Nutritional Failure: An Adaptive Response to Critical Illness?

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For decades, intensive care unit (ICU) physicians have been administering artificial nutrition to improve recovery and outcome. This intensified nutritional support has been associated with a better outcome in several large observational studies (Alberda et al. 2009), though unfortunately, it is impossible to distinguish cause and consequence by association. Large randomised controlled trials (RCTs) comparing feeding with no, or poor, feeding have until recently never been performed. This article will discuss the importance of nutritional intake in critical illness as well as the incidence of nutritional interruption and nutritional loss.

Is Enteral Nutrition the Way to Go?

When simple nutrition by mouth is inadequate, enteral nutrition (EN) has always been preferred above parenteral nutrition (PN) (Martindale et al. 2009; Singer et al. 2009). EN is cheaper, more physiological and probably safer. Indeed, PN provokes metabolic deregulation, particularly hyperglycaemia and perhaps thereby more infections (Peter et al. 2005). The physiologic impact of infusing lipids, amino acids and glucose intravenously has been studied in mechanistic experiments, but remains controversial. PN, in particular intravenous lipids, might worsen pulmonary gas exchange and immune function (Versleijen et al. 2010; Faucher et al. 2003; Smirniotis et al. 1998; Nordenstrom et al. 1979). Meta-analyses of studies comparing EN to PN in the critically ill are conflicting (Peter et al. 2005; Heyland et al. 1998).

Less than Optimal Enteral Nutrition

The gastrointestinal route seems the way to go. Moreover, most of us believe that EN should be started early: within 24 hours. This is an assumption based on meta-analyses of a few studies comprising 240 patients altogether (Doig et al. 2009). There may, however, be an important discrepancy between the amount of EN we think we are giving and what has really been taken up by the patient (De Jonghe et al. 2001). These EN losses, in the broader sense of the word, are the focus of this contribution. Moreover, should we care about insufficient nutritional intake (early) in critical illness? The importance of hidden micronutrient losses, among others, by renal replacement therapy falls beyond the scope of this overview (Berger et al. 2004).

Enteral Nutrition Simply not Given

Several papers described the difference between EN prescription, "optimal" intake according to established calculations, and the amount of EN truly administered every day (De Jonghe et al. 2001). EN is interrupted regularly for many reasons, among them airway management, surgical and diagnostic procedures, and fear of regurgitation and pulmonary aspiration of gastric liquids (Cook et al. 1998). Interruptions of EN often go unnoticed, sometimes nutrition simply continues in the patient file while it is stopped in reality. Hopefully EN delivery pumps coupled to a patient data management system will improve the quality of clinical nutrition data (Berger et al. 2006). Also, energy intake is often described as a percentage of target; but in fact no one knows what this target should be. Weight or height based calculations are not dynamic, so indirect calorimetry is assumed the gold standard. The question remains, however, whether amount of endogenous energy being burnt indicates how much exogenous nutrients should be given. Also, the accuracy of indirect calorimeters is questionable (Sundstrom et al. 2013).

Measurement of Gastric Residual Volumes

Many ICUs, including the Leuven Intensive Care Department, interrupt EN twice a day for two hours. Gastric residual volumes are quantified thereafter in order to assess gastric emptying. Whether this practice is useful and prevents complications, in particular aspiration pneumonia, has never been established (Ridley and Davies 2011). Also, the gastric residual volume (GRV) cutoff for the safe increase of the EN flow rate is

unclear. A large Spanish study demonstrated safe administration of EN with an upper GRV limit of 500 ml rather than the classical 200 or 250 ml. This approach allowed enhanced EN delivery (Montejo et al. 2010). Another practical question with GRV is: what should be done with the collected mixture of EN and gastric secretions? If up to 500 ml of GRV is discarded twice every day, this might result in 1000 kcal or more of EN not truly given to the patient. Re injecting more than one syringe (mostly 50 ml) of gastric fluid requires collecting the liquid in a clean or sterile container before re-injecting it. Therefore, this unpleasant smelling juice is often thrown away in practice. The amount of EN lost when discarding GRV can be measured by refractometry. This simple bedside method has been bench validated (Chang et al. 2005); however, when mixing EN with gastric juice from critically ill patients rather than clear water, we found a somewhat larger inaccuracy with this tool (Stuer et al. 2010). A very simple solution might be to abandon measuring GRV and to instead administer the EN without interruptions (Ridley and Davies 2011).

Bypassing Delayed Stomach Emptying

When the stomach doesn't empty adequately into the duodenum, some pharmacological or mechanic solutions exist. It is not sure if they should be used. Gastroprokinetics improve gastric emptying. Erythromycin is more effective than metoclopramide (Ridley and Davies 2011); moreover, metoclopramide may prolong the QT interval. The promising results of post-bulbar EN tubes in neurosurgical patients have not been confirmed in larger RCTs (Marik and Zaloga 2003), and perhaps such studies should be repeated in particular at risk populations or in patients who failed initially by the gastric route (Berger and Soguel 2010). Systematic introduction of a post-bulbar tube, by gastroscopy or magnetoscopy, in all patients may rather delay feeding than enhance it. Finally, delayed gastric emptying could be a sign that a patient is not yet ready to be fed.

