Conference on ‘Malnutrition matters’

Satellite Symposium: Throw another fish on the fire: the role of $n$-3 in inflammation

Providing optimal nutritional support on the intensive care unit: key challenges and practical solutions

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Many patients in the intensive care unit are malnourished or unable to eat. Feeding them correctly has the potential to reduce morbidity and even mortality but is a very complex procedure. The inflammatory response induced by surgery, trauma or sepsis will alter metabolism, change the ability to utilise nutrients and can lead to rapid loss of lean mass. Both overfeeding and underfeeding macronutrients can be harmful but generally it would seem optimal to give less during metabolic stress and immobility and increase in recovery. Physical intolerance of feeding such as diarrhoea or delayed gastric emptying is common in the intensive care unit. Diarrhoea can be treated with fibre or peptide feeds and anti-diarrhoeal drugs; however, the use of probiotics is controversial. Gastric dysfunction problems can often be overcome with prokinetic drugs or small bowel feeding tubes. New feeds with nutrients such as $n$-3 fatty acids that have the potential to attenuate excessive inflammatory responses show great promise in favourably improving metabolism and substrate utilisation. The importance of changing nutrient provision according to metabolic and physical tolerance cannot be understated and although expert groups have produced many guidelines on nutritional support of the critically ill, correct interpretation and implementation can be difficult without a dedicated nutrition health care professional such as a dietitian or a multidisciplinary nutritional support team.

Enteral nutrition: Parenteral nutrition: Intensive care: Critical illness

The intensive care unit (ICU) will inevitably contain the sickest, most metabolically stressed patients in any care setting. This in turn means that it is the area where we are likely to encounter many of the most malnourished patients, but their severe illness and corresponding changes in metabolism make nutritional support far from straightforward. However, there is good evidence that appropriate nutritional support can improve outcomes and may even reduce mortality. In order to confer these benefits, it is vital that the right amount of energy, protein and micronutrients are given at the right stage of critical illness. In most cases, enteral feeding, where nutrition is infused directly into the gut through a tube is the preferred method. However, the critically ill patient’s gut may not always function correctly and special feeds, tubes or drugs may be required. In some cases, intravenous feeding is indicated either on its own or in combination with enteral feeding. As the metabolic response to surgery, trauma or sepsis affects the utilisation of nutrients, many special feeds have been developed. Nutrients such as $n$-3 fatty acids or antioxidant vitamins may have the ability to modulate the metabolic effects of critical illness and the evidence to support their use will be discussed.

Abbreviations: ASPEN, American Society for Parenteral and Enteral Nutrition; EN, enteral nutrition; ESPEN, European Society for Clinical Nutrition and Metabolism; GRV, gastric residual volumes; ICU, intensive care unit; NICE, National Institute for Health and Clinical Excellence; PN, parenteral nutrition.

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Why feed critically ill patients?
It has been estimated that up to 43% of ICU patients are malnourished(1) which in turn increases the risk of complications including muscle loss and weakness, increased infection and a prolonged period of mechanical ventilation. Rehabilitation after a period of critical illness can be a very drawn out and difficult process(2) which will be much harder if the patient is malnourished, weak and depleted of skeletal muscle. However, studies have shown that an appropriate nutritional support can improve outcomes and possibly even reduce mortality(3). In the ACCEPT study, this was achieved through more complete enteral nutrition (EN; tube feeding) without the decline of parenteral (intravenous) feeding if necessary(3).

Although the benefits of feeding critically ill adults have now been well defined(3), doing it correctly is often far from straightforward. In addition to the fact that many of the patients are malnourished, all critically ill patients will have an altered metabolism due to their inflammatory response. It is therefore vital that the right amount of nutrients be provided through the right route at the right time and although there are many barriers to achieving this, they can be overcome.

Inflammatory response
The inflammatory response, or acute phase response, occurs following an insult that may include trauma, infection, surgery or sepsis. It is mediated by cytokines such as TNFα, IL-1β, IL-6, eicosanoids and stress hormones including cortisol. Its purpose is to mobilise nutrient stores including glucose and amino acids to fuel the immune response, synthesise acute phase proteins, and form white cells, collagen and fibroblasts. It must be stressed that the inflammatory response is a positive entity that has evolved for a reason, but an excessive or prolonged response can be harmful and in some cases lead to the systemic inflammatory response syndrome or multiorgan dysfunction syndrome.

