

Bringing Nutritional Support on the ICU into the New Millennium

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Anorexia and reduced food intake are characteristic of severe illness. In hospitalised patients, further limitation of nutritional intake occurs because of traditional "nil-by-mouth" practices prior to procedures requiring anaesthesia or sedation and, in many cases, a lack of emphasis on nutrition as part of medical management. For many patients admitted to the intensive care unit (ICU) it is not uncommon for nutritional intake to have been already compromised for some days. Once in the ICU, patients are generally unable to ensure the adequacy of their own nutritional intake. Intuitively, therefore, food must be provided to ICU patients at some point, to stave off the effects of prolonged starvation, but it is not yet defined at which point in illness reduced food intake becomes a problem. Although it is established teaching that nutrition be provided "early" and "enterally" to ICU patients, two recent systematic reviews have come to differing conclusions as to whether early enteral nutrition is of proven benefit.^{1,2}

Nutrition is also required in critical illness because, in addition to anorexia and the effects of iatrogenic starvation, there is a pronounced catabolic response that can lead to massive loss of structural body proteins, predominantly from skeletal muscle. The metabolic and physiological responses to starvation and to critical illness are quite different. In the former, both fat and protein are lost, but nitrogen loss is modified until the very late stages by mobilisation of fat, with enhanced fat oxidation being the principal source of calories. These changes are readily reversed by provision of nutrition. Critical illness is characterised by the breakdown of lean tissue to constituent amino acids, which provide substrate for acute-phase protein synthesis and for gluconeogenesis. In this setting, apparently adequate nutritional support can only attenuate the process and breakdown of lean tissue continues. For ICU patients, it is incorrect to consider the effects of the catabolic state and of starvation in isolation, however, as for most patients elements of both processes occur simultaneously.

That starvation is a problem for many hospitalised patients is under-recognised. Ronald Koretz, in 1995, wrote that "... the risk of true starvation will only arise after several weeks of a disease process. Given the expense and risks of the therapy, it is a reasonable policy to wait those weeks out. ..." We know, however, from hunger strikes by Irish Republican prisoners in 1981 that previously healthy young males will die approximately 60 days after ceasing food intake.⁴ In the setting of catabolic illness, the effects of starvation on body protein stores may become rapidly apparent, so that if

nutritional support is not provided both early and in adequate amounts loss of body protein may occur.

Robert Graves, in the mid-nineteenth century, was possibly the first physician to appreciate the link between nutritional support and outcome from illness. He showed that mortality from typhus fever was reduced by giving food and drink to patients, overturning the established dogma that treatment of fever consisted of bleeding, purging and starvation! Unfortunately, there are no controlled trials that demonstrate a benefit from nutrition against no nutrition in illness, and, for obvious reasons there are never likely to be. In this chapter, I address the question of how most recent evidence from clinical trials can guide us to best practice in providing nutritional support to patients with critical illness.

Do feeding targets matter?

The past 25 years have seen a significant shift in the amount of calories and nitrogen recommended for critically ill patients. In the 1960s and 70s, it was not uncommon for patients to be prescribed up to 40 kcal/kg/day in non-protein energy with up to 3g protein/kg/day. These estimated requirements were predicated on the belief that "negative nitrogen balance" represented the result of massive increases in energy and substrate demand (hypermetabolism), based on results of inappropriate over-estimation of normal resting energy expenditure (REE) and excessive estimates of the impact of illness on REE. Work by Kinney measuring REE and nitrogen balance in surgical and trauma patients demonstrated that, after major surgery, REE increased by only up to 10% and, even following major trauma, only reached a 25% increase.⁵ From work by Hill and others, it became clear that in sepsis (for example) providing protein in excess of 1.5g/kg/day does not improve nitrogen balance,⁶ and the optimal non-protein energy requirement is between 20-35 kcal/kg/day.⁷ Excessive administration of calories and nitrogen leads to hyperglycaemia, hypertriglyceridaemia and hepatic steatosis. Zaloga has even argued that "permissive under-nutrition" should be the standard of care.⁸

Is there any evidence that meeting nutritional targets affects outcome in critically ill patients? There are few published studies directly addressing this issue, and much of the literature on nutrition in critical illness comes from trauma or elective surgical populations which may not be characteristic of most Australian ICUs. Taylor reported the effect of an "enhanced" enteral feeding protocol on outcome in head injury patients.⁹ Protocol patients were prescribed feed to a nutritional target from day 1 of ICU admission, whereas control patients had their feeding escalated "as tolerated". Protocol patients received significantly more feed in the first 7 days of ICU stay, and this was associated with reduced infections and general complications, as well as improved neurological recovery at 3 months. There is also some suggestive evidence of a relationship between target feed delivery and outcome from the published enteral immunonutrition trials.¹⁰ In these studies, benefit was only seen in patients who absorbed (or at least received) more than predetermined quantities of feed, or in the setting of assiduously achieved feed delivery targets.

