EMERGENCY MEDICINE

Openventio PUBLISHERS

ISSN 2379-4046 Open Journal http://dx.doi.org/10.17140/EMOJ-2-123

Case Report

*Corresponding author
Emily Rose, MD, FAAP, FAAEM, FACEP
Assistant Professor of Clinical Emergency Medicine
Keck School of Medicine of the University of Southern California
Los Angeles County + USC Medical Center
Department of Emergency Medicine
1200 North State Street, Room 1011
Los Angeles, CA 90033, USA
Tel. 626-644-6890
Fax: 323-226-6454
E-mail: emilyrose010@gmail.com

Volume 2 : Issue 1
Article Ref. #: 1000EMOJ2123

Article History
Received: April 12th, 2016
Accepted: May 9th, 2016
Published: May 10th, 2016

Citation
Harada M, Greenberg J, Rose E. A case of possible acute refeeding syndrome: A review of a rare, but potentially life-threatening diagnosis *Emerg Med Open J*. 2016; 2(1): 17-22. doi: 10.17140/EMOJ-2-123

A Case of Possible Acute Refeeding Syndrome: A Review of a Rare, But Potentially Life-Threatening Diagnosis

Melissa Harada, MD[1]; Justin Greenberg, DO[1]; Emily Rose, MD, FAAP, FAAEM, FACEP[2*]

[1]Resident Physician, Department of Pediatrics, Los Angeles County + USC Medical Center Los Angeles, CA, USA

[2]Assistant Professor of Clinical Emergency Medicine, Keck School of Medicine of the University of Southern California, Los Angeles County + USC Medical Center, Department of Emergency Medicine, Los Angeles, CA, USA

ABSTRACT

An 18-year-old Hispanic male presented to the Pediatric Emergency Department with acute onset of bilateral lower extremity edema. He had no history of similar symptoms. He had recently lost 70 pounds in the past six-months by restricting himself to an extreme diet and exercise regimen. Two days prior to presentation, he resumed a normal diet. In this illustrative case, we describe a case report of possible refeeding syndrome and discuss the presentation, risk factors, management and potential complications of this diagnosis.

KEYWORDS: Acute refeeding syndrome; Lower extremity edema; Hypophosphatemia.

INTRODUCTION

There is an obesity epidemic in the western world and unfortunately childhood is not immune to its reaches. Nearly 20 percent of children in the United States are overweight or obese. Many quick fixes and crash diets are advertised to aid patients to lose weight. However, without lifestyle and behavior modification, it is nearly impossible to keep off the weight lost during extreme dieting. Additionally, there are risks to extreme dieting which is exemplified in this case.

CASE REPORT

An 18-year-old Hispanic male presented to the Pediatric Emergency Department with acute onset of bilateral lower extremity edema. He had no history of similar symptoms. His recent medical history was significant for an intentional 70-pound weight loss over the past 6 months. This was achieved by restricting his diet to fruits, vegetables, and water only and intermittent vigorous and lengthy exercise. He reported increased urinary frequency and that his urine had been "frothy". One week prior, he had a syncopal episode while showering. An extensive infectious, neurologic and exposure review of systems was negative. Two days prior to his Emergency Department presentation, the patient resumed a regular diet including carbohydrates and meat. On examination, patient was alert and well appearing. Vitals signs: T: 36.5 ˚C; HR: 70; RR: 18; BP: 117/74; SpO_2: 99%; WT: 65 kg. There was no lymphadenopathy, no thyromegaly, no erosions over his knuckles, no parotid gland swelling; his heart had a regular rate and rhythm; his lungs were clear; his abdomen was soft, non-tender, non-distended, without hepatosplenomegaly. On neurologic examination, he had 5/5 muscle strength bilaterally. Lower extremity exam noted 2+ pitting edema noted to bilateral ankles and feet, with symmetrical edema also appreciated to pretibial space (Figure 1), capillary refill was less than 2 seconds, and his extremities were warm and well perfused.