Amino acids are predominately liberated from skeletal muscle; a process known as catabolism. These may form glucose through gluconeogenesis or be used to make acute phase proteins. This process can lead to a negative N balance of up to 20 g/d(4) and it has been estimated that acute ICU patients can lose up to 5–10% of their skeletal muscle a week(5). In addition being bedbound alone will also lead to loss of lean mass(6). Other effects of the inflammatory response include anorexia, liberation of TAG and hyperglycaemia induced by increased gluconeogenesis and insulin resistance. Giving appropriate nutritional support can attenuate the negative effects of the inflammatory response(7) and it should be given to all critically ill patients who cannot eat even if they are not classically malnourished on admission to the ICU.

Nutritional support can be delivered to critically ill patients by three main methods: EN where the feed is infused into the gut through a tube, parenteral nutrition (PN), where it is delivered intravenously and oral nutrition; simply encouraging patients to eat and drink. The use of oral nutrition in extremely unwell patients is often limited due to mechanical ventilation, anorexia and sedation so EN is usually the preferred route.

Delivery of nutritional support
EN is most commonly given via a nasogastric tube in the ICU; however, small bowel feeding through a nasojejunal tube may sometimes be indicated if the patient has delayed gastric emptying. Tubes placed directly into the stomach (gastrostomy) or small bowel (jejunostomy) are also sometimes encountered. Compared to PN, EN is cheaper, has less metabolic complications and is therefore safer(7), it may preserve gut barrier function and if tolerated it may be associated with a better outcome.

The evidence to support EN is considerable and was reviewed by Heyland(7) with the conclusion that there were significantly less septic complications with EN compared to PN but no difference in mortality between the two treatments. Eight randomised controlled trials comparing early EN (established in the first 24–48 h) with delayed EN found reduced mortality and infections in the early feeding group, along with improved N balance and nutritional status. The American Society for Parenteral and Enteral Nutrition (ASPEN) and the Society of Critical Care Medicine have recently published guidelines for feeding the critically ill(8) and recommend starting EN in the first 24–48 h as there is good evidence this will result in a significant reduction in morbidity and length of stay (LOS). It is thought that EN brings about these benefits by reducing the production of pro-inflammatory cytokines and thereby modulating the inflammatory response(7). Furthermore, EN may maintain gut barrier function and prevent the translocation of bacteria from the gut reducing the risk of dangerous systemic reactions such as multiorgan dysfunction syndrome(8). The gut is a very important immunological organ and feeding it supports immunocytes and the Ig producing gut-associated lymphoid tissue(9). ASPEN also recommended that nasogastric feeding should be considered as the first line of access for EN as although nasojejunal feeding may be indicated in patients with gastric dysfunction, care must be taken if they are haemodynamically unstable and therefore unable to safely perfuse their gut as this could lead to fatal bowel necrosis.

Enteral nutrition: common problems
While the potential benefits of early enteral feeding in the ICU cannot be understated, problems in establishing it are frequently encountered but can be overcome. One particular problem is gastric dysfunction or delayed gastric emptying. A common practice to assess gastric function and hence tolerance of enteral feed is to measure gastric residual volumes (GRV). A feed is given at a set rate for a particular period, for example, 25 ml/h for 4 h(10), after which a syringe is used to see how much feed can be aspirated back from the stomach. In the UK, GRV of less than 250 ml are commonly accepted as an indication that the stomach is emptying and the feeding rate can be increased or maintained. However, despite their acceptance in the daily practice, on most ICU there is a great deal of
Another frequently encountered barrier to successful enteral feeding on ICU is diarrhoea. It may be multifactorial in origin but is almost certainly not due to anything in the feed itself. Possible causes may include infection, conditions such as inflammatory bowel disease, medications or abnormal colonic motility \(^{(16)}\). Antibiotics are known to cause diarrhoea (17). Soluble fibres or prebiotics such as fructo-oligosaccharides or inulin are fermented by beneficial bacteria such as the bifidobacteria in the colon to produce SCFA that feed colonocytes and stimulate the uptake of water and electrolytes, while increasing the numbers of beneficial bacteria may also help as they can compete with pathogens \(^{(18)}\). Many commercially available enteral feeds contain blends of prebiotics with soluble and insoluble fibre. Interestingly, ASPEN \(^{(8)}\) advised against the use of insoluble fibre, arguing that it may increase the risk of bowel obstruction in the critically ill. However, the evidence to support this recommendation is very limited and it is largely based on expert opinion.