The best evidence to date of an effect of nutrition on outcome in ICU patients may come from a Canadian study currently published as an abstract only.¹¹ When hospitals were randomised to develop and implement evidence-based nutritional guidelines versus continue with current practice, a significant reduction in mortality was demonstrated in guideline hospitals. The main effects of guideline implementation were

earlier delivery of enteral feeds and an increase in the total use of enteral feeds and of both enteral or parenteral feeds.

Thus, there appears to be a positive relationship between feed delivery and outcome, yet current feeding practice in many ICUs is suboptimal. In a survey of five ICUs in the UK, Adam and Batson found that only 76% of prescribed feed quantity was delivered, and the prescription varied between 76 and 103% of estimated energy requirement.¹² Similarly, in the USA, McClave found that physicians prescribed a daily mean volume of feed which was 65% of estimated requirements, with only 78% actually delivered.¹³ There are several reasons for failing to achieve target requirements with enteral feeding. Problems with gastric motility are probably the most common patient-related reason. However, stopping feeds, often inappropriately, for procedures is clearly of considerable importance. Montejo analysed 3778 feeding days in 400 patients from 37 Spanish ICUs over a single month. Gastrointestinal complications related to feeding occurred in 63% of patients and resulted in withdrawal of feeding by the enteral route in 15%.¹⁴ Of interest, patients with gastrointestinal complications had a lower ratio of volume of feed delivered to that prescribed. They suffered a longer length of stay and a higher mortality when compared with patients with similar APACHE II scores who did not have gastrointestinal complications, again suggesting a link between effective feeding and good outcome.

Strategies to achieve feeding target goals in the critically ill

The Canadian guidelines study suggests that implementation of evidence-based practice can improve feeding target compliance.¹¹ Evidence-based guidelines would include advice on appropriate use of prokinetic agents and the timing and methods to use for passing post-pyloric feeding tubes, which constitute the mainstay of approaches to counter early failure of nasogastric feeding in the critically ill. Interval measurement of gastric residual volume is the usual method of assessing gastroparesis, with high aspirates generally being the trigger for ceasing feeds, prescription of prokinetics or placement of post-pyloric tubes. Whether there is a good relationship between measured gastric residual volume and the presence of gastroparesis is unclear however. McClave found that although critically ill patients were more likely than normal volunteers to have gastric residual volumes of greater than 150 ml eight hours after commencement of nasogastric feeding, a significant number of both groups with low residuals had abnormal gastric emptying on radiology.¹⁵ However, no patient had clinical feed intolerance (i.e. vomiting, aspiration). Thus, the level of gastric residual volume that indicates feed intolerance is not clear.

There is evidence that the use of prokinetic drugs can increase gastric emptying in the critically ill. Boivin has shown that use of erythromycin in nasogastrically fed patients is as effective as transpyloric tube placement in terms of meeting nutritional goals.¹⁶ MacLaren found that both metoclopramide and cisapride, when compared with erythromycin or placebo, resulted in more rapid gastric emptying as assessed by paracetamol absorption.¹⁷ Gastric residual volumes were not different between agents in this study, but in a subsequent study use of metoclopramide was associated with significantly lower gastric residual volumes than was cisapride.¹⁸ Concerns regarding the pro-arrhythmic potential of cisapride and the use of an antibiotic (erythromycin) for a non-antimicrobial indication may limit the acceptability of these agents in clinical practice, suggesting that metoclopramide is probably the prokinetic agent of choice.

Where nasogastric feeding, with use of prokinetic agents as indicated, fails, passage

of post-pyloric tubes is recommended. A recent randomised controlled trial found that uncomplicated first-time insertion of a nasojejunal tube by endoscope is possible in 98% of patients.¹⁹ In comparison with nasogastric feeding, nasojejunal feeding was associated with reduced gastric residual volumes and a strong trend to improved tolerance of enteral nutrition. Access to endoscopy services may be difficult to organise in many ICUs, but alternative methods for tube insertion have been described with claimed high success rates.²⁰

For a significant number of patients without gastrointestinal failure, even with these manoeuvres, achievement of feeding targets by the enteral route is not possible in the short term. Daily pursuit of enteral feeding targets commits these patients to de facto malnutrition. In many ICUs, the use of parenteral nutrition (PN) is vigorously avoided in patients without gastrointestinal failure, because of the perceived risk of increased complications associated with its use.

Supplemental parenteral nutrition

Is there evidence against the use of PN as a supplement to enteral nutrition in these situations?

