SMGroup

SM Journal of Nutrition and Metabolism

Review Article

# Undernutrition Treatments, Prevention and Risk of Refeeding Syndrome

**Maria Gabriella Gentile***

*Chief Eating Disorders Unit, Centro Diagnostico Italiano, Italy*

**Article Information**

Received date: Jul 23, 2015
Accepted date: Oct 16, 2015
Published date: Nov 09, 2015

***Corresponding author**

Maria Gabriella Gentile, Chief Eating Disorders Unit, Centro Diagnostico Italiano, Italy; Email: mariagabriella.gentile@gmail.com



**Keywords** Undernutrition; Undernutrition Treatments; Refeeding Syndrome Prevention; Refeeding Syndrome Treatment; Anorexia Nervosa; Hypophosphatemia; Oral Nutritional Supplements; Enteral Nutrition

**Abbreviations** BMI = Body Mass Index; EN = Enteral Nurtition; PN = Parenteral Nutrition; NG = Nasogastric; IV = Intravenous

## Abstract

In hospital care, disease related to undernutrition results in: increased complications such as wound infections, chest infections, pressure ulcers; increased numbers of patients who are readmitted to hospital; increased numbers of deaths. Poor nutritional status or moderate-to-severe nutritional risk results in about 50% prolongation of hospital stay.

Undertreated severe undernutrition affects every body area: the cardiovascular and respiratory systems, metabolism and immune systems, bone marrow depression, gut and brain with a detrimental effect on mental state.

Several guidelines, papers and reviews provide guidance for medical and nursing staff managing patients with severe undernutrition and/or at risk of refeeding syndrome. So, caring for severely starved patients and re-starting nutrition command close monitoring seeking for early signs or symptoms of refeeding and specialized care operating, with in a timely plan.

Goals of treatment for undernourished patients are:

1. Treat physical complications and correct nutritional deficiencies.

2. Restore patients to a healthy weight, according with age and disease related.

Nutritional rehabilitation should be regarded as a process developing through different levels (not mutually exclusive):

(a) Improving energy and nutrient intake from ordinary food for out end in-patients

(b) Use of oral nutritional supplements

(c) Use of artificial nutrition.

Refeeding critically ill patients is a particularly complex and hard issue. Critically undernourished patients should be moved from a starved state to an anabolic state, and they may develop complications of the refeeding syndrome, that should be prevented as much as possible.

## Introduction

Undernutrition is a form of malnutrition resulting from a reduced supply of food or from inability to digest, assimilate, and use the necessary nutrients.

Nutritional risk is defined by the present nutritional status and risk of impairment of present status, due to increased requirements caused by stress metabolism of the clinical condition.

It has been estimated that are at risk of undernutrition: 25-34% of patients admitted to hospital; 30-42% of patients admitted to care homes, 18-20% of patients admitted to mental health units [1].

Despite the prognostic role of disease related undernutrition in negatively affecting the patient's outcome (mortality, morbidity, healthcare costs, functional status and quality of life), surveys suggest that nutritional care routines by healthcare professionals are still poor [2]. In particulary in hospital care, disease related to undernutrition results in: increased complications such as wound infections, chest infections, pressure ulcers; increased numbers of patients who are readmitted to hospital; increased numbers of deaths. Poor nutritional status or moderate-to-severe nutritional risk results in about 50% prolongation of hospital stay [3].

Undertreated severe undernutrition affects every body area :the cardiovascular and respiratory systems, metabolism and immune systems, bone marrow depression, gut and brain with a detrimental effect on mental state; because the brain is especially vulnerable to undernutrition, causing shrinking and many behavioural and psychosocial effects as rigidity, emotional dysregulation, and social behavior; particularly negative effects are present in anorexia nervosa adolescence patients at the time of brain reorganization. Also depression, obsessional thinking, anxiety and other psychiatric symptoms could represent the reversible effects of undernutrition on the brain [4,5] (see table 1).