EMERGENCY MEDICINE

Openventio PUBLISHERS

ISSN 2379-4046 Open Journal http://dx.doi.org/10.17140/EMOJ-2-123

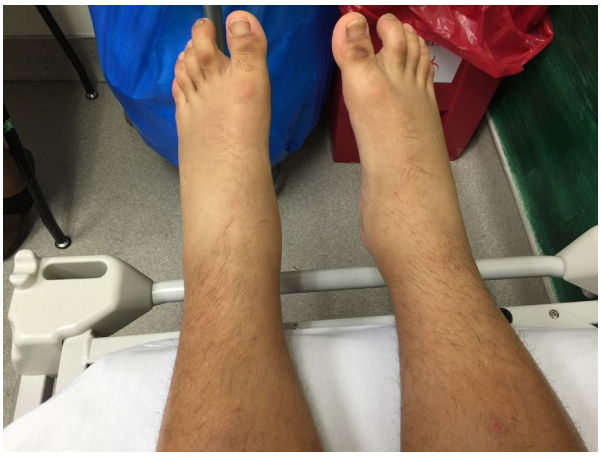

Figure 1: Patient with acute onset of bilateral lower extremity edema.

An ECG demonstrated a normal sinus rhythm without prolonged intervals. CXR was normal without cardiomegaly, effusions or vascular cephalization. Laboratory values are listed in the following tabulation:

Investigation	Finding	Normal Range
Na	146	(135-145)
K	3.8	(3.5-5.1)
Cl	104	(100-110)
CO2	26	(20-30)
BUN	9	(8-22)
CR	0.6	(0.5-1.3)
Glucose	78	(65-99)
Total protein	6.4	(6.0-8.0)
AST	27	(10-40)
ALT	26	(10-55)
Total bilirubin	0.3	(0.0-1.0)
AlkPhos	104	(40-130)
Pro BNP	141	(0-125)
HIV Ab	Nonreactive	Reactive/Nonreactive
Mg	1.8	(1.7-2.3)
Ca	9	(8.5-10.3)
Phos	1.5	(2.5-4.5)
ALB	4.4	(3.5-5)
pre-alb	18.6	(19-38)
Vit B1	74	(78-185)
Vitamin D 25 OH	31	(30-96)
PTH	21	(15-65)
WBC	7.3	(3.7-10.3)
Hbg	12	(13.8-16.9)
Hct	35.9	(41.0-50.0)
Plt	120	(150-350)
UA specific gravity	1.008	(1.005-1.030)
UA pH	6.5	(5.0-8.0)
UA	Negative	for protein, glucose, ketones, bilirubin, blood, leukocytes, nitrites

The patient was admitted to the hospital for electrolyte replacement including 2 grams intravenous magnesium, a total of 50 mmol potassium phosphate intravenously and 1 mg thiamine (vitamin B1) orally. A nutritionist was consulted and his diet was slowly advanced. The patient was discharged two days later with normal electrolytes and improvement, but not complete resolution, of his bilateral lower extremity edema. The patient is now seeing a nutritionist as an outpatient as well as regular check-ups with an internal medicine/pediatrics clinic. However, despite these resources, he was gained nearly 20 pounds in the last two months secondary to unhealthy eating.

DISCUSSION

Refeeding Syndrome (RFS) is a complication of acute nutritional rehabilitation (oral, enteral or parenteral) in individuals who are undernourished.[1] It is characterized by metabolic and clinical changes that occur secondary to electrolyte disturbances (principally low serum concentrations of intracellular ions: phosphate, magnesium and potassium) and shifts in fluid balance. Hypophosphatemia is the hallmark of this syndrome. RFS essentially reflects a change from catabolic to anabolic metabolism.[2] Table 1 shows differential diagnosis of RFS.

Malignancy
Alcoholism
Sepsis
Respiratory alkalosis
Hyperparathyroidism
Vitamin D deficiency
Chronic diarrhea
Fanconi syndrome
Metabolic disorders that affect ATP formation

Table 1: Differential diagnosis for RFS.

Acute refeeding syndrome was clinically suspected in this patient. However, as it is a clinical diagnosis RFS was not able to be confirmed with certainty. Additional etiologies

ISSN 2379-4046 Open Journal http://dx.doi.org/10.17140/EMOJ-2-123

of electrolyte abnormalities were pursued with vitamin D levels and parathyroid hormone levels. Normal liver enzymes, renal function and lack of cardiac abnormalities make alternative etiologies of peripheral edema less likely. The diagnosis of Kwashiorkor was also considered as an alternative etiology of patient's edema but patient and family were emphatic that the edema began immediately after a regular diet was resumed and did not occur previously as would be expected if the etiology was protein-deficiency. Additionally, the albumin level was normal making kwashiorkor unlikely.