Table 1
Infections and parenteral feeding: Randomised trials comparing parenteral with enteral nutrition in critically ill patients

Author, year	No. of Subjects	Population	Outcome
Adams 1986 ²¹	46	Trauma laparotomy	No difference in complications
Moore 1989 ³⁴	59	Major abdo. trauma	↑ infections & septic morbidity with PN
Kudsk 1992 ³⁵	98	Major abdo trauma, — blunt & penetrating	↓ pneumonia, intra-abdo abscesses & line sepsis with EN
Borzotta 1994 ³⁶	48	Head injury	No difference in infections
McClave 1997 ³⁷	30	Pancreatitis	? earlier resolution of stress response with EN
Gianotti 1997 ³⁸	260	GI cancer; EN vs PN vs immuno-EN	No difference between EN & PN. ↓ infections with immuno-EN
Bozzetti 2001 ³⁹	257	Upper GI cancer	No difference in nutritional, immunologic & inflammatory goals, complications, length of stay or mortality

The principal adverse effect attributed to PN is increased rates of infectious complications. This observation is based predominantly on studies comparing enteral or no nutritional support with PN in elective surgical and trauma populations (Table 1). A common failing of these studies is that they do not compare equivalent groups. It is intuitive that, if a patient can be adequately fed enterally, then PN has no role and thus it is inappropriate to randomise to PN patients who can be fed adequately enterally. On the other hand, if patients are "allocated" to PN only if enteral feeding fails, it is inappropriate to compare outcomes between this group and patients who have tolerated enteral feeding. A common characteristic of studies comparing enteral and parenteral feeding is that PN-fed patients receive significantly more calories and nitrogen than enterally fed groups. In many of the classically quoted papers, the total caloric intake of parenterally fed patients reached what today would be considered

hyperalimentation. In a study in which caloric intakes were standardised, no difference between parenteral and enteral feeds could be detected.²¹

There are, however, good theoretical reasons why PN might predispose to increased infective complications. First is the suggestion that lipid emulsions have immune-suppressing properties.^{22, 23} Commercial lipid emulsions contain predominately long chain fatty acids of the ω -6 variety. These tend to favour the formation of dienoic prostaglandins, in particular prostaglandin E₂ (PGE₂). This has a direct suppressant effect on leucocyte function *in vitro*. In the laboratory, fat emulsions have been shown to depress the reticuloendothelial system and pulmonary function. Whether lipid emulsions modify immune responses *in vivo* in man has not been definitively proven. New lipid formulations are expected in the near future which will have theoretical advantages over traditional formulations in terms of immune modulation.²⁴ A more important explanation for why use of PN might increase infectious complications is the relationship between use of PN and hyperglycaemia. There is now good evidence that allowing hyperglycaemia to persist in critically ill patients is associated with poor outcome. Van den Berghe and colleagues randomised patients to have blood sugars controlled between 4 and 6 mmol/l or allowed a more liberal target of less than 12 mmol/l.²⁵ Although the study was complicated by an unusual feeding regimen employing an infusion of 50% glucose on the first day, there was a 50% reduction in ICU mortality in those patients with aggressive control of blood sugar. It remains unclear whether the benefit in this study was due to control of hyperglycaemia or administration of insulin *per se*; nonetheless, the study suggests that hyperglycaemia should be controlled in the critically ill.

The third major concern with use of PN is promotion of gut mucosal atrophy and consequent increase in gut permeability. Rodents develop villous atrophy within three days of commencement of total PN. While such changes are commonly reported in studies involving small animals, they are poorly characterised in man.²⁶ Human reports to date have involved long term total PN use and/or total PN administration in children. Increased gut permeability and bacterial translocation have not been convincingly demonstrated to occur in man, and have not been correlated with use of PN. It is unlikely that short term use of PN in critically ill patients without gastrointestinal failure will have deleterious effects on the gut, especially if given as a supplement to some enteral feed and if, as discussed below, glutamine is included.

The use of supplemental PN in patients with critical illness has been reported by Bauer and colleagues.²⁷ These authors studied 120 patients from two tertiary ICUs. Patients were randomised to receive either enteral combined with PN or enteral nutrition combined with saline as control. The patients received the same amount of enteral feed in each group and, indeed, the same amount of "theoretical" PN, with an increase in enteral and decrease in PN from days 1 to 7. The total caloric intake was significantly different between the groups, however, with the supplemental group more rapidly and consistently achieving targets. There was no effect on mortality in this small study but, equally, no adverse effect of PN was observed. The supplemental group demonstrated a small but significant reduction in hospital length of stay and improvement in the nutritional markers prealbumin and retinol binding protein.

