 3.5 mEq/L) and hypomagnesemia (below 1.8 mg/dL) are also commonly related to electrolyte imbalances with RFS [23]. A mild reduction of potassium and magnesium serum levels may induce nausea, vomiting, constipation, diarrhea, muscle twitching, or weakness. In contrast, a more severe reduction of the serum levels of these electrolytes can cause dysrhythmias, cardiac dysfunction, skeletal muscle weakness, seizures, and metabolic acidosis.

Children may suffer more from short periods of starvation because their bodies need more energy to grow, while adults may be able to handle more prolonged periods of starvation better [24].

PREDICTIVE CRITERIA

An example of criteria especially designed for predicting RFS and nutritional support in adults—Britain's National Institute for Health and Care Excellence (NICE) guideline—was published in 2006 [8]. This guideline was established based on previously reported reviews and the authors' expertise and agreed upon based on an unofficial consensus. The Short Nutritional Assessment Questionnaire (SNAQ) is an example of screening criteria designed for malnutrition that are validated for diagnosing malnutrition and have also been validated for predictive value in RFS [25]; the usefulness of these two previously mentioned tools is questionable because their contribution to predicting less severe hypophosphatemia, hypokalemia, or hypomagnesemia is undefined, and their performance in predicting severe hypophosphatemia is poor [26].

In 2017, the American Society for Parenteral and Enteral Nutrition (ASPEN), the Parenteral Nutrition Safety Committee, and the Clinical Practice Committee established consensus recommendations for discovering patients with or at risk for RFS (Figure 1) and recommendations for the avoidance and treatment of RFS in at-risk pediatric patients (Table 1) [6]. As of today, these are the only recommendations for the pediatric population. Still, the predictive validity of these unique and novel recommendations has yet to be studied [9].

CLINICAL FEATURES

Severe hypophosphatemia causes impaired neuromuscular function with paresthesia, seizures, cramps, weakness, impaired muscular contractility, and rhabdomyolysis. The consequence for the respiratory system is hypoventilation, which may be followed by respiratory failure [27]. It can also present as a central nervous system dysfunction in the form of confusion or coma. Phosphate deficiency also leads to hematologic disorders such as thrombocytopenia, damaged clotting, and leukocyte dysfunction, and the red blood cells show a deteriorated capacity to release oxygen [28].

Both hypomagnesemia and hypokalemia lead to neuromuscular dysfunction, which presents as weakness, paralysis, paresthesia, confusion, rhabdomyolysis, respiratory depression, cardiac arrhythmias, and cardiac arrest. Additionally, due to starvation, stress, inflammation, and increased insulin release, sodium retention increases, and the consequence is extracellular fluid expansion followed by edema. As mentioned above, the disorders, when associated with thiamine deficiency, lead to tachyarrhythmias, enlargement of the heart, severe edema, and finally, congestive cardiac failure with lung edema. Thiamine deficiency also causes Wernicke-Korsakoff syndrome in the central nervous system and neuropathy in the peripheral nervous system [29].

Most clinical signs and symptoms during an RFS are nonspecific (Figure 2.) [30]. The primary and most common symptoms are tachycardia, tachypnea, and peripheral edema. However, such signs may also be due to other conditions in hospitalized patients with different diseases, especially those in intensive care departments.

AVOIDANCE AND TREATMENT

Prevention and early recognition of at-risk patients, careful monitoring before and during refeeding, and proper individualized nutrition rehabilitation are the keys to successful management and outcome [31]. Various studies have evaluated preventive approaches for RFS, mainly guided by hypocaloric nutrition, electrolyte substitution, and thiamin infusions. Management of confirmed RFS should be conducted in two ways: by improving the underlying electrolyte imbalances and by lowering or slowing the advancement of calories, according to the final aim. “Refeeding syndrome” can be seen with any pattern of nutritional support: oral diet, enteral nutrition (EN), parenteral nutrition (PN), or intravenous dextrose solutions [32]. The ASPEN consensus recommendations for avoiding and treating RFS presented in Table 2 are universal. They should be adapted to individuals and particular populations, such as those with decreased renal function. These recommendations are based on consensus and, in the future, will need to be investigated in randomized clinical trials in general and specific populations with different comorbidities to define their actual benefits and utility [33].