REVIEW OF ACUTE REFEEDING SYNDROME

Pathophysiology

To understand the mechanism behind RFS, it is important to understand the physiology behind starvation/under nutrition. In starvation, the body shifts from an anabolic metabolism to a state of catabolism in an effort to compensate for lack of available energy. This change results in a shift from carbohydrate metabolism to protein and fat catabolism. The metabolism of proteins results in a breakdown of lean body mass, which directly affects major organs. In the heart, atrophy of the myocardium causes poor contractility and decreased cardiac output. Atrophy of the liver causes decreased protein production, which exacerbates the metabolic state. Additionally, during starvation there is intracellular loss of electrolytes (potassium magnesium and phosphate). Insulin secretion decreases, the basal metabolic rate slows and the body becomes bradycardic, hypothermic and hypotensive all in an effort to conserve protein and organ function.[3]

When nutritional rehabilitation is started, the body immediately shifts to an anabolic state, metabolizing carbohydrates instead of proteins and fat. This new glucose load causes the body to increase insulin secretion and cells begin to uptake glucose, potassium, magnesium and phosphate.[3] This is the cause of the electrolyte disturbances commonly seen in refeeding syndrome (hypokalemia, hypomagnesemia and hypophosphatemia). Additionally, insulin has a natriuretic effect on the kidneys, resulting in sodium retention and an increase in extracellular volume.[3]

Risk Factors

There is no standardized definition for RFS, however, there are proposed clinical criteria to determine those patients at risk.[2] Table 2 outlines a risk stratification tool for adults.[4]

A study by Dun et al and several additional case reports have shown that in the Pediatric population, one of the most frequent risk factors for RFS is a calculated body weight less than 80% of the ideal body weight.[5] Additional risk factors for RFS in pediatric patients are shown in Table 3.[3]

Clinical Presentation and Medical Complications

The features of RFS result from various electrolyte, hormonal and fluid disturbances. As such, patients may present with symptoms of hypophosphatemia, hypokalemia, hypomagnesemia, hyperglycemia, fluid overload or thiamine deficiency.[3] These findings are outlined below:

Patients are at risk for RFS if they have:

One of the following: Body mass index (BMI) <16 kg/m^2 Unintentional body weight loss >15% in the preceding 3 to 6 months Very little or no nutritional intake for >10 days Low concentrations of plasma potassium, phosphate or magnesium prior to feed
Or two of the following: BMI <18.5 kg/m^2 Unintentional body weight loss >10% in the preceding 3 to 6 months Very little or no nutritional intake for >5 days History of alcohol or drug abuse[4]

Table 2: Risk factors for RFS.

Anorexia Nervosa
Patients underfed or not fed for at least 10-14 days (including those on prolonged intravenous fluids without adequate calories or protein)
Acute weight loss >10% in the past 1-2 months (including obese patient with extensive weight loss in a short period)
Kwashiorkor
Marasmus
Chronic medical conditions causing malnutrition (uncontrolled diabetes mellitus, cancer, congenital heart disease, chronic liver disease)
Mal absorptive syndromes (inflammatory bowel disease, cystic fibrosis, chronic pancreatitis and short bowel syndrome)
Cerebral palsy and other conditions causing dysphagia Children of neglect
Postoperative patients, including after bariatric surgery

Table 3: Pediatric Risk Factors for RFS.

ISSN 2379-4046 Open Journal http://dx.doi.org/10.17140/EMOJ-2-123

Hypophosphatemia: The hallmark feature of RFS is hypophosphatemia. Starvation results in loss of total body phosphate and refeeding causes cells to uptake phosphate for anabolic processes and the synthesis of phosphorylated intermediates of glycolysis (i.e.: ATP and 2-3-diphosphoglycerate).[6] These processes can result in severe extracellular (serum) hypophosphatemia. The hypophosphatemia seen in RFS generally presents within 24-72 hours of reintroduction of nutrition,[5] with a nadir during the first week.[6]

Phosphate has ubiquitous actions in humans. It is essential for intracellular buffering and is also a major structural component of phospholipids, nucleoproteins and nucleic acids. It is needed for glycolysis and oxidative phosphorylation and plays a role in nervous system conduction, chemotaxis, phagocytosis and platelet aggregation.[2] Therefore, signs and symptoms of hypophosphatemia may include:

- Cardiac: Hypotension, decreased stroke volume.
- Respiratory: Poor respiratory function from decreased diaphragm contractility Neurologic: paresthesias, weakness, cramps, seizures.
- Hematologic: Leukocyte dysfunction, hemolysis, thrombocytopenia.
- Psychologic: Confusion, altered mental status, coma.[1]

Hypokalemia: By the same mechanisms described in hypophosphatemia, refeeding can also result in hypokalemia. Potassium is crucial to cell membrane function and acid-base balance. Signs and symptoms of hypokalemia may include:

- Cardiac: Arrhythmias.
- Respiratory: Respiratory failure.
- Neurologic: Weakness, paralysis.
- Gastrointestinal: Nausea, vomiting, constipation.
- Muscular: Rhabdomyolysis.[1]

Hypomagnesemia: Another electrolyte abnormality that can be seen in RFS is hypomagnesemia. Magnesium is an essential cofactor for various enzymes (in ATP production and oxidative phosphorylation) and is important for cell membrane function and cell structure.[2] It is also involved in the structural integrity for DNA, RNA and ribosomes.[3] Additionally, low magnesium levels may induce hypokalemia by impairing Na^+/K^+ ATPase activity. It is also needed for parathyroid function, so hypomagnesemia can cause hypocalcemia.[3] Signs and symptoms of hypomagnesemia may include:

- Cardiac: Arrhythmias.
- Neurologic: Weakness, tremor, tetany, seizures, altered mental status.
- Gastrointestinal: Nausea, vomiting, diarrhea.
- Other: Refractory hypokalemia and hypocalcemia.[1]

Thiamine and Vitamin Deficiencies: Thiamine (vitamin B_1) is an essential nutrient for humans, since it cannot be synthesized in the human body. It is an important cofactor in many metabolic pathways and its deficiency can result in beri-beri and metabolic/lactic acidosis.[2] The half-life of thiamine is 9.5-18.5 days, so thiamine deficiency can manifest in less than 28 days.[7] Clinical manifestations of thiamine deficiency include Korsakov's psychosis and Wernicke's encephalopathy syndrome which may present with ataxia, coma, confusion or seizures.[2] Signs and symptoms of thiamine deficiency may include:

- Neurologic: Encephalopathy.
- Other: Lactic acidosis, Death.[1]
- Other vitamin deficiencies, such as vitamin B12 and vitamin B6 as well as folate can also been seen in refeeding syndrome, though the mechanism is unclear.[2]

Alterations in Fluid Balance: Fluid overload can be seen in RFS secondary to sodium retention. In refeeding with carbohydrates, there is an insulin surge that decreases renal excretion of water and sodium[3] and results in expansion of the extracellular fluid compartment and weight gain.[2] Additionally, the insulin surge stimulates an intracellular influx of phosphate, potassium and magnesium. In order to maintain electro neutrality of the extracellular space, sodium and subsequently, water is retained. Signs and symptoms of fluid overload may include:

- Peripheral edema.
- Pulmonary edema
- Cardiac compromise[1]

Hyperglycemia: When feeding is reinitiated after starvation, increased glucose load inhibits gluconeogenesis and reduces the amount of amino acid use. This results in a decreased ability to metabolize glucose and subsequent hyperglycemia.[3] Additionally, during refeeding the body undergoes a stress response that increases glucocorticoids and further exacerbates hyperglycemia.[8] This state of elevated glucose can cause hyperosmolar nonketotic coma, ketoacidosis, metabolic acidosis, osmotic diuresis and dehydration. Lastly, with the increased surge of insulin there is increased lipogenesis which, if paired with excess fat intake, can cause fatty liver, hypertriglyceridemia, thrombocytopenia, increased carbon dioxide production, hypercapnia and respiratory failure in some patients.[2] To summarize, some of the symptoms associated with hyperglycemia may include:

- Cardiac: hypotension.
- Respiratory: hypercapneic failure.
- Other: ketoacidosis, coma, dehydration, impaired immune function.[1]

DIAGNOSIS

Refeeding syndrome is a clinical constellation of symptoms, as described above, that results from electrolyte imbalances and fluid shifts. It is diagnosed clinically and can be supported by measuring patient electrolyte levels including phosphate, magnesium, and thiamine.

ISSN 2379-4046 Open Journal http://dx.doi.org/10.17140/EMOJ-2-123

MANAGEMENT

In order to prevent RFS, it is essential to identify those patients who are at an increased risk and to strictly monitor nutritional intake, electrolyte and fluid replacement.[2] The following sections will outline the prevention and management of various components in RFS.