As result severe and protracted undernutrition nearly always leads to marked changes in body spaces (e.g. intra-extracellular water), in body masses (e.g. potassium, phosphate, magnesium

**Table 1:** Symptoms, signs and side effects of undernutrition

| Common symptoms | Signs | Most common side effects |
|---|---|---|
| • Depression and anxiety<br>• tiredness and fatigue<br>• low blood pressure<br>• breathing difficulties<br>• aching joints<br>• soft and tender bones<br>• lower sex drive<br>• lower body temperature<br>• diarrhoea<br>• dizziness<br>• bleeding and/or swollen gums<br>• irritability<br>• loss of reflexes and lack of coordination<br>• scaling and cracking of the lips and mouth. | • loss of body fat and muscle mass<br>• poor memory<br>• chewing and/or swallowing problems<br>• sunken cheeks<br>• white fungal growth on the tongue<br>• hollow eyes<br>• abdominal swelling and constant bloating<br>• protruding bones<br>• thinning, dry, cold and pale skin<br>• dry and sparse hair that falls out easily<br>• apathy, introversion, self-neglect and deterioration in social interactions<br>• in more severe cases, sufferers may even show signs of unresponsiveness (stupor). | • respiratory and cardiac failure<br>• higher risk of hypothermia and pneumonia<br>• weaker immune system thus increased risk of catching an infection and longer recovery time<br>• poor wound healing<br>• fertility problems<br>• organ failure<br>• urinary infections<br>• development of health conditions such as edema, anaemia and jaundice<br>• total starvation could be fatal if no calories have been consumed for a long period of time.<br>• **Iron deficiency -** Can cause anaemia.<br>• **Zinc deficiency -** Affects the body's ability to fight infection and causes skin rashes.<br>• **Vitamin B12 deficiency -** Linked to anaemia as well as problems with neurological complications.<br>• **Vitamin D deficiency -** Causes bone diseases such as osteomalacia in adults and rickets in children.<br>• **Vitamin C deficiency -** Can cause scurvy.<br>• **Vitamin A deficiency -** Leads to night blindness |

**Table 2:** Signs and symptoms of refeeding syndrome [7-11].

| Signs and symptoms | Determined by |
|---|---|
| **Cardiovascular** | |
| Arrhythmia | hypophosphataemia, hypokalaemia, hypomagnesaemia, fluid intolerance |
| Hyper/hypotension | hypophosphataemia, hypokalaemia, hypomagnesaemia |
| Reduces cardiac contractily | hypophosphataemia, muscle wasting |
| Congestive cardiac failure | hypophosphataemia, fluid intolerance |
| Cardiomyopathy | hypophosphataemia, muscle wasting |
| Cardiac arrest | hypokalaemia |
| Sudden death | hypophosphataemia, hypokalaemia, hypomagnesaemia, fluid intolerance |
| **Neurological** | |
| Weakness | hypophosphataemia, hypokalaemia, hypomagnesaemia |
| Paraesthesia | hypophosphataemia, hypomagnesaemia |
| Tremor | hypomagnesaemia |
| Seizures | hypophosphataemia, hypomagnesaemia |
| Paralysis | hypophosphataemia, hypokalaemia |
| Ataxia | hypomagnesaemia |
| Tetany | hypomagnesaemia |
| Vertigo | hypomagnesaemia |
| Wernicke's encephalopathy | thiamine deficiency |
| Korsakoff's syndrome | thiamine deficiency |
| **Haemathological** | |
| Platelet dysfunction | hypophosphataemia |
| Haemolitic anaemia | hypophosphataemia |
| Leucocyte disfunction | hypophosphataemia |
| **Muscular** | |
| Weakness | hypophosphataemia, hypokalaemia |
| Myalgia | hypophosphataemia, hypokalaemia |
| Rhabdomyolysis | hypophosphataemia, hypokalaemia |
| **Respiratory** | |
| Failure or ventilator dependency | hypophosphataemia, muscle wasting |
| Pulmonary oedema | hypokalaemia |
| Retention of carbon dioxide | hypokalaemia, glucose intolerance |