Most clinical trials investigating risk factors for RFS are conducted according to criteria developed by the NICE guidelines. However, Goyale et al. and Zeki et al. found these factors had low sensitivity and specificity in predicting RFS [34, 35]. According to the NICE guidelines, feeding should be started gradually (maximum 0.042 MJ/kg/24 hours) and individually adapted for patients at high risk of developing refeeding syndrome [8]. Also, the NICE guidelines advocate that in very undernourished patients (body mass index ≤14 or

insignificant food intake for more than two weeks), refeeding should start at a maximum of 0.021 MJ/kg/24 hours, with cautious monitoring on an electrocardiogram. The NICE recommendations also state that correcting hydroelectrolyte imbalances should be done in conjunction with refeeding; doing it before starting with feeding is not imperative. All guidelines agree that vitamin supplementation should be started promptly before and for the first ten days of nutritional rehabilitation. The required levels of supplements cited by NICE are only grade-level D recommendations.

Additionally, the circulatory volume should also be reestablished. Regarding further patient monitoring, in the first week, electrolyte levels should be controlled once a day and at least three times in the following week. Urine electrolytes could also be checked for closer monitoring and assessment of hydroelectrolyte status, wasting, and replacement.

CONCLUSION

Even though RFS is reported most often in adults, it can also occur in childhood. This condition is frequently undiagnosed, particularly in the pediatric population, so becoming familiar with the pathophysiology, clinical manifestations, and treatment models will help clinicians avoid unnecessary life-threatening conditions. New sets of criteria, like those suggested by ASPEN, may be able to predict RFS in children. High-quality scientific evidence regarding the clinical syndrome is absent, so we need further research in all areas related to RFS, from validation to better identification of risk factors, definitions of RFS, and standardization of treatment protocols. Even though ASPEN's recommendations have been provided, their most significant shortcomings are that they are based on consensus and must be examined in randomized controlled trials in general and specific populations with different comorbidities to define their utility in pediatric and adult populations. For now, clinicians must remain vigilant to protect patients from the potentially devastating consequences of RFS.

Ethics: The authors declare that the article was written according to ethical standards of the Serbian Archives of Medicine as well as ethical standards of medical facilities for each author involved.

Conflict of interest: None declared.

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Figure 1. Risk factors for refeeding syndrome [1]