Glutamine and immunonutrients

Glutamine is the principal metabolic fuel for gut mucosal cells. In health, gut mucosa obtains most of its glutamine requirement from luminal contents. In illness,

however, body glutamine requirements appear to be increased. Glutamine is mobilised from skeletal muscle and carried to the splanchnic region where it is utilised in acute-phase protein synthesis, synthesis of anti-oxidants such as glutathione and as a substrate for immune cell replication. In this situation, despite increased splanchnic glutamine supply, gut requirements may not be met without increased dietary intake. Unfortunately, most enteral and parenteral nutrition solutions do not contain glutamine. Therefore, it is probable that supplemental glutamine should be provided to critically ill patients receiving PN, and possible that this is necessary in all critically ill patients. Despite extensive literature on the advantages of glutamine enriched feeds in a number of clinical scenarios, there are few adequate clinical trials in the critically ill. Those published to date are all probably under-powered (Table 2). Nonetheless, from the amassed literature, there does seem to be a signal to suggest that glutamine enriched parenteral feeds are of benefit.²⁸

Several other nutrients shown to affect immunological and inflammatory responses have been studied in randomised controlled trials. These include arginine, ω -3 fatty acids and nucleotides. Unfortunately, *in vivo* studies have to date involved the enteral administration of commercially provided formulations, termed "immunonutrition", and there is no information on the effects of the individual substances. The studies of enteral immunonutrition formulations have recently been the subject of a systematic review.²⁹ Overall, it appears that immunonutrition is associated with a reduction in infectious complications and this may be associated with reduced hospital length of stay, but no mortality advantage. There is significant heterogeneity between the studies limiting the strength of these results. Of concern, the authors of this review found that those studies with the best methodological quality appeared to show increased mortality with immunonutrition in ICU patients. Pending further large scale studies, it would seem that their conclusion that immunonutrition cannot be recommended

Table 2
Studies evaluating glutamine-enriched nutrition in critically ill patients

Author, year	Population & No subjects	Outcome
<i>Parenteral nutrition</i>		
Tremel, 1994 ⁴⁰	n=12	Improved intestinal absorption capacity.
Weingartmann 1996 ⁴¹	Polytrauma, n=16	Required high dose to sustain plasma gln levels.
Palmer, 1996 ⁴²	n=38, muscle	Failed to influence muscle glutamine biopsies in 16 with five days of feeding
Griffiths, 1997 ³³	n=84	Improved survival at six months
de Beaux, 1998 ⁴³	Severe pancreatitis, n=14	Reduced IL-8, trend to improved lymphocyte proliferation
Powell-Tuck, 1999 ⁴⁴	n=168, clinically indicated to receive TPN (not all ICU)	Reduced hospital length of stay & isonitrogenous
<i>Enteral nutrition</i>		
Jensen, 1996 ⁴⁵	ICU patients, n=28	Blunting of hyper-aminoacidemic response to injury
Long, 1996 ⁴⁶	Trauma, n=30	Ineffective at maintaining plasma gln level
Houdijk, 1998 ⁴⁷	Trauma, n=72	Reduction in sepsis, bacteraemia and pneumonia. Soluble TNF receptors reduced.
Jones, 1999 ⁴⁸	ICU patients, n=78	? ineffective. Reduced costs using complex analysis.

for critically ill patients is prudent. A formulation containing eicosapentaenoic acid, γ -linolenic acid and antioxidants has been evaluated in patients with acute respiratory disease syndrome (ARDS).³⁰ 146 patients were randomly allocated the trial feed or an isonitrogenous, isocaloric control. Use of the trial feed was associated with significant improvements in oxygenation and ventilator variables, which were in turn associated with reduced days of mechanical ventilation and a shorter ICU length of stay. The trial was potentially flawed, however, as the study groups were not comparable in gender distribution and the ventilation management was not standardised. The findings have yet to be replicated by other workers.

Table 3
Optimal management of nutrition support in the critically ill

Feed early ³¹
Develop evidence-based guidelines ¹¹
Assess likelihood of successful enteral feeding from day 1: ³²
— consider metoclopramide as prokinetic if required ¹⁸
— consider post-pyloric tube if nasogastric feeding results in difficulties ¹⁹
— any doubt on achieving targets? — add supplemental PN ²⁷
Manage hyperglycaemia aggressively ²⁵
Use glutamine-enriched PN for critically ill patients unable to tolerate EN ³³
Assess feeding targets daily

Summary

Suggested principles of optimal management of nutrition support of critically ill patients at the start of the new millennium are shown in Table 3. Nutrition research is bedevilled by under powered studies, so unfortunately, few of these principles have been adequately submitted to evaluation by a randomised, controlled trial. Nutritional and metabolic support of the critically ill patient remains in its infancy and there is much work to be done.

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