The use of live organisms as probiotics is also very controversial on the ICU. Although it has been suggested that these may be used to prevent antibiotic-related diarrhoea in hospitals \(^{(19)}\), a randomised study of probiotic administration to ICU patients with severe acute pancreatitis \(^{(20)}\) found a significant increase in mortality in the probiotic group. However, as the increased mortality was attributed to gut ischaemia, it is possible to speculate that this was due to the aggressive administration of the probiotic preparation along with enteral feed to haemodynamically unstable patients via a jejunal tube that caused the problems rather than the organisms themselves. Until further evidence from well-designed trials of probiotics in the critically ill are available, it would be prudent to urge caution when considering probiotics to treat or prevent diarrhoea on the ICU.

Another approach to treating diarrhoea is to try to minimise the residue reaching the colon and some authors recommend considering pre-digested feeds that may contain peptides and medium-chain TAG rather than whole proteins and long-chain TAG \(^{(8)}\). These may be of particular benefit where there is pancreatic insufficiency and inadequate availability of enzyme for digestion. If the previously mentioned measures are not effective, anti-diarrhoea drugs such as loperamide can be considered once an infective cause has been ruled out.

**Parenteral nutrition: intravenous feeding**

If enteral feeding cannot be established due to poor gut function, PN or intravenous feeding can be considered. PN can be associated with numerous complications including hyperglycaemia, line sepsis, hypertriglyceridaemia, hypercapnia, bacterial translocation, hepatic steatosis (fatty liver) and abnormal liver function \(^{(21)}\) and its use in the ICU is immensely controversial. PN gained notoriety following the publication of a meta-analysis of PN studies in the critically ill by Heyland in 1998 \(^{(22)}\). This found increased septic morbidity in patients given PN compared to those given standard treatment (intravenous dextrose and diet), with benefit only being found in malnourished surgical patients. It is possible to explain the negative outcomes though as many of the studies were carried out when giving extremely high-energy and N loads was the trend, whereas it is now known that most of the complications of PN are due to excess provision of macronutrients \(^{(21)}\). In addition, the included studies predated the use of intensive insulin therapy to avoid hyperglycaemia which may be particularly harmful \(^{(23)}\). More recent studies have shown that PN may actually be safer than EN in surgical patients with questionable gut function \(^{(24)}\) and a 2005 meta analysis of using PN on an intention-to-treat basis found improved survival with PN in patients who could not be successfully fed enterally in the first 24 h on the ICU \(^{(25)}\). The diversity of current opinion on PN is illustrated by the conflicting recommendations in two recent sets of expert guidelines on ICU feeding. ASPEN \(^{(8)}\) recommended withholding PN for up to 10 d in most critically ill patients, whereas
European Society for Clinical Nutrition and Metabolism (ESPIN) suggested PN should be started on all patients who cannot be established on EN in the first 24–48 h in ICU. When making a decision on starting PN it seems logical to consider the patient’s nutritional status. If they are malnourished, giving PN may improve survival, whereas if they are not, holding off PN may reduce septic complications.

Classically PN is used where the gut is not functioning e.g. obstruction, ileus, short bowel syndrome or anastomotic stenosis, but in the critically ill determining whether the gut is functioning may not be clear cut, particularly if the patient is able to tolerate some enteral feeding but not meet their full requirements. In such cases, it is possible to use supplemental PN, where as much EN as possible is given and the remainder of the estimated requirements topped up parenterally. Use of equal energy density PN and enteral feed make this practice easier as they can be titrated against each other ml for ml according to the tolerance of EN.