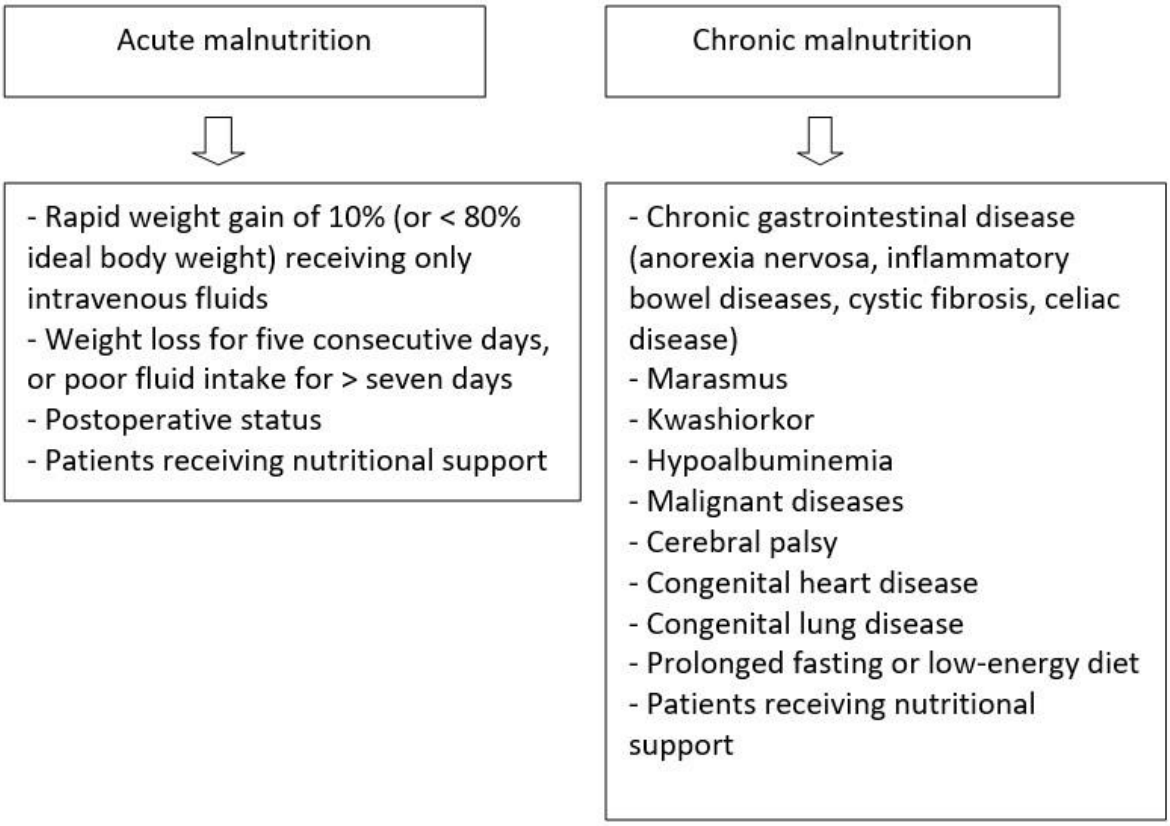

Table 1. ASPEN Consensus Criteria for Identifying Pediatric Patients at Risk for Refeeding Syndrome [9]

Parameters	**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 to -1.9 *z*-score that is a change from baseline	-2 to -2.9 *z*-score that is a change from baseline	-3 *z*-score or greater that is a change from baseline
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[b]	Mildly abnormal or decreased to 25% below lower limit of normal	Moderately/significant 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 (see Table 4)	Mild disease	Moderate disease	Severe disease
Loss of subcutaneous fat	Evidence of mild loss ORMid-upper arm circumference *z*-score of -1 to -1.9 *z*-score	Evidence of moderate loss ORMid-upper arm circumference *z*-score of -2 to -2.9	Evidence of severe loss ORMid-upper arm circumference *z*-score of -3 or greater
Loss of muscle mass	Evidence of mild or moderate loss ORMid-upper arm circumference *z*-score of -2 to -2.9		Evidence of severe loss ORMid-upper arm circumference *z*-score of -3 or greater

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

[a]Not intended for use in patients at ≤ 28 days of life or ≤ 44 weeks corrected gestational age.

[b]Please note that electrolytes may be normal despite total-body deficiency, which is believed to increase risk of refeeding syndrome

Figure 2. Signs and symptoms of refeeding syndrome [30]

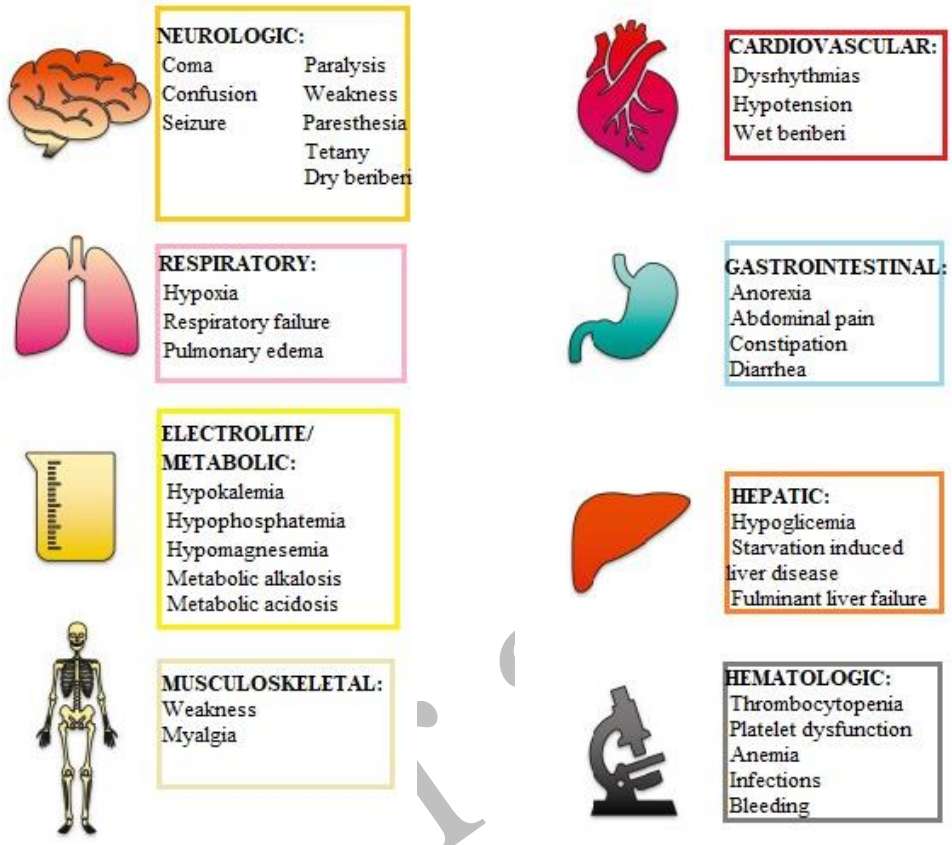

Table 2. ASPEN Consensus Recommendations for Avoidance and Treatment of RFS in At-Risk Pediatric Patients [9]

Aspect of Care	Recommendations
Initiation of nutrition	- Initiate nutrition at a maximum of 40–50% goal, but usually starting the glucose infusion rate around 4–6 mg/kg/min and advancing by 1–2 mg/kg/min daily as blood glucose levels allow until you reach a max of 14–18 mg/kg/min. This includes enteral as well as parenteral glucose. - Calories from IV dextrose solutions and medications being infused in dextrose should be considered in the limits above and/or initiated with caution in patients at moderate to severe risk for RS. If the patient is already receiving IV dextrose for several days and/or medications in dextrose and has been asymptomatic with stable electrolytes, calories from nutrition may be reintroduced at a higher amount than recommended above.
Fluid restriction	No recommendation
Sodium restriction	No recommendation
Protein restriction	No recommendation
Electrolytes	- Check serum potassium, magnesium, and phosphorus before initiation of nutrition. Monitor every 12 hours for the first 3 days in high-risk patients. May be more frequent based on clinical picture. - Replete low electrolytes based on established standards of care. - No recommendation can be made for whether prophylactic dosing of electrolytes should be given if prefeeding levels are normal. - If electrolytes become difficult to correct or drop precipitously during the initiation of nutrition, decrease calories/grams of dextrose by 50% and advance the dextrose/calories by approximately 33%of goal every 1–2 days based on clinical presentation. Recommendations may be changed based on practitioner judgment and clinical presentation, and cessation of nutrition support may be considered when electrolyte levels are severely and/or life-threateningly low or dropping precipitously.

Thiamin and multivitamins	- Thiamin 2 mg/kg to a max of 100–200 mg/d before feeding commences or before initiating IV fluids containing dextrose in high-risk patients. - Continue thiamin supplementation for 5–7 days or longer in patients with severe starvation, chronic alcoholism, or other high risk for deficiency and/or signs of thiamin deficiency. - Routine thiamin levels are unlikely to be of value. - MVI is added to PN daily, unless contraindicated, as long as PN is continued. For patients receiving oral/enteral nourishment, add complete oral/enteral multivitamin once daily for 10 days or greater based on clinical status and mode of therapy. - Once patient is within adult weight ranges, refer to adult multivitamin recommendations
Monitoring and long-term care	- Recommend vital signs every 4 hours for the first 24 hours after initiation in those at risk. - Cardiorespiratory monitoring is recommended for unstable patients or those with severe deficiencies, based on established standards of care. - Daily weights with monitored intake and output. - Estimation of energy requirements as needed for oral feeding patients. - Evaluate short- and long-term goals for nutrition care daily during the first several days until the patient is deemed stabilized (eg, no requirement for electrolyte supplementation for 2 days) and then based on institutional standards of care.

ASPEN – American Society for Parenteral and Enteral Nutrition; IV – intravenous; MVI – multivitamin injectable; PN – parenteral nutrition; RS – refeeding syndrome

