Refeeding syndrome: relevance for the critically ill patient

Rianne Boot, Kristine W.A.C. Koekkoek, and Arthur R.H. van Zanten

Purpose of review
To provide an overview of recent findings concerning refeeding syndrome (RFS) among critically ill patients and recommendations for daily practice.

Recent findings
Recent literature shows that RFS is common among critically ill ventilated patients. Usual risk factors for non-ICU patients addressed on ICU admission do not identify patients developing RFS. A marked drop of phosphate levels (>0.16 mmol/l) from normal levels within 72 h of commencement of feeding, selects patients that benefit from hypocaloric or restricted caloric intake for at least 48 h resulting in lower long-term mortality.

Summary
RFS is a potentially life-threatening condition induced by initiation of feeding after a period of starvation. Although a uniform definition is lacking, most definitions comprise a complex constellation of laboratory markers (i.e. hypophosphatemia, hypokalemia, hypomagnesemia) or clinical symptoms, including cardiac and pulmonary failure. Recent studies show that low caloric intake results in lower mortality rates in critically ill RFS patients compared with RFS patients on full nutritional support. Therefore, standard monitoring of RFS-markers (especially serum phosphate) and caloric restriction when RFS is diagnosed should be considered. Furthermore, standard therapy with thiamin and electrolyte supplementation is essential.

Keywords
caloric restriction, hypocaloric feeding, hypophosphatemia, nutrition, refeeding syndrome, starvation trophic feeding

INTRODUCTION

Refeeding syndrome (RFS) is associated with reintroduction of oral or (par)enteral feeding after deprivation of caloric intake, either acute or chronic [1,2,3▪]. Burgers first described it in 1948 in liberated prisoners who were fed again after a period of starvation. These soldiers were advised a conservative caloric intake, to prevent gastrointestinal, pulmonary or cardiac complications, such as abdominal distension and diarrhea, dyspnea and pulmonary edema, tachycardia and heart failure [4,5,6▪]. Despite an adequate nutritional intake, mortality of about 20% was observed [4,5].

Although it was described for the first time more than 70 years ago, RFS and its relevance in critical illness remains unclear. This issue is mainly caused by the lack of a uniform RFS definition. However, regardless of the definition used, RFS is associated with significant morbidity and mortality, and therefore highly relevant in daily clinical practice [7▪,8]. This narrative review aims to summarize what is currently known on this topic, focusing on the latest acquired insights.

DEFINITION OF REFEEDING SYNDROME

Standard definitions of RFS are hallmarked by hypophosphatemia, combined with low concentrations of serum magnesium and potassium. This may lead – if untreated – to gastrointestinal, pulmonary or cardiac complications. Other symptoms may include sodium

Department of Intensive Care Medicine, Gelderse Vallei Hospital, Ede, The Netherlands

Correspondence to Arthur R.H. van Zanten, MD, PhD, Internist-Intensivist, Medical Advisor Executive Team, Department of Intensive Care, Gelderse Vallei Hospital, Willy Brandtlaan 10, 6716 RP Ede, The Netherlands. Tel: +31 318 43 41 15; e-mail: zantena@zgv.nl

Curr Opin Crit Care 2018, 24:235–240
DOI:10.1097/MCC.0000000000000514

1070-5295 Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

KEY POINTS

- Refeeding hypophosphatemia and RFS may frequently be encountered during prolonged critical illness.
- Clinical signs and symptoms of RFS are indistinguishable from multiple-organ dysfunction syndrome.
- Serum phosphate monitoring during the initiation phase of nutrition support (<72 h) to observe a drop in phosphate levels induced by feeding is essential as no other factors can identify patients on ICU admission that will develop RFS.
- Cornerstones of the treatment of RFS are electrolyte (phosphate, potassium, magnesium) and thiamine supplementation, correction of fluid overload and glucose control with insulin.
- During refeeding hypophosphatemia and RFS, hypocaloric feeding improves survival rates and caloric restriction (<500 kcal/24 h) for 48 h should be considered.

and fluid imbalances, thiamine (vitamin B1) deficiency as well as changes in protein, glucose and fat metabolism including insulin resistance [1]. A general definition with clear cutoff points of RFS is lacking, making a comprehensive study on this topic confusing. Furthermore, specific data on critically ill patients is scarce. In a recent systematic review conducted by Friedli *et al.* [6▪], only 38 of the 45 included studies reported an RFS definition, all being highly heterogeneous. Some definitions were only based on electrolyte disturbances with different cutoff values, whereas other studies also included clinical symptoms. Most commonly used definitions were based on hypophosphatemia, with cutoff values ranging from 0.32 to 1 mmol/l, and/or a fall from baseline greater than 30% or more than 0.16 mmol/l [6▪].