How much should we give?

Another major controversy is the amount of nutrition critically ill patients should receive. With their tendency to lose huge amounts of lean weight it would seem logical to give as much energy and protein as possible. However, this practice that was common in the 1980s and often referred to as hyperalimentation may be particularly harmful. Due to the previously outlined changes in metabolism, overfeeding can lead to hyperglycaemia, raised energy expenditure, increased oxygen consumption and CO₂ production, hepatic steatosis (fatty liver) and hyperlipidaemia. Hyperlipidaemia may in turn lead to fatty infiltration of lung tissue and the hepatic reticuloendothelial system, impairing gas exchange and antibody production, respectively. It is likely that at best hyperalimentation may lead to fat weight gain and studies on enforced bed rest have suggested that a positive energy balance leads to increased loss of lean mass.

Although the risks of overfeeding have been well documented, it is becoming clear that underfeeding can also be dangerous. In one study, a cumulative negative energy was associated with increased complications and mortality. However, it is important to realise that energy requirements will change throughout ICU stay and while it is inevitable that patients will lose lean mass during critical illness they may be able to replenish losses as they recover, and the importance of adjusting energy provision to account for this cannot be understated. This point was made by ESPEN in their 2006 guidelines on enteral feeding where they recommended that we should avoid giving more than 84–105 kJ/kg in the initial stages of critical illness but that we should increase to 125–150 kJ/kg in the ‘anaabolic flow phase’ or recovery in other words. Unfortunately, ESPEN do not give any guidance on how to recognise the ‘anaabolic flow phase’ but it seems logical that the following can be regarded as signs of recovery: a drop in inflammatory markers such as C-reactive protein, resolving oedema, reduced hyperglycaemia and insulin requirements and a return of appetite and mobility. In addition, Bernstien suggested that a 40 mg rise in weekly serial prealbumin levels indicates the switch to anaabolism.

Protein requirements

If energy requirements are controversial, protein may be even more so. While most experts now agree to an extent about the dangers of over and under provision of energy, views on protein are more polarised. Some experts argue that generous amounts of protein should be given in an attempt to reverse the massive negative N balance and skeletal muscle loss that critically ill patients often experience. It is hypothesised that reducing muscle loss will assist ventilatory function and hasten rehabilitation. Indeed, ASPEN recently recommended giving 1.2–2 g protein/kg. However, there is no evidence that going above 1.5 g protein/kg improves N balance and it has been argued that giving large amounts is actually dangerous. During the inflammatory response different amino acids are required to the normal anabolic state for the synthesis of acute phase proteins such as Ig. Working on the theory that the loss of appetite in acute illness evolved to cut off the supply of exogenous nutrients, such as the wrong type of amino acids, allowing the body obtain what it needs from its own stores, it is possible to see why excessive protein could be harmful. Apart from the added metabolic burden of breaking down and excreting the by-products of unrequired amino acids, there is evidence that excessive protein increases mortality when refeeding famine victims. Furthermore, the bedbound nature of ICU patients may compound the futility of giving large protein loads as the muscle of immobilised limbs cannot synthesise tissue as well as non-immobilised limbs even when an abundance of amino acids are given. Until more hard scientific evidence is available regarding the optimum amount of protein for ICU patients, it would seem logical to adopt the same approach as with energy, giving modest amounts (0.8–1.5 g/kg) during metabolic stress and increasing in recovery when a normal anabolic state has returned. The same signs of recovery as previously mentioned can be used.
Amino acids

The concept that catabolic ICU patients have different amino acid requirements has been well documented in the literature.\(^7\) For example, they may require more phenylalanine, tryptophan and tyrosine for acute phase protein synthesis, glutamine, arginine and aspartate for lymphocyte proliferation and glutamine and glycine for synthesis of glutathione, an antioxidant tripeptide that can protect cells from reactive oxygen species such as peroxides and free radicals.\(^37,40,41\) Stroud has hypothesised that many of the non-essential amino acids may be more important in critical illness as the body has retained the ability to synthesise them when the exogenous supply is limited by the anorexia induced by inflammation.\(^37\) Despite this, specific recommendations by the expert groups regarding amino acid provision remain limited. ESPEN and ASPEN give recommendations in terms of whole proteins, N or ‘balanced amino acid mixtures’ for PN.\(^3,25,35\) They do make some recommendations about giving extra glutamine, especially in PN, and extra arginine as part of enteral feeds referred to as immunonutrition but apart from this the issue of specific amino acid requirements for the acute phase response remains largely unaddressed.