Nutritional Support

Current guidelines regarding the initiation of nutritional support in patients at risk for RFS recommend slow, low energy feeds. The National Institute for Clinical Excellence (NICE) suggests a gradual increase in energy intake with a goal weekly body weight gain of 0.5 to 1 kg.[9] Other proposed recommendations suggest starting feeds at 25-75% of resting energy expenditure and in both adult and pediatric patients, to increase the caloric intake 10-25% per day over 4-5 days until their calorie goals are met.[3] Additionally, there are suggestions that the actual composition of nutrition in refeeding may be more important than the energy content alone. For example, there have been observations that RFS is more likely to occur when carbohydrate is the main source of energy,[10] while feeds that are low in amino acids are less likely to develop hypophosphatemia.[11] Therefore, the recommendations include:

- Carbohydrates: Maximum of 40% total energy intake.
- Protein: 1.2-1.5 g/kg.
- Fat: 3.8 g of lipid/kg (maximum daily lipid-elimination capacity).[2]

Fluid and Electrolyte Management

Fluid balance and daily weights should be closely monitored to avoid fluid overload and cardiac compromise. Sodium should be limited to 20 mEq/d and total fluid intake to 1000 mL/d or less in order to reduce refeeding edema.[12] While some sources suggest that electrolyte deficiencies be corrected prior to the initiation of feeding,[3] others state that the abnormalities can be corrected while refeeding, so nutritional support is not delayed.[13]

Hypophosphatemia

There is no universal agreement on the best way to treat severe hypophosphatemia in RFS and some proposed treatment regimens are not effective in correcting it. In some cases, oral phosphate replacements have been used, but they can cause diarrhea and nausea.[2] As such, other guidelines suggest the use of intravenous (IV) phosphate replacement as its absorption is more reliable. One guideline proposed by the Lucile Packard Children's Hospital at Stanford suggests IV replacement doses as follow:

- Children: initial dose of 0.08-0.24 mmol/kg with a maximum single dose of 15 mmol and a maximum daily dose of 1.5 mmol/kg.
- Adults: initial dose of 0.08 mmol/kg if mild hypophosphatemia (2.3-2.7 mg/dL), a dose of 0.16 mmol/g if severe hypophosphatemia (<1.5 mg/dL) with a maximum dose of 0.24 mmol/kg per dose.

These should be given over 6-12 hours and serum phosphate level should be obtained 2-4 hours after the completion of the infusion.[3]

Hypokalemia

Like many of the other oral electrolyte replacements, oral potassium can also cause GI upset, so IV potassium replacement is often suggested.[2] Additionally, prior to the initiation of potassium replacement, urine output should be greater than 0.5 mL/kg/hr and the patient should be on a cardiac monitor[3] given the risk of hyperkalemia and potential arrhythmias. Guidelines for potassium replacement include:

- Children and Adults: 0.3-0.5 mEq/kg per dose with a maximum dose of 30 mEq.

Replacement should be administered over at least 1 hour and serum potassium should be obtained within 2 hours of completion of the infusion.[3]

Hypomagnesemia

Hypomagnesemia can be corrected orally, but can be poorly absorbed and cause diarrhea, so IV forms are often used.[2] Guidelines for IV magnesium sulfate replacement suggest:

- Children: 25-5- mg/kg per dose with a maximum single dose of 2000 mg.
- Adults: 1 g every 6 hours for four doses for mild-moderate hypomagnesemia (1-1.8 mg/dL) and 8-12 g/d in divided doses for severe hypomagnesemia (<1 mg/dL).

Replacement should be given over 4 hours.[3]

Thiamine and Vitamin Supplementation

Daily multivitamin supplementation should be started with refeeding and continued for at least 10 days.[14] Specifically for thiamine deficiency or Beriberi, guidelines suggest:

- Children: 10-25 mg/d IV or intramuscular (IM) if ill or 10-50 mg per dose orally every day for 2 weeks and then 5-10 mg/d for 1 month.
- Adults: 5-30 mg per dose 3 times a day either IV or IM and then 5-30 mg/d orally for one month.[3]