Enteral Nutrition not Absorbed by the Patient.

Too easily, we consider all nutrition infused into the patient as absorbed by the patient. Recently a Dutch study quantified the amount of nutrients lost in faeces. Despite the patients in this study not being at risk for compromised enteral feeding, the proportion of EN found in faeces was often significant (Wierdsma et al. 2011). Weighing faeces daily might contribute to correct assessment of true enteral delivery. What can be done, however, if EN absorption is inadequate? Several strategies for reducing diarrhea have been tested in practice. Fibre-rich EN reduces the volume and frequency of stools (Spapen et al. 2001), while semi-elemental EN, though physiologically promising, failed as therapy for diarrhoea despite the absence of proteins in the preparations (Mowatt-Larssen et al. 1992). None of these studies, however, have been validated for EN absorption. The endpoint in these studies was instead on volumes or frequency of diarrhoea.

Failure to Deliver Adequate Nutrition: Is it a Problem?

In summary, many patients receive fewer nutrients than what is estimated as optimal; but is this a problem? Most observational studies suggest that it is (Alberda et al. 2009; Dvir et al. 2006). Nevertheless, the "Impact of Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients" (EPaNIC) trial was the first adequately powered randomised controlled trial which tested whether up-to-target feeding really improves clinical outcome (Casaer et al. 2011). Surprisingly, it did not. Patients in this trial were randomised to either receiving early PN, with intravenous nutrition initiated at day three and achieving the nutritional target by the end of day four, if EN was insufficient; or late PN. Here, patients received no PN, no matter how unsuccessful EN was. Patients in the late PN group, despite an important nutritional deficit, recovered faster from critical illness than patients in the early PN group. Also, fewer patients in the late PN group developed a new infection. Duration of organ support was shorter for patients in the late PN group and patients in this group were discharged from the ICU and hospital earlier. This improved outcome from less aggressive therapy resulted in an overall cost reduction of 2.3 million euros (Vanderheyden et al. 2012).

Limitations of the EPANIC Trial: Wrong Food for the Wrong Patient?

The results of the EPaNIC trial were a wakeup call to the ICU and nutrition community. A long-standing dogma was challenged by the first available clinical data. The first question was: Are these results applicable to patients with true gastrointestinal failure? This was the case. A subgroup of more than 500 patients, who were admitted with a surgical contraindication for EN, benefited even more from late PN than the overall EPaNIC patient population (Casaer et al. 2011). Experts wondered whether early PN would only be beneficial in the most severely ill patients, but harmful in the least severely ill; but a post hoc study of the EPaNIC trial, studying the effect of late PN in subgroups divided by the APACHE II score and cardiac versus non cardiac surgery admission diagnoses, rejected this hypothesis (Casaer et al. 2012). If anything, late PN was found to be even more beneficial in more severely ill patients. Also, more than 800 patients admitted with the highest nutritional risk scores (NRS: five, six and seven), reflecting a very low body mass index (BMI) or extremely reduced nutrition intake before inclusion in the EPaNIC trial, experienced similar benefit from semi-starvation (Casaer et al. 2011). Recently, an alternative score aiming to predict improved outcome by enhanced nutrition, the Nutrition Risk in the Critically Ill (NUTRIC) score, was developed. Its ability to predict mortality has been established in a large patient population (Heyland et al. 2011). Whether this NUTRIC score truly identifies patients likely to benefit from enhanced feeding remains to be validated. A final aspect of the EPaNIC study that was questioned was that the wrong nutrition had been given, i.e. too much glucose and not enough protein or amino acid. Observational analysis of the relative contribution of glucose versus protein to worse outcome in the EPaNIC study identified protein/amino acids rather than glucose as the culprit (Casaer et al. 2012). The absence of glutamine in the PN therapy administered in the EPaNIC study is no longer an issue. Indeed, a recent large and well conducted RCT, the REDOXS study, reporting increased mortality with glutamine in the ICU, was presented by Dr. Daren Heyland at the Update on Metabolism and Nutrition in Intensive Care Medicine round table discussion, which took place in Rome from 16-19 December 2012. These results torpedoed another ICU-nutrition dogma.

Benefit of Early Semi-Starvation in the ICU?