EPIDEMIOLOGY

Due to different definitions, the actual incidence of RFS remains unknown in both critically ill and non-critically ill (i.e. anorexia nervosa) patients. In the systematic review conducted by Friedli *et al.* [6▪], 11 of 32 studies reported an incidence of 0%. This may be caused by narrow definitions of RFS used. Furthermore, studies were performed among heterogeneous patient groups. Other studies using broader definitions reported RFS incidences up to 80%, mainly occurring in the first 72 h after the start of nutritional support. In a prospective cohort study conducted by Rio *et al.*, a so-called three-facet criteria design was used to confirm the diagnosis of RFS unequivocally. These criteria comprised disturbed electrolyte balances, acute peripheral edema or circulatory fluid overload combined with disturbances in organ function. According to these criteria, an incidence rate of only 2% was reported ($n = 3$) [8,9▪].

In critically ill patients, RFS is most often defined by the occurrence of electrolyte disturbances (mainly hypophosphatemia) within 72 h of the initiation of feeding, not attributed to other causes. The incidence of refeeding hypophosphatemia is reported to be 34–52% in critical illness [10▪,11–13].

OUTCOMES OF PATIENTS WITH REFEEDING SYNDROME

Friedli *et al.* noticed that only 11 studies reported on outcomes in RFS patients versus non-RFS patients. Although lacking methodological quality, four studies described more extended hospital stays, and five studies reported higher mortality rates in the RFS patient groups [6▪].

Recently, Matthews *et al.* [9▪] studied the prevalence rate of RFS as a cause of death. They conducted a retrospective observational study amongst patients who passed away in Queensland Hospitals (Australia) between 1997 and 2015 not exclusively treated in ICUs. Over these 18 years, approximately 260 000 patients died; however, only five patients had RFS as an underlying cause of death mentioned on their official death certificates. All but one were assessed as being at risk for RFS on admission. In none of these patients, RFS was the primary cause of death (mortality rate 0%) [9▪].

However, when focusing on critically ill patients, Olthof *et al.* [10▪] performed a retrospective study amongst exclusively mechanically ventilated (>7 days) patients at a mixed medical–surgical ICU. A total of 337 patients were enrolled in this study, of whom 124 (36.8%) developed RFS. No statistical significance in length of hospital stay was observed between both groups. Concerning long-term outcomes, no difference in 6-month mortality was observed (33.9% in RFS and 31.5% in non-RFS, $P = 0.65$) [10▪]. This is in contrast with results published by Coşkun *et al.* [11] who reported significant differences in length of hospital stay ($P = 0.025$) and mortality rates ($P = 0.037$), both in favor of patients without RFS. However, this may be due to different cutoff values of hypophosphatemia, as well as the fact that Coskun *et al.* included many patients with comorbidities (70%) and malignant diseases (20%). On the other hand, mortality rates found in patients with anorexia nervosa and other severe malnutritional states have been reported at 10–29%, although it can be questioned whether these deaths should be primarily attributed to RFS [14,15].

Although it is debatable whether RFS is directly correlated with mortality, there is evidence that

Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

appropriate treatment – as will be described later – will ultimately lead to better overall survival (OS). Therefore, it is highly relevant to identify individuals at risk appropriately.

PATHOPHYSIOLOGY

To date, the pathophysiology of RFS is not entirely understood. The metabolic derangements following the reintroduction of feeding include hormonal and electrolyte disturbances.

METABOLIC CHANGES DURING STARVATION

In normal circumstances, the primary fuel of the body consists of glucose, derived from carbohydrate breakdown. At least 100–150-g of glucose is needed daily for optimal brain function and to prevent protein breakdown [3▪]. Excess of carbohydrate and protein intake can be stored as fat.

