Parenteral nutrition in critical care

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Metabolic changes in critical illness

During critical illness, profound metabolic changes occur: protein catabolism increases, basal metabolic rate (BMR) increases by up to 40%, and a state of relative insulin resistance occurs. Malnutrition in critically ill patients is associated with impaired immune function, muscle weakness, and results in increased ventilator-dependent days and intensive care length of stay. Provision of nutrition in critically ill patients decreases morbidity and mortality. Indeed, the degree of cumulative energy deficit has been shown to be directly proportional to the number of complications they experience.

General nutritional guidelines

The National Institute for Health and Clinical Excellence (NICE) guidelines recommend nutritional support for people who are malnourished based on BMI (body weight accounting for height) and amount of unintentional weight loss. It is also recommended in those who have eaten little or nothing for more than 5 days or are likely to eat little or nothing for the next 5 days and people who have poor absorptive capacity, high nutrient losses, or increased nutritional needs from causes such as catabolism. Most patients admitted to critical care would fall into one or all of the above categories.

The ESPEN (European Society of Parenteral and Enteral Nutrition) and Canadian guidelines state that all patients who are not expected to be on normal nutrition within 3 days should receive nutritional support within 24–48 h of admission. ESPEN recommend parenteral nutrition (PN) is commenced within 24–48 h if enteral nutrition (EN) is contraindicated or cannot be tolerated. ASPEN (American Society of Parenteral and Enteral Nutrition) guidelines recommend if early EN is not feasible or available in the first 7 days no nutrition support therapy should be provided, that PN should be reserved for and initiated only after the first 7 days of hospitalization. A recent study has shown faster recovery and fewer complications in patients receiving late PN (day 8) vs early PN (day 3). However, the study does have limitations and further research is needed in this area.

Feeding can be given via three principal routes: oral, enteral, or parenteral. Oral feeding is generally not possible in the critically ill patient. Enteral feeding, either through an oral or a nasal tube, or directly into the gastrointestinal (GI) tract via a gastrostomy or jejunostomy is the preferred method in critical care. Advantages of feeding via the enteral route as opposed to parenteral include cost, maintenance of GI tract structure and function, and a decreased risk of stress ulceration. Enteral feeding is also associated with a lesser incidence of hyperglycaemia, enhanced gut immune function, and possibly a lower risk of infections. Intolerance of enteral feeding is common in critically ill patients due to impaired GI motility. Patients at high risk of impaired GI motility include those with head injury, burns, sepsis, and multi-system trauma. Additionally, drugs commonly used in critical care (e.g. opioids, sedatives, adrenoceptor agonists, and proton-pump inhibitors and anticholinergics) can impair gastric motility. This can lead to complications including regurgitation causing ventilator-associated pneumonia and bacterial translocation from the gut causing sepsis. Success of enteral feeding can be maximized by the use of prokinetic agents and by post-pyloric feeding. Prokinetic agents encourage gastric motility by increasing both luminal transport and the force of contraction. The most commonly used prokinetic drugs in critical care patients are erythromycin 250 mg b.d. i.v. (motilin agonist) and metoclopramide 10 mg q.d.s. (dopamine D2 receptor antagonist). Combination therapy of the two agents may be beneficial with lower rates of tachyphylaxis reported compared with monotherapy. Successful enteral feeding has been defined as maintenance feeding of ≥40 ml h⁻¹ with 4 hourly NG aspirates totalling <250 ml. It is
however sometimes impossible to attain adequate nutrition enteral. In this situation, PN can be used to supplement or entirely meet nutritional requirements.²,⁴,⁵

Assessment of nutrition

Assessment of nutritional status is the first step in deciding the nutritional support required. In most clinical situations, the BMI is a useful indicator. With critically ill patients, a number of factors limit the use of BMI, including practical difficulties in weighing patients and the presence of oedema. Individual patients’ resting metabolic rate (RMR), possibly the gold standard method of assessment of energy requirements in an individual patient, can be assessed using indirect calorimetry. This however requires specialist equipment and is impractical for routine use on the intensive care unit (ICU). As a result, a number of different equations and methods for calculating estimated energy requirements have been developed. One of the most commonly used equations is the Schofield equation. This is not specific for critical care patients but estimates BMR (based on age, sex, and weight) with subsequent percentage adjustments for thermogenesis, activity, and additional stress factors (e.g., infection and trauma) to produce an estimated kilocalories per day requirement. (BMR and RMR are technically different, but in practical terms, there is little difference between the two.)