Clinical Monitoring for Complications

Patients should be closely monitored for the development of complications of RFS. Electrolyte abnormalities typically occur

in the first days of starting nutritional supplementation, cardiac complications within the first week and altered mental status thereafter.[15] During re-feeding, patients may require continuous cardio respiratory monitoring and neuromuscular and mental status checks.[3] Daily body weights and strict monitoring of intake and output are essential to preventing fluid overload.[2] Daily measurement of electrolytes and weekly prealbumin and albumin levels have also been suggested. If complications of RFS emerge during feeding, nutritional supplementation should be stopped and corrective measures should be taken (ie: respiratory support, diuretics, vasopressors) prior to the re-initiation of feeds.[3]

CONCLUSION

Refeeding syndrome is rare but most commonly seen within the first two weeks of nutritional replenishment and can have numerous non-specific symptoms, affecting many organ systems. Electrolyte disturbances are most common, especially hypophosphatemia, hypokalemia, and hypomagnesemia. In the Emergency Department, it is important to recognize this syndrome and its potentially serious complications including multisystem organ involvement/failure.

CONFLICTS OF INTEREST

Drs. Harada, Greenberg and Rose do not have any conflicts of interest to report.

CONSENT

Informed consent for photography and case write-up was obtained from the patient and his family.

REFERENCES

1. Alderman HS, M. Nutrition, Food Security, and Health. In: Kleigman RM, ed. *Nelson Textbook of Pediatrics*. 19 ed. Philadelphia, PA, USA: Elsevier; 2011:170-179.

2. Crook MA. Refeeding syndrome: problems with definition and management. *Nutrition*. 2014; 30(11-12): 1448-1455. doi: 10.1016/j.nut.2014.03.026

3. Fuentebella J, Kerner JA. Refeeding syndrome. *Pediatr Clin North Am*. 2009; 56(5): 1201-1210.

4. Rio A, Whelan K, Goff L, Reidlinger DP, Smeeton N. Occurrence of refeeding syndrome in adults started on artificial nutrition support: prospective cohort study. *BMJ open*. 2013; 3(1): e002173. doi: 10.1136/bmjopen-2012-002173

5. Dunn RL, Stettler N, Mascarenhas MR. Refeeding syndrome in hospitalized pediatric patients. *Nutr Clin Pract*. 2003; 18(4): 327-332. doi: 10.1177/0115426503018004327

6. Kraft MD, Btaiche IF, Sacks GS. Review of the refeeding syndrome. *Nutr Clin Pract*. Dec 2005; 20(6): 625-633. doi: 10.1177/0115426505020006625

7. McCray SWS, Parrish CR. Much ado about refeeding. P*ract Gastroenterol*. 2005; 29(1): 26-44. Web site. http://www.nutrition411.com/wp-content/uploads/2013/09/McCrayArticle.pdf. Accessed April 11, 2016

8. Lauts NM. Management of the patient with refeeding syndrome. *J Infus Nurs*. 2005; 28(5): 337-342. Web site. http://journals.lww.com/journalofinfusionnursing/pages/articleviewer.aspx?year=2005&issue=09000&article=00007&type=abstract. Accessed April 11, 2016

9. (NICE) NIfHaCE. *Nutrition support in adults. Clinical guideline CG32*. 2006.

10. O'Connor G, Goldin J. The refeeding syndrome and glucose load. *Int J Eat Disord*. 2011; 44(2): 182-185. doi: 10.1002/eat.20791

11. Bonsante F, Iacobelli S, Latorre G, et al. Initial amino acid intake influences phosphorus and calcium homeostasis in preterm infants--it is time to change the composition of the early parenteral nutrition. *PloS one*. 2013; 8(8): e72880. doi: 10.1371/journal.pone.0072880

12. Palesty JA, Dudrick SJ. The goldilocks paradigm of starvation and refeeding. *Nutr Clin Pract*. 2006; 21(2): 147-154. doi: 10.1177/0115426506021002147

13. Mehanna HM, Moledina J, Travis J. Refeeding syndrome: what it is, and how to prevent and treat it. *BMJ*. 2008; 336(7659): 1495-1498. doi: 10.1136/bmj.a301

14. Crook MA, Hally V, Panteli JV. The importance of the refeeding syndrome. *Nutrition*. 2001; 17(7-8): 632-637. doi: 10.1016/S0899-9007(01)00542-1

15. Malone AM. Monitoring for efficacy, complications, and toxicity. In: Bankhead R, Boullata JI, Compher CW. *Clinical Nutrition: Enteral and Tube Feeding*. 4th ed. Philadelphia, PA, USA: Elsevier Saunders; 1997: 286-287.