During a short period of fasting (up to 24 h), glycogen – which is stored in the liver and muscles – can be utilized after glycogenolysis to provide glucose. During prolonged fasting, metabolism switches to fat and protein utilization after the glycogen stores have been depleted. Glucose is produced by degradation of amino acids, fatty acids, lactate and pyruvate through gluconeogenesis [3▪,16]. When the fasting period prolongs, the metabolic rate decreases by 20–25% [1,3▪]. Concomitantly, intracellular electrolytes and vitamin supplies are depleted [3▪,6▪,7▪].

METABOLIC CHANGES AND CLINICAL SYMPTOMS DURING REFEEDING

When a refeeding program is started, whether oral or (par)enteral, metabolism switches back from protein and fat metabolism to the breakdown of carbohydrates [1,2,3▪]. This results in a marked increase in insulin secretion, leading to increased intracellular uptake of glucose, but also of electrolytes such as phosphate, potassium and magnesium. This shift, along with already depleted electrolyte storages, may lead to dangerously low electrolyte concentrations [3▪]. Simultaneously, insulin resistance is observed – marked by the coexistence of hyperinsulinemia and hyperglycemia – resulting in increased sodium and water retention, most likely due to an antinatriuretic effect of insulin on the renal tubules [3▪]. This may result in extracellular volume expansion, leading to peripheral edema and – if severe enough – to heart failure and pulmonary edema [1,6▪]. Transcellular shifts and redistributions of electrolytes may result in cardiac (arrhythmia), neuromuscular (muscle weakness, spasms, rhabdomyolysis) and hematopoietic (anemia, reduced oxygen supply) impairment, finally leading to organ dysfunction, organ failure and ultimately death if not appropriately treated [6▪,10▪,16]. Many clinical signs and symptoms of RFS are indistinguishable from multiple organ dysfunction syndrome, complicating the diagnosis [7▪].

THE OUTCOME OF REFEEDING SYNDROME DURING CRITICAL ILLNESS RELATED TO NUTRITION SUPPORT

In a recent retrospective cohort study, Olthof *et al.* [10▪] describe the effect of (hypo)caloric intake on outcome in critically ill mechanically ventilated patients during refeeding hypophosphatemia. They observed no statistical differences in clinical outcomes between the RFS and non-RFS patients groups. However, within the RFS population, reduced 6-month mortality was observed in the patients who were treated with hypocaloric intake (<50% of calculated target) compared with patients who received higher amounts of calories (adjusted hazard ratio 0.39, 95% confidence interval 0.16–0.95%, $P = 0.037$). At day 180 after ICU admission, lower caloric intake during RFS was associated with an increased OS.

This is consistent with findings by Doig *et al.* who in a randomized controlled trial comparing standard versus restricted caloric intake (<500 kcal/day) in critically ill RFS patients identified by refeeding hypophosphatemia, who were mechanically ventilated. They observed that the full caloric strategy was associated with higher mortality rates at 60 and 90 days posthospitalization [17▪▪].

In the studies by Olthof *et al.* [10▪] and Doig *et al.* [17▪▪], the Kaplan–Meier survival curves do not separate RFS patients with low caloric intake or caloric restriction from patients on full support during the early phase of the emergence of electrolyte abnormalities and the RFS diagnosis. However, mortality rates seem to separate from 2 weeks after the diagnosis, suggesting that not the acute electrolyte abnormalities play a significant role, but the metabolic consequences of RFS are more critical. The exact mechanism of these observations warrants further research.

ELECTROLYTE CHANGES DURING REFEEDING SYNDROME

Phosphate

Phosphate is essential for the structural integrity of the cell membrane. Moreover, it is an essential mineral for several intracellular processes, such as

1070-5295 Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

glucose metabolism and energy storage (ATP), as well as the activation of enzymes and second messengers [1,6▪]. Hypophosphatemia is associated with impaired glucose tolerance and insulin resistance [16]. Furthermore, phosphate regulates the affinity of hemoglobin for oxygen. Hypophosphatemia results in lowered levels of 2,3-diphosphoglyceride, resulting in an impaired oxygen release to peripheral tissues [3▪].

Potassium

Potassium is essential in maintaining the electrochemical membrane potential. When derangements occur, this may lead to cardiac arrhythmias and ultimately cardiac arrest [1,6▪].