Although the British Association of Parenteral and Enteral Nutrition have not produced guidelines for feeding the critically ill, their founder groups did contribute substantially to the NICE guidelines for nutritional support in adults,\(^13\) which cover in detail the nutritional requirements of metabolically stressed patients such as those found in ICU. NICE seem to be the only group to really consider the potential risks of provision of the wrong type of amino acids and recommend giving about 50% of estimated N requirements or about 0.12 g N/kg for the first week before increasing. Until further research is carried out or feeds with specific amino acid profiles for critical illness are available, it would seem logical to adopt the NICE approach; however, there do not appear to have been any surveys to clarify how many UK ICU do this. It is the author’s belief that many ICU will pick and choose recommendations from ESPEN, ASPEN and NICE depending on their own personal views and use them to justify their clinical practice.

The reason why expert groups prefer to make recommendations in terms of whole protein or N could be because the source in many feeds is casein which contains the amino acids required in a normal metabolic state. Whey protein is rich in cysteine, which can improve glutathione synthesis;\(^42\) however, developing feeds with the precise amino acid profile for the catabolic state could be difficult or costly. Currently, the addition of extra glutamine or arginine and the use of whey protein are the only concessions feed manufacturers have made to address this issue. Glutamine may promote the immune function, prevent gut mucosal atrophy, reduce septic complications and reduce hospital LOS, especially when given in high doses parenterally (\(>0.2 \text{g/kg}\)).\(^43\) It does not appear to have any adverse effects\(^43\) and so its use is generally recommended. Arginine is a precursor of NO and therefore has the capacity to improve organ perfusion through vasodilatation,\(^43\) but its use is more controversial as enteral feeds supplemented with it have been associated with increased mortality in severely septic patients, especially those who do not tolerate the full dose.\(^35\) It appears that when arginine levels are low NO synthase may form a toxic peroxide called peroxynitrite,\(^45\) which could explain the adverse events. Advocates of arginine suggest that this problem is caused by feeds with low levels of arginine supplementation and the problem can be overcome by including larger amounts of \(>12 \text{g free arginine per litre}\).\(^45\) However, as severely septic patients are notoriously hard to feed due to delayed gastric emptying, attempting to give arginine in large amounts will always be a gamble irrespective of the concentration in the feed and for this reason ESPEN advise against using the immunonutrition feeds that contain it in this group of patients.\(^35\)

**n-3 Fatty acids**

Taking into account the massive changes in metabolism induced by critical illness, there has been growing interest in nutrients that may modify the inflammatory response and allow more effective nutritional support. The n-3 fatty acids EPA and DHA have the potential to attenuate the inflammatory response by reducing the production of pro-inflammatory mediators such as eicosanoids and cytokines.\(^46\) It has been suggested that the optimum dose of n-3 to do this is in the region of \(3–10 \text{g/d}\) or approximately \(0.1–0.2 \text{g/kg}\).\(^46\) As n-3 fatty acids compete with n-6 fatty acids in the synthetic pathway for pro-inflammatory eicosanoids, providing the correct ratio of fatty acid types may also be important. Mizock\(^47\) suggested an optimum ratio of \(1:2\) n-6 to n-3 whereas other authors have suggested \(1:3\).\(^46\) White clearly some n-6 fatty acids are essential, they are pro-inflammatory and another way of possibly reducing the amount in enteral feeds would be to substitute some of the long-chain TAG for medium-chain TAG. There is also the possibility that medium-chain TAG may improve tolerance in patients with exocrine insufficiency or other malabsorption states; however, there appear to be no specific studies in the critically ill to date.