A problem with using calculations in the critically ill is the addition of activity, stress, and feeding factors to a BMR can lead to an apparent indication for sicker patients to receive very large quantities of energy. Although metabolic requirements of these patients are often high, they diminish quickly and since net catabolism cannot be stopped, they also receive considerable nutrient supply from the breakdown of their own tissues. This puts critically ill patients at potential risk of overfeeding, which results in worse outcomes and should be avoided. Study outcomes in intensive care patients showed that survival was best among patients receiving 33–66% of estimated nutritional needs compared with those who received fewer than 33, or >66% of them.⁶ NICE and ESPEN guidelines recommend calculation of nutritional requirements based on kilocalories per kilogram per day for calories and gram per kilogram per day for nitrogen in short-term feeding, and therefore, this may be the most appropriate method in critically ill patients.¹,² NICE recommends 25–35 kcal kg⁻¹ day⁻¹ and ESPEN recommends 20–25 kcal kg⁻¹ day⁻¹ in the initial phase of critical illness and 25–30 kcal kg⁻¹ day⁻¹ in the recovery/anaesthetic phase. It is difficult to be precise about an individual figure as often a major determinant of exact calorie content is determined by the constituent preparations/manufacturers’ formulae used, hence the use of a range rather than an exact figure.

PN administration

PN is generally supplied as an all-in-one complete balanced parenteral formulation and is usually administered continuously, ideally through a central venous catheter (CVC) via a dedicated lumen, or through a peripherally inserted central catheter (PICC line). If it is anticipated that this will be administered for more than 1 month, a tunnelled central venous line is usually inserted.

Line infection is a significant risk with administration of PN. This is minimized by:

(i) Strict asepsis when handling the line and connecting/disconnecting feeds.
(ii) The use of a dedicated lumen on a CVC or a PICC line for administration of PN.
(iii) Use of antimicrobial-coated lines.

Peripheral venous lines can be used to deliver low osmolality feeds. Peripheral PN that can provide full nutritional requirements tends to be of larger volume and greater fat content and limited by restrictions in electrolyte content to reduce osmolality, which overall reduces their routine application. Although there is some variation depending on the PN chosen, a typical comparison might be between a volume of 1.5 litre centrally vs 2.5 litre peripherally to give equivalent calories, nitrogen, and electrolytes.

Composition of PN

The composition of PN feeds can be varied according to the requirements of individual patients. Some PN manufacturers offer a broad range of “off-the-shelf” feeds that only require addition of vitamins, trace elements, and additional electrolytes to patients’ individual requirements. Some hospitals have an Aseptic Dispensing Unit that can compound feeds from basic components that are tailored even more closely to a patient’s needs. All additions to a PN regimen must be carried out in a sterile environment. The precise composition of PN varies in its carbohydrate, lipid, and protein formulation ratios between different preparations.

Carbohydrate

Carbohydrate is supplied as glucose. Tissues such as red blood cells, immune cells, and renal medullary cells which have no mitochondria are dependent on glucose supply for their energy through ATP production. Brain metabolism is also partially dependent on plasma glucose concentration: it can use lactate or ketones for energy supply when blood glucose decreases gradually. Brain metabolism accounts for the majority of blood glucose oxidation in the body. In the absence of an exogenous supply of glucose, the body can call upon hepatic glycogen stores and can synthesize glucose from lactate, lipids, and amino acids through gluconeogenesis.

The catabolic and relatively insulin-resistant state encountered in critical illness is thought to be a potential mechanism whereby glucose can be diverted away from less vital areas to help in wound healing (injured tissue has been shown to lack this insulin resistance) while providing substrate for gluconeogenesis through muscle breakdown. The aim of feeding is to attempt to minimize...
muscle loss while providing exogenous glucose to promote tissue healing.

Insulin resistance in the critically ill means that infusion of large amounts of glucose result in an increase in blood glucose levels. It has been documented that the maximum oxidation rate of glucose in the stressed patient is 4–7 mg kg\(^{-1}\) min\(^{-1}\) (or 400–700 g day\(^{-1}\) for a 70 kg patient). Therefore, in order to decrease the risk of metabolic alterations, the maximum rate of glucose infusion should probably not exceed 5 mg kg\(^{-1}\) min\(^{-1}\). For a 70 kg patient, this would be \(~\)2000 kcal glucose and this is not generally exceeded in standard PN regimes.

Hyperglycaemia has proinflammatory effects, and indeed outcomes in critically ill patients whose blood glucose levels are not controlled are poorer. The NICE-SUGAR study suggests that outcomes are best when blood glucose levels are kept below 10 mmol litre\(^{-1}\), with increased mortality secondary to hypoglycaemia being associated with more intensive control (4.5–6 mmol litre\(^{-1}\)).\(^{10}\) Besides the deleterious effects of infusion of large amounts of glucose on blood sugar levels, it has also been shown that supplying glucose at a rate greater than its maximum oxidation rate increases CO\(_2\) production in the critically ill patient, through lipogenesis (respiratory quotient, RQ of fat=0.7 and RQ of glucose=1). This can be detrimental to patients with respiratory failure, especially those who are experiencing difficulty in weaning.

**Lipid**

The use of lipid in PN regimens has a number of advantages. It is a source of essential fatty acids, which have vital roles in the maintenance of cell membrane structure and function, and in modulating immune and inflammatory responses. It is a concentrated energy source and has a lower osmolality compared with glucose.