| | |
|---|---|
| **Renal** | |
| Osmotic diuresis | glucose intolerance |
| Prerenal azotaemia | glucose intolerance |
| Decreased ability of the renal tubules to concentrate urine | hypokalaemia |
| **Metabolic** | |
| Alkalosis | hypokalaemia |
| Glucose intolerance | hyperglycaemia, hypokalaemia |
| Hypernatraemia | hypokalaemia, glucose intolerance |
| Ketoacidosis | hypokalaemia, glucose intolerance |
| Metabolic acidosis | hypokalaemia, glucose intolerance |
| **Gastrointestinal** | |
| Constipation | hypokalaemia, hypomagnesaemia |
| Abdominal pain | hypomagnesaemia |
| Paralytic ileus | hypokalaemia |

**Table 3:** Decision path for extreme undernourished subject [14, 25].

| | |
|---|---|
| 1. | Establish BMI and degree of unintentional weight loss in the last 3-6 months |
| 2. | Restore circulatory volume, monitor fluid balance, blood pressure, heart rate, ECG, if necessary cardiac monitoring |
| 3. | Take blood samples: electrolyte levels should be measured at baseline and then daily for the first weeks. Replace them if needed |
| 4. | Before nutritional therapy, provide oral/enteral thiamine and vitamin B supplementation (twice recommended dosage) |
| 5. | Start administration of intravenous fluid with 5-10% glucose (20-40 ml/hour) to prevent hypoglicemia |
| 6. | Start slowly with enteral feeding or oral nutritional supplements |
| 7. | Start immediately with phosphate supplements oral/NG/or IV infusion; and continue according to serum levels |
| 8. | Start with potassium, magnesium supplements as soon as you have plasma levels; go on |
| 9. | Monitor body temperature and correct hypothermia with blankets and appropriate clothes |
| 10. | Organize and monitor bed rest |

NG = nasogastric; IV = intravenous; BMI = Body Mass Index

overall and compartmental stores), in equilibrium relationships between bodily spaces, concentrations and in feedback mechanisms which are set at new pathological levels of functioning [3,6].

These changes set the body at risk of refeeding syndrome, i.e. the disturbances caused by a too rapid/or unbalanced refeeding which the deranged bodily system just referred to cannot support [7,8].

Main signs and symptoms of the refeeding syndrome include:

1) Salt and water retention, leading to oedema and heart failure, which may be aggravated by cardiac atrophy;

2) Hypophosphatemia due to a profound derangement of cellular processes, affecting almost every physiological system, beginning with energy storage in the form of adenosine triphosphate;

3) Depletion of other several essential electrolytes like potassium and magnesium and vitamins as B1, B6, etc which can lead to paralysis, rhabdomyolysis and changes in myocardial contraction and signal conduction;

4) Depletion of the thiamine co-factor of glycolysis, potentially leading to Wernicke's encephalopathy and/or cardiomyopathy (see table 2).

Patients should be considered to be at high risk of developing refeeding syndrome if has:

A) One or more of the following: BMI less than 16 kg/m$^2$; unintentional weight loss greater than 15% within the last 3-6 months; little or no nutritional intake for more than 10 days; low levels of potassium, phosphate or magnesium prior to feeding.

B) Two or more of the following: BMI less than 18.5 kg/m$^2$; unintentional weight loss greater than 10% within the last 3-6 months; little or no nutritional intake for more than 5 days; a history of alcohol abuse or drugs including insulin, chemotherapy, antacids or diuretic [9].

Disease groups to greater risk of refeeding syndrome are: anorexia nervosa, chronic alcolism and neoplastic disease.

## Clinical and nutritional assessment

Several guidelines, papers and reviews provide guidance for medical and nursing staff managing patients with severe undernutrition and/or at risk of refeeding syndrome. There are also many reports of medical complications in refeeding patients [9,10].