Magnesium

Just like phosphate, magnesium depletion is associated with insulin resistance and impairment of glucose tolerance [16]. Furthermore, magnesium is necessary for the structural integrity of ribosomes, DNA and RNA and plays an essential cofactor role in most enzyme systems, including the production of ATP. Moreover, magnesium is – like potassium – essential for maintaining the electromechanical membrane potential. When magnesium is depleted, this may result in cardiac and neuromuscular dysfunction [1,6▪,16].

Vitamin deficiency

All vitamins may become depleted during starvation, but the water-soluble thiamine (vitamin B1) has been considered – until now – the most important vitamin to become deficient as a consequence of RFS. Thiamine is an essential coenzyme for three enzymes in the glucose metabolism. When thiamine is deficient, the conversion of pyruvate to acetyl CoA is impossible, resulting in lactate overproduction and lactic acidosis. It is also crucial in preventing Wernicke's encephalopathy or Korsakoff's syndrome [1,3▪]. During the administration of carbohydrates during refeeding after starvation, thiamine needs may increase and thiamine deficiency may become clinically relevant.

RISK FACTORS FOR REFEEDING SYNDROME

Risk factors for RFS have been described in the guidelines of the National Institute for Health and Care Excellence, and include: low BMI and/or unintentional weight loss within the last 6 months, a negligible food intake for more than 5 days, low electrolyte (phosphate, potassium, magnesium) levels prior to nutritional support, poor absorptive capacity, catabolism and chronic alcoholism [18]. Other risk factors not mentioned in these guidelines include age (>70 years), low (pre)albumin or insulin-like growth factor, overfeeding, intravenous glucose infusion before nutritional support, or scoring at least 3 points on the nutritional risk screening [6▪,8,19]. Rio *et al.* reported a sensitivity and specificity of these risk factors of 67% and more than 59%, respectively. Only low baseline serum magnesium levels were able to predict RFS independently ($P = 0.021$); other independent risk factors were nonsignificant [8]. In daily practice, it may be hard to identify critically ill patients based on these criteria as electrolyte differences between RFS and non-RFS patients are small [10▪,20]. Remarkably, in this study conducted by Rio *et al.*, only three of the 133 (2.3%) patients who were at risk, were diagnosed with RFS.

Utilizing universal preventive strategies based on risk scoring systems, such as electrolyte and thiamine supplementation, and hypocaloric refeeding schemes may then result in unnecessary delays until adequate nutritional support to malnourished patients [8,9▪]. Therefore, it is essential to know whether critically ill patients should be treated with caloric restriction or not.

IDENTIFICATION, DIAGNOSIS AND TREATMENT OF REFEEDING SYNDROME IN THE ICU

In the studies by Doig *et al.* [17▪▪] and Olthof *et al.* [10▪], refeeding hypophosphatemia was used to identify patients with RFS. In both studies, most patients also showed other diagnostic RFS criteria such as hypomagnesemia and hypokalemia. In the Olthof study, RFS patients needed more phosphate, potassium and insulin supplementation suggesting that refeeding hypophosphatemia identifies patients with more signs and symptoms of RFS. Moreover, the outcome of patients in both the Doig and Olthof studies were influenced by low caloric intake or caloric restriction. As in the Olthof study, no suggested clinical risk factor was able to identify RFS patients on ICU admission with enough accuracy, phosphate monitoring seems the only way to separate patients with RFS from those without RFS [10▪] (Table 1).

As common risk factors fail to identify RFS patients, regular phosphate and other electrolyte monitoring can be recommended at least once daily, in particular during the first 72 h after the initiation of nutritional support [1,9▪,10▪] (Table 1).