Lipids, however, have been associated with immune dysfunction, decreases in oxygenation and pulmonary function and with hepatic steatosis when given parenterally. The proportion of carbohydrate to lipid in any given PN formula varies as indeed do individual patients’ needs at any particular point in their illness.

The fatty acids linoleic acid and α-linoleic acid cannot be synthesized in the body and are thus essential. They are present in large quantities in soybean oil, and hence this is used as the lipid source in many PN preparations. However, soybean oil is rich in omega 6-long-chain triglycerides (LCTs) which have theoretical disadvantages (e.g. platelet aggregation and impairment of immune function) which have led to the development of several alternatives which vary in the fatty acid chains attached to the glycerol moiety. Medium-chain triglycerides (MCTs) such as may be found in coconut oil, for example, can be cleared from the blood stream more rapidly and this may improve tolerance and limit long-term adverse effects on the liver. It is thought that PN containing mixtures of LCTs and MCTs are associated with better outcomes in the critically ill, in terms of nutritional markers, physiological parameters, and disease outcome, although this does need validation in a prospective randomized controlled trial. Olive oil-based lipid products contain a high proportion of the monounsaturated fatty acid, oleic acid. This may reduce oxidative damage and improve immune function and lipid profiles in the short term.\(^{11}\) The addition of fish oil, which contains the anti-inflammatory omega 3 fatty acids eicosapentanoic acid and docosahexaenoic acid, may decrease synthesis of inflammatory eicosanoids and result in better patient outcomes.

**Protein**

Protein, given as amino acid mixes in PN, is not given as an energy substrate but in order to replace nitrogen losses and in an attempt to prevent further skeletal muscle breakdown. Calculation of actual nitrogen balance in critically ill patients is difficult, so usually 0.13–0.24 g kg\(^{-1}\) day\(^{-1}\) of nitrogen is given (again based on NICE guidance and the practicalities of administration, although we would estimate and aim to administer 0.2 g kg\(^{-1}\) day\(^{-1}\), towards the higher end of the range for the first 24–48 h, until the patient has had a nutrition/dietician review). In critical illness, glutamine, an amino acid which participates in many metabolic processes, becomes an essential amino acid. This is because the increased utilization of glutamine in the critically ill exceeds the endogenous production rate causing plasma levels to decrease. Low glutamine plasma levels have been associated with a worse outcome in some studies, although it is controversial whether glutamine supplementation in PN has been shown to improve patient morbidity, mortality, and length of hospital stay.\(^ {12}\)

**Trace elements, vitamins, and electrolytes**

Trace elements such as copper, zinc, and selenium are not present in commercially produced PN solutions for stability reasons, and these must be prescribed separately. Assessment of trace element status on the ICU is impossible due to the effects of the acute phase response; however, increased losses of these can be anticipated in particular pathological states, for example, patients with burns often have large losses of copper, zinc, and selenium, while those on renal replacement therapy require extra selenium, zinc, and thiamine. Supplementation with selenium, an important component of the antioxidant glutathione peroxidase, has been shown to improve outcome in patients with sepsis and possibly to reduce the number of new infections on ICU.\(^ {13}\)

NICE guidelines state that vitamins must also be included in every feed. Thiamine and B-vitamin replacement is important in intensive care patients who may have preexisting deficiency, for example, alcoholics, in order to avoid possible neurological complications.

Electrolytes and fluid should be given as part of PN based on typical daily requirements, clinical state, and monitored serum levels. Electrolytes are sometimes prescribed as acetate or phosphate and chloride salts in order to minimize the risk of developing hyperchloraemic acidosis.
**Refeeding syndrome**

All patients who have had no or very little nutritional intake for >5 days are at risk of refeeding syndrome, which is associated with severe electrolyte abnormalities including hypokalaemia, hypomagnesaemia, and hypophosphataemia, caused by movement of phosphate, fluids, and other electrolytes intracellularly after a sudden carbohydrate load. A history of alcohol abuse or being on drugs such as insulin, chemotherapy, antacids, or diuretics are risk factors for developing refeeding syndrome. Refeeding syndrome can be associated with respiratory, cardiac, and neuromuscular complications. NICE guidelines advise commencing nutritional support at 50% of estimated energy requirements for 2 days in patients at risk of refeeding syndrome, thereafter increasing by 200–400 kcal every day. Nutrients and fluids should not be initiated without electrolytes and micronutrients. Close monitoring of serum potassium, magnesium, and phosphate levels is required once feeding has been initiated. Sample regimens for PN are illustrated (Table 1).

### Monitoring

Surveillance of all patients on PN should be ongoing. Metabolic status, in terms of regular blood glucose level assessment, and at least daily urea, creatinine, and electrolytes including chloride, bicarbonate, phosphate, and magnesium should be performed. Plasma triglyceride levels should be monitored regularly. In critical illness, there are no known good nutritional markers: markers which traditionally reflect nutritional status such as albumin and prealbumin do not reflect the true status of the patient. A better marker of a critically ill patient’s nutritional status may be wound healing and general clinical status. Signs of infection