Feeding less than the nutritional target early in critical illness might be harmless and perhaps even beneficial, independent of the route of administration. Indeed the "Early Versus Delayed Enteral Feeding to Treat People With Acute Lung Injury or Acute Respiratory Distress Syndrome" (EDEN) RCT, allocating patients to trickle enteral feeding (equivalent to almost no feeding) versus feeding up to target, showed no benefit of the latter (Rice et al. 2012). The population selected in this study, however, might preclude a generalised conclusion. A smaller trial even demonstrated harm by early enteral feeding (Ibrahim et al. 2002). Finally, combining EN and PN, if necessary, to reach caloric target as assessed by indirect calorimetry, induced more infections and prolonged stay in the ICU in "The Tight Calorie Control Study" (TICACOS) (Singer et al. 2011). Starvation-induced autophagy might explain improved outcome by nutrient restriction. The highly conserved autophagy pathway clears cellular damage, toxic protein aggregates, dysfunctioning organelles and intracellular micro-organisms, all typical of early critical illness. Suppressed autophagy compromises cellular integrity (Komatsu et al. 2005). Vanhorebeek and colleagues observed such suppressed

autophagy in critically ill patients (Vanhorebeek et al. 2011). Meanwhile, animal experiments identified enhanced PN, and in particular amino acids, as the culprit behind autophagy inhibition and organ damage (Derde et al. 2012). Another notable result from the EPaNIC trial was that early PN compromised muscle integrity and was unable to prevent loss of muscle volume (Casaer et al. 2013).

Other Recent RCTs of Nutrition in the ICU

In two smaller trials, early as opposed to later PN apparently provoked no harm. The answer to this apparent controversy might be that the patients administered with later PN in these trials received too many nutrients to experience any benefit of enhanced autophagy by nutrient restriction. Indeed, the first Swiss trial included no patients with a contraindication for EN (Heidegger et al. 2012). All patients in this trial were therefore relatively well fed via EN by the day of inclusion in the trial. Initiation of PN on day four rather than eight reduced the incidence of infections occurring after day nine, without any impact on clinical outcome. The larger, Australian, early PN trial compared PN administered within one hour after ICU admission to eventual PN started not earlier than day two in the ICU, at the physician's discretion. This intervention—in fact, comparing extremely early PN with early PN—had no impact on hard clinical outcome endpoints, confirmed one of the study's researchers, Dr. Gordon Doig, at The European Society for Clinical Nutrition and Metabolism (ESPEN) congress held in Spain from 8-11 September, 2012.

Why do RCTs not Confirm the Hypotheses Generated by Observational Trials?

All the above RCTs—together including more than 6000 patients—agree on one point: tolerating important underfeeding as compared to feeding up to nutritional target does not affect mortality at all. This is in contrast with treatment effect estimates based on large observational trials, which predict excess mortality with every 1000 kcal of energy deficit (Alberda et al. 2009). Should we then distrust RCTs? No, on the contrary; these results point out once more that only adequate RCTs allow the prediction of treatment effect (Peduzzi et al. 2002). Correct trial and endpoint registration; concealed treatment allocation by randomisation; blinding of, at least, the outcome assessors; use of relevant, strong predefined endpoints; inclusion of a sufficient number of patients to achieve adequate credence; and attribution of all events occurring after randomisation to the randomised intervention are needed to provide correct treatment effect assessment. Failure to comply with these requirements increases the risk of the results being distorted by bias. The general bias in nutritional research is that nutrition works.

A specific problem with observational studies in nutritional research is that patients are more easily fed once they are doing better. This mostly results in an increase in average nutritional intake along with ICU stay, while nutritional deficit continues to accumulate. Indeed, many patients never reach nutritional target. The association between nutritional efficacy and recovery will, therefore, depend on the chosen parameter. We recently solved this issue by analysing the effect of nutrition, given over the same time period, on recovery in the upcoming days (Casaer et al. 2012). These analyses revealed delayed recovery with increasing intake, even at very moderate doses. Another problem with observational trials in the ICU is the handling of competing events. What if one treatment shortens ICU/hospital stay, but the outcome of interest is mortality in ICU/hospital? Should patients discharged from the ICU/hospital be censored on the day of discharge, although they are more likely to survive? Doing so is an error named "informative censoring" (Schetz et al. 2013). Certainly, a shorter stay in the ICU/hospital would falsely inflate the mortality in survival analysis (Weijs et al. 2012). In conclusion, more large RCTs are needed to correctly guide nutrition management in the ICU, and observational trials can yield interesting research hypotheses
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So What Should We Do?

Hidden losses and overt failure of EN is common, but failing to reach nutritional targets early in critical illness perhaps isn't that much of a problem. The question now is: how should we manage nutrition until more data is available? Patients able and desiring to eat should do so unless absolutely contraindicated. In all patients, micronutrient status should be assessed and deficiencies, in particular during refeeding, avoided. If nutrition by mouth is impossible or insufficient, initiation of EN shall be attempted. If delayed gastric emptying hampers EN, this can probably be tolerated for several days. PN administration should probably be restricted to patients with intestinal anastomosis leakage or bowel necrosis and even then not be initiated before day eight. Optimal nutritional targets are unknown and are probably much lower than previously assumed. In conclusion: first do not harm!

Published on : Thu, 14 Mar 2013