Standard treatment of RFS comprises electrolyte supplementation, insulin therapy in case of hyperglycemia, volume correction if necessary and

Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

Table 1. Identification of critically ill patients at risk for refeeding syndrome

Daily monitoring of serum phosphate and other electrolytes such as potassium, magnesium, especially during the first 72 h after the start of nutritional support, irrespective of the route of feeding used
A decrease of serum phosphate levels of at least 0.16 mmol/l to below 0.65 mmol/l from normal levels on ICU admission within 72 h after the commencement of nutrition after excluding other causes of hypophosphatemia (refeeding hypophosphatemia) is suggestive for refeeding syndrome
Among reasons not to classify patients as having refeeding hypophosphatemia or refeeding syndrome based on low serum phosphate levels are ongoing renal replacement therapy, recent parathyroidectomy or pharmacologic treatment for hyperphosphatemia

Table 2. Treatment strategy for critically ill patients with refeeding hypophosphatemia and refeeding syndrome

Electrolyte supplementation (phosphate, magnesium, potassium)
Glucose monitoring to prevent hypoglycemia and hyperglycemia
Intravenous insulin administration in case of hyperglycemia
Correction of fluid overload if necessary
Thiamine supplementation at a minimum dose of 100 mg daily, for at least 7–10 days
Restriction of total caloric intake to a maximum of 500 kcal/24 h during the first 48 h after the diagnosis of refeeding hypophosphatemia and refeeding syndrome
Consider the amount of nonnutritional calories from propofol, citrate (renal replacement therapy) and intravenous carbohydrate solutions as these may increase the total caloric load
Gradually advance feeding after 48 h of caloric restriction in daily steps of 25% of the target until the nutrition target is reached

vitamin supplementation in particular vitamin B1 (Table 2).

Based on the recent observations by Doig *et al.* [17▪▪] and Olthof *et al.* [10▪], caloric intake restriction at 500 kcal/24 h for 48 h can be recommended. It is essential to include additional sources of caloric intake (nonnutritional calories) in total caloric intake calculations, such as propofol infusion and citrate administration from renal replacement therapy, as in individual patients these nonnutritional calories may be even higher than this arbitrary cutoff for caloric restriction [21].

As glucose intake followed by insulin secretion is the primary trigger for RFS, restricted nutritional intake should be accompanied by adequate glucose control to prevent both hyperglycemia and hypoglycemia [3▪].

CONCLUSISON

RFS is a potentially life-threatening condition caused by metabolic, endocrine and electrolyte derangements induced by the initiation of feeding after a period of starvation. Although a uniform definition is lacking, for critically ill patients, phosphate monitoring after the start of nutritional support for at least 72 h seems the most straightforward method to identify patients with RFS as refeeding hypophosphatemia best identifies such patients. Immediate supplementation of electrolytes, vitamin B1 and – if necessary – insulin is warranted. However, also marked caloric restriction for several days can be recommended during critical illness as this nutritional strategy has been shown to be associated with improved long-term outcomes. After this, restriction period gradually advancing to nutritional targets can be performed.

Acknowledgements

All authors drafted the article, critically revised the article, agreed to be fully accountable for ensuring the integrity and accuracy of the work, and have read and approved the final article.

Financial support and sponsorship

None.

Conflicts of interest

R.B. and K.W.A.C.K. declare not to have any conflicts of interest. A.R.H.v.Z. reported having received honoraria for advisory board meetings, lectures and travel expenses from Abbott, Baxter, BBraun, Danone-Nutricia, Fresenius Kabi, Lyric and Nestlé-Novartis. Inclusion fees for patients in clinical trials were paid to the local ICU research foundation.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ▪ of special interest
- ▪▪ of outstanding interest

1. Mehanna HM, Moledina J, Travis J. Refeeding syndrome: what it is, and how to prevent and treat it. BMJ 2008; 336:1495–1498.

1070-5295 Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

2. Zeki S, Culkin A, Gabe SM, *et al.* Refeeding hypophosphataemia is more common in enteral than parenteral feeding in adult in patients. Clin Nutr 2011; 30:365–368.
3. ■ McCray S, Walker S, Parrish CR. Much ado about refeeding. Pract Gastroenterol 2004; 28:26–44.

Comprehensive discussion of the pathophysiology of refeeding syndrome (RFS), including the identification of patients at risk. Provides practical guidelines for prevention and treatment.

4. Burger GC, Drummond J, Sandstead HR. Appendices to malnutrition and starvation in western Netherlands September 1944–July 1945 (Part II). The Hague, The Netherlands: The General State Printing Office; 1948 [Internet]; available from: http://apps.who.int/iris/bitstream/handle/10665/101051/WHA4_4_eng.pdf;jsessionid=0B41E6B899758A8FA62BEA1BAB03EDAA?sequence=1. [Accessed 20 April 2018]
5. Schnitker MA, Mattman PE, Bliss TL. A clinical study of malnutrition in Japanese prisoners of war. Ann Intern Med 1951; 35:69–96.
6. ■ Friedli N, Stanga Z, Sobotka L, *et al.* Revisiting the refeeding syndrome: results of a systematic review. Nutrition 2017; 35:151–160.