There is evidence to support the use of n-3 enriched enteral feeds on the ICU. Among the first n-3 products to be used on the ICU were those referred to as immunonutrition. These contain a cocktail of potentially immune modulating ingredients including n-3 fatty acids, arginine, glutamine, nucleotides and antioxidants. Many small but well-designed trials of these products have been carried out with one review showing decreased infections, ventilation days and LOS in ICU patients.\(^48\) However, because these products contain a cocktail of ingredients, it is difficult to elucidate exactly whether the benefits are due to n-3 or other nutrients. Similarly, a feed enriched with n-3 fatty acids, gamma linoleic acid and antioxidants has been shown to have potential benefits from reducing the time patients require mechanical ventilation\(^49\) to decreasing mortality.\(^50\) Once again, though it is hard to say if the benefits are due to n-3 or other ingredients and this highlights the need for manufacturers of products that contain a variety of metabolically active nutrients to carry out randomised controlled trials of their particular blend in the
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critically ill. Although it is pure conjecture, there is a possibility that by dampening down excessive inflammation, n-3 enriched feeds may lead to a more efficient use of nutrients such as protein, allowing more to be given safely. A well-designed study of n-3 fatty acid supplementation alone and its effect on nutrient utilisation and body composition would therefore be invaluable.

Antioxidants

While it is clear that large doses of macronutrients have the potential to do harm in metabolically stressed patients, it is possible that large doses of certain micronutrients could be beneficial. Conditions such as multiorgan dysfunction syndrome and systemic inflammatory response syndrome are associated with greater oxidative stress and there is evidence that giving large doses of antioxidants such as vitamin C, vitamin E or selenium may have the potential to reduce LOS, ventilation requirements, multiorgan dysfunction syndrome and even mortality\(^{(51,52)}\).

Practical implementation

With the growing evidence that giving the right nutrients at the correct time via the correct route influences morbidity and mortality, it is surprising that many UK ICU have a very casual approach to nutrition. Some resist the multidisciplinary approach recommended by the British Association of Parenteral and Enteral Nutrition (BAPEN)\(^{(53)}\) and NICE\(^{(13)}\) and feed all patients the same amount of feed at the same rate e.g. 80 ml/h of standard feed over 24 h (approximately 8500 kJ) throughout their ICU stay. This extremely questionable practice means that a 80 kg 21-year-old male gets the same amount of nutrition as a 40 kg 80-year-old female which could be considered at least suboptimal and at most life threatening. The value of having an expert such as a dietician focusing on the nutritional needs of each individual patient cannot be understated. Even though expert groups such as ESPEN have published guidelines on nutrient requirements per kg, these can be difficult to interpret in the clinical setting due to obesity or the massive oedema encountered in the critically ill. Dedicated nutrition staff will be familiar with the use of predictive formulae such as the Harris– Benedict or Schofield equations and with appropriate adjustment for stress and activity they are probably superior to kJ/kg as they take into account age, weight and gender. kJ/kg may overestimate requirements in large patients and underestimate in small ones\(^{(54)}\). In some cases, dry weights can be estimated from BMI using anthropometry\(^{(55)}\) and use of obesity-adjusted weight will make predictive formulae more accurate\(^{(56)}\). Although indirect calorimetry may be the gold standard for determining energy expenditure\(^{(57)}\) results will still require the expert interpretation of a dedicated nutritionally trained member of ICU staff.

Conclusions

There is a high incidence of malnutrition in critically patients. Even those who are not malnourished on admission are likely to develop some degree of malnutrition while in the ICU. The inflammatory response will lead to loss of lean mass, hyperglycaemia and a limited ability to utilise nutrients. Provision of an appropriate amount of nutrition may help to attenuate muscle loss, reduce LOS and septic morbidity. It may even improve survival. The amount of nutrition required varies according to the patient’s metabolism and should be assessed and modified by an expert. Generally, patients require less in acute illness and more in recovery. The enteral route is preferable, but PN should not be withheld if gut function is questionable. Nutritional substrates capable of modifying metabolism such as n-3 fatty acids show great potential, but more studies are required in the critically ill before firm recommendations can be made, particularly if they are combined with other potentially active substrates in particular feeds.

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