So, caring for severely starved patients and re-starting nutrition command close monitoring seeking for early signs or symptoms of refeeding and specialized care operating, within a timely plan, and for patients with mental disease as anorexia nervosa patients both at a physical (first) and emotional level (successively), the final goal being to restitute a better healthy achievable condition (see table 3) [11-13].

Initial comprehensive assessment should include the following components:

### Clinical assessment

- Medical status: a detailed clinical history, a full physical examination, measurement of weight, height, calculation of BMI, pulse rate, blood pressure (seated and standing), an electrocardiogram, body temperature.

- Psychiatric comorbidity: anxiety, depression, substance misuse, suicidality, personality disorders. However, clinicians should be aware that depression, obsessional thinking, anxiety and other psychiatric symptoms could represent the reversible effects of undernutrition on the brain.

- Biochemical test: serum test to detect hypokalaemia, hypoglycaemia, hypophosphataemia, hypomagnesaemia, metabolic alkalosis or acidosis, kidney and liver function tests; blood test looking for undernutrition-induced bone marrow suppression such as neutropaenia, and low lymphocytes.

### Nutritional assessment

- Nutritional history should include dietary restriction, weight loss for adults, height and weight retardation or interruption of growth for children, the rapidity of weight loss, inability to restore weight, fluid intake, and for anorexia nervosa patient's fears about weight gain, excessive exercise, purging, binging, use of medications to lose or maintain low weight (laxative, diuretics).

- Dietetic enquiries should be performed by trained dietitians.

## Clinical and nutritional management

Goals of treatment for undernourished patients are:

1. Treat physical complications and correct nutritional deficiencies.

2. Restore patients to a healthy weight, according with age and disease related.

For many years, the recommendations for nutritional treatment in severe undernutrition have been quite cautious. For instance, in UK and Australia, recommended nutritional regimens start with as little as 200 to 600 kcal per day i.e. an initial refeeding rate of between 10 and 20 Kcal/kg per day, [11,14]; in US the usual recommendations are to begin at around 1200 kcal per day, and then to progress slowly adding 200 kcal every other day [15].

Most current guidelines aim to avoid the refeeding syndrome mainly by restricting the intake of energy, but refeeding of severely undernourished patients poses two very complex and conflicting tasks: to avoid "refeeding syndrome" caused by a too fast correction of undernutrition and avoid "underfeeding" caused by an overly cautious nutritional rehabilitation [13,16].

Therefore in severely undernourished patients the energy intake should be planned after indirect calorimetric measurements (resting energy expenditure measurements should be performed within 24-48 h after hospital admission), since resting energy expenditure is the main component of daily expenditure particularly in severely undernourished bed rest patients.

Nutritional rehabilitation should be regarded as a process developing through different levels (not mutually exclusive):

(a) Improving energy and nutrient intake from ordinary food for out end in-patients

(b) Use of oral nutritional supplements

(c) Use of artificial nutrition.

Weight gain results improvements in most of clinical and psychological derangements.

Initial refeeding may be associated with mild transient fluid retention, but patients (as it may happen in purgative anorexia nervosa) who abruptly stop laxatives or diuretic may develop marked fluid retention caused by secondary hyperaldosteronism; sometimes a competitive aldosterone antagonist diuretic is needed [17] .

Patients may experience abdominal bloating or delayed gastric emptying or constipation feeling. Constipation may be ameliorated with stool softeners and/or fiber.

### Weight restoration

In the in-patient setting weight gain should be set at 0.5-1 kg per week. We should consider the high individual variability, weight gain may be slow; but weight must be progressively restored.

Ordinary food

Patient should be encouraged – not forced- to eat the planned amount.

Dietary inquiries through diary forms should be used daily also in and out-patients. Dietitian should help patients to choose their own meals and provide a personalized structured meal plan that ensures nutritional adequacy and inclusion of all major food groups, suggesting food rich of phosphorus and protein like semi hard or hard cheese to contribute in the hypophosphataemia prevention; but it is necessary to include setting goals of treatment and a plan for monitoring to ensure that these goals are met.

### Oral nutrition support

If simple measures, as oral food, are not working or where the patient has a reduced appetite, or is too ill to eat enough it is indicated the use oral nutritional supplements, and vitamin and mineral supplement.

In severe undernourished patients supplementing the diet with oral nutritional support may be useful to achieve the prescribed energy goal and it will be a very effective strategy to achieve weight gain. Their intake should be adequately monitored by dietitians or nurses [13,18,19].

#### Artificial nutrition

For patients who are unable to eat, or with severe undernutrition patient (BMI $\leq$ 13 kg/m$^2$) disposed to intake less than 100% of the energy needs or with body weight not increasing, however in life threatening conditions artificial nutrition should be considered as a life-saving treatment.

The international guidelines on the use of artificial nutrition state that "if the gut works you must use it" [20,21].

In the majority of critically ill patients, the preferred way of feeding is Enteral Nutrition (EN), because it is safer compared to parenteral nutrition as it is well documented in numerous prospective randomized controlled trials involving the effects of critical illness on mortality.

There is more than substantial evidence of most consistent outcome effect of EN is a reduction in infection morbidity, a positive

impact on the duration of treatment, and a faster normalization of the endocrine and metabolic status [22,23].

Also for anorexia nervosa patients when it is necessary to use artificial nutrition the international guidelines suggest to choose EN unless there is significant gastrointestinal dysfunction [14-16].

EN must be closely monitored and regulated via an electronically operated pump. The naso -gastric route shows lower risk of complication, and is cost effective; most comfortable naso-gastric tubes being small (6-8 French units), and built with silicone and polyurethane. Usually a polymeric lactose-free, gluten-free, high nitrogen completely fluid formula is suggested.

If it is necessary to reduce fluid overload and gastric discomfort, it is indicated the use of a commercially high caloric (1.7-2.2 kcal/ml), polymeric lactose-free, gluten-free, high nitrogen completely fluid formula [24]. Continuous feeding is preferable; flow rate should be kept constant during 24/h by a pump; the continuous infusion helps preventing hypoglycemic episodes and promote to tolerance. Initial rate should be at 20-30 ml/h and progressively raised, usually in 3-4 days, to a target rate of 40-50 ml/h or more if tolerated. Flushing of the feeding tube with the suggested amount of water every 6-8 h is indicated to prevent of feeding tube obstruction. Oral feeding must be continued and encouraged if it is accepted.

If early EN is not feasible or available we should use Parenteral Nutrition (PN).

PN is an important therapeutic modality that is used in adults, children, and infants for a variety of indications. PN is a complex prescription therapy associated with significant adverse effects. Deaths have occurred when safe practice guidelines were not followed; the safe prescribing of PN requires a thorough knowledge of protein and energy requirements, macronutrients, micronutrients, fluid homeostasis, and acid-base balance.

Appropriate monitoring parameters for PN should include fluid requirements, serum electrolyte concentrations, serum glucose concentrations, hepatic function, renal function, serum triglyceride concentrations, and signs or symptoms of vascular access device complications [25].

## Discussion

Refeeding critically ill patients is a particularly complex and hard issue. Critically undernourished patients should be moved from a starved state to an anabolic state, and they may develop complications of the refeeding syndrome. Many case reports continue to be reported [26-28]. They suggest the need of early identification of the patient at risk and the improvement of the knowledge of risk factors, pathology, and pertinent findings to optimize outcomes.

A recent systematic review cases give evidence that hypophosphatemia is almost universally present [28]. Depending on the demand of phosphorus in anabolic phase, serum phosphorus levels can drop precipitously, and phosphorus levels below normal are associated with poor outcomes. The risk of refeeding syndrome with contaminant hypophosphatemia is largely correlated to the degree of undernutrition and how undernutrition is managed, i.e., the amount of calories, vitamins, and macro/micronutrients supplied [29,30]. So we can consider the paramount importance to add supplements of phosphate (besides to vitamins and other micronutrients) also when basal value are normal. The amounts of phosphate provided can vary quite extensively and require strict, daily, monitoring of serum level.

The effects of undernutrition are devastating to the body's ability to function as well as to the thinking and behavioral pattern of the patient. Admission to an Intensive Care Unit (ICU) at time of life-threatening crises should reduce mortality. One of few study conducted in France [31] on randomly selected 30 ICU reported a crude mortality of about 10%. In this retrospective study including 68 anorexia nervosa patients (BMI 12 ±3 kg/m$^2$), at admission major diagnoses were metabolic and refeeding problems (41% of patients), voluntary drug intoxication, and infection (26% of patients). Refeeding syndrome was diagnosed in seven patients, but hematological complications were in 30 % patients and hypophosphatemia or hypokalemia, respectively, in 16 % and 24 % of patients; these complications may be considered early warning of refeeding syndrome (see table 2).

Refeeding syndrome is a potentially fatal complication that can occur during the initial phase of refeeding process in undernourished patients receiving parenteral, enteral nutrition, or oral diet.

Severe undernutrition leads to marked changes in body spaces as alterations of intra-extracellular water and in body composition as compartmental stores of phosphate, potassium, sodium, and magnesium. These changes set the body at risk of refeeding syndrome; a too rapid and/or unbalanced refeeding may impose a disproportionate strain on the deranged body spaces and compartments already mentioned, and more derangements ensue.

So, caring for severely starved patients and restarting feeding require close monitoring, seeking for early signs or symptoms of refeeding, and specialized appropriate caring according to a timely multifaceted plan.

## References

1. Russel CA, Elia M. Nutrition Screening Survey In The Uk And Republic Of Ireland In 2011. A report by the British Association for Parenteral and Enteral Nutrition (BAPEN) Hospitals, Care Homes And Mental Health Units Nutrition Screening Week Survey And Audit. 2012.
2. Bavelaar JW, Otter CD, van Bodegraven AA, Thijs A, van Bokhorst-de van der Schueren MA. Diagnosis and treatment of (disease-related) in-hospital malnutrition: the performance of medical and nursing staff. Clin Nutr. 2008; 27: 431-438.
3. Norman K, Pichard C, Lochs H, Pirlich M. Prognostic impact of disease-related malnutrition. Clin Nutr. 2008; 27 :5-15.
4. Norrington A, Stanley R, Tremlett M, Birrell G. Medical management of acute severe anorexia nervosa. Arch Dis Child Educ Pract Ed. 2012; 97: 48-54.
5. Keys A, Brozek J, Henschel A. The biology of human starvation. Minneapolis: University of Minnesota Press. 1950.
6. Stanga Z, Brunner A, Leuenberger M, Grimble R F, Shenkin A, Allison S P, et al. Nutrition in clinical practice - the refeeding syndrome: illustrative cases and guidelines for prevention and treatment. Eur J Clin Nutr. 2008; 62: 687-694.
7. Marinella MA. Refeeding Syndrome and Hypophosphatemia. J Intensive Care Medicine. 2005; 20: 155-159.
8. Hearing SD. Refeeding Syndrome. BMJ. 2004; 328: 908-909.
9. Mehanna HM, Moledina J, Macmillan JT. Refeeding syndrome: what it is, and how to prevent and treat it. BMJ. 2008; 336: 1495-1498.
10. Khan LUR, Ahmed J, Khan S, MacFie J. Refeeding Syndrome: A Literature Review. Gastroenterology Research and Practice. 2011; 2011,410971: 6.

11. Beumont P, Hay P, Beumont D, Birmingham L, Derham H, Jordan A, et al. Royal Australia and New Zealand College of Phychiatrists Clinical Practice Guidelines Team for Anorexia nervosa: Australian and New Zealand clinical practice guidelines for the treatment of anorexia nervosa. Australian and New Zealand Journal of Psychiatry. 2004; 38: 659-670.

12. Boateng AA, Sroram K, Meguid MM, Crook M. Refeeding syndrome: treatment considerations based on collective analysis of literature. Case reports. Nutrition. 2010; 26: 156-167.

13. Gentile MG, Pastorelli P, Ciceri R, Manna GM, Collimedaglia S. Specialized refeeding treatment for anorexia nervosa patients suffering from extreme undernutrition. Clin Nutr. 2010; 29: 627-632.

14. NICE. Eating disorders – core interventions in the treatment and management of anorexia nervosa and related disorders. National Institute for Health and Care Excellence Clinical Guideline London: NICE, 2004.

15. American Psychiatric Association. Treatment of patients with eating disorders (3rd ed). Am J Psychiat. 2006; 163: 4-54.

16. Marpisan Group. Marpisan: Management of Really Sick Patients with Anorexia Nervosa. College Report CR162 Royal College of Physicians. 2010: 1-58.

17. Gentile MG. Pseudo Bartter Syndrome from Surreptitious Purging Behaviour in Anorexia Nervosa. J Nutrition Disorder & Therapy. 2012; 2: 107.

18. Gentile MG, Manna GM, Ciceri R, Rodeschini E. Efficacy of inpatient treatment in severely malnourished anorexia nervosa patients. Eating weight disorder. 2008; 13: 191-197.

19. Philipson TJ, Snider JT, Lakdawalla DN, Stryckman B, Goldman DP. Impact of oral nutritional supplementation on hospital outcomes. Am J Manag Care. 2013; 19:121-128.

20. Kreymann KG, Berger MM, Deutz NE, Hiesmayr M, Jolliet P, Kazandjiev G, et al. ESPEN Guidelines on Enteral Nutrition: Intensive care. Clin Nutr. 2006; 25: 210-223.

21. McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2009; 33: 277.

22. Wischmeyer PE, Heyland DK. The future of critical care nutrition therapy. Critical Care Clinics. 2010; 26: 433-441.

23. Hegazi RA, Wischmeyer PE. Clinical review: optimizing enteral nutrition for critically ill patients- a simple data- driven formula. Critical Care. 2011; 15: 234.

24. Gentile MG. Enteral Nutrition for Feeding Severely Underfed Patients with Anorexia Nervosa. Nutrients. 2012; 1293-1303.

25. Mirtallo J, Canada T, Johnson D, Kumpf V, Petersen C, Sacks G, et al. A.S.P.EN. Board of Directors and Task Force for the Revision of Safe Practices for Parenteral Nutrition. Safe practices for parenteral nutrition (published correction appears in JPEN J Parenter Enteral Nutr. 2006; 30:1) JPEN. 2004; 28: S39-S70.

26. O'Connor G, Nicholls D. Refeeding Hypophosphataemia in Adolescent With Anorexia Nervosa: A Systematic Review. Nutrition in Clinical Practice. 2013; 28: 358-364.

27. Byrnes MC, Stangenes J. Refeeding in the ICU: An adult and pediatric problem. Current Opinion in Clinical Nutrition and Metabolic Care. 2011; 14: 186-192.

28. Skipper A. Refeeding Syndrome or Refeeding Hypophosphataemia: A Systematic Review of Cases Nutrition in Clinical Practice. 2012; 27: 34-40.

29. Gentile MG, Manna GM. Refeeding hypophosphataemia in malnutrition patients: Prevention and treatment. Clinical Nutrition. 2012; 31: 429.

30. Brown CA, Sabel AL, Gaudiani JL, Mehler PS. Predictors of Hypophosphatemia during Reffeding of Patients with Severe Anorexia Nervosa Int J Eat Disord. 2015; 48: 898-904.

31. Vignaud M, Constantin JM, Ruivard M, Villemeyre-Plane M, Futier E, Bazin JE et al. Refeeding syndrome influences outcome of anorexia nervosa patients in intensive care unit: an observational study. Critical Care. 2010; 14: R172.