A systematic review on (standardized) definitions, epidemiology, risk factors, treatment strategies, mortality and other adverse outcomes of RFS.

7. ■ van Zanten AR. Nutritional support and refeeding syndrome in critical illness. Lancet Respir Med 2015; 3:904–905.

Provides an overview of the pathophysiology and clinical signs and symptoms of RFS.

8. Rio A, Whelan K, Goff L, *et al.* Occurrence of refeeding syndrome in adults started on artificial nutrition support: prospective cohort study. BMJ Open 2013; 3:e002173.
9. ■ Matthews KL, Capra SM, Palmer MA. Throw caution to the wind: is refeeding syndrome really a cause of death in acute care? Eur J Clin Nutr 2018; 72:93–98.

In this article, the case histories of patients who passed away with RFS as underlying cause are examined.

10. ■ Olthof LE, Koekkoek WACK, van Setten C, *et al.* Impact of caloric intake in critically ill patients with, and without, refeeding syndrome: a retrospective study. Clin Nutr 2017; 10:. https://www.clinicalnutritionjournal.com/article/S0261-5614(17)30268-6/fulltext.

Reports a high incidence of refeeding syndrome in ICU patients. Typical risk factors fail to identify RFS patients on ICU admission, and low caloric intake during RFS is associated with improved outcome compared with a high caloric intake.

11. Coşkun R, Gündoğan K, Baldane S, *et al.* Refeeding hypophosphatemia: a potentially fatal danger in the intensive care unit. Turk J Med Sci 2014; 44:369–374.
12. Fuentes E, Yeh D, Quraishi S, *et al.* Hypophosphatemia in enterally fed patients in the surgical intensive care unit. Nutr Clin Pract 2016; 32:252–257.
13. Ralib A, Ismail CAN, Hassan MZH, *et al.* Refeeding hypophosphatemia in a Malaysian intensive care unit: incidence, risk factors, and outcomes. Brunei Int Med J 2015; 11:65–73.
14. Vignaud M, Constantin JM, Ruivard M, *et al.* Refeeding syndrome influences outcome of anorexia nervosa patients in intensive care unit: an observational study. Crit Care 2010; 14:R172.
15. Hernández-Aranda JC, Gallo-Chico B, Luna-Cruz ML, *et al.* Malnutrition and total parenteral nutrition: a cohort study to determine the incidence of refeeding syndrome. Rev Gastroenterol Mex 1997; 62:260–265.
16. Obeid OA, Hachem DH, Ayoub JJ. Refeeding and metabolic syndromes: two sides of the same coin. Nutr Diabetes 2014; 30:e120.
17. ■■ Doig GS, Simpson F, Heighes PT, *et al.* Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomized, parallel-group, multicentre, single-blind controlled trial. Lancet Respir Med 2015; 3:943–952.

The only randomized controlled trial performed among critically ill patients showing lower mortality endpoints in RFS patients treated with a caloric restriction for 48 h.

18. Nutrition support for adults: oral nutrition support, enteral tube feeding, and parenteral nutrition. Guidance and guidelines. NICE [Internet]. Nice.org.uk. 2018. Available from: https://www.nice.org.uk/guidance/cg32/chapter/1-Guidance#screening-for-malnutrition-and-the-risk-of-malnutrition-in-hospital-and-the-community. [Cited 22 May 2018].
19. Kondrup J, Rasmussen HH, Hamberg O, *et al.* Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clin Nutr 2003; 22:321–336.
20. Koekkoek KWAC, van Zanten ARH. Nutrition in the ICU: new trends versus old-fashioned standard enteral feeding? Curr Opin Anaesthesiol 2018; 31:136–143.
21. Bousie E, van Blokland D, Lammers HJ, *et al.* Relevance of nonnutritional calories in mechanically ventilated critically ill patients. Eur J Clin Nutr 2016; 70:1443–1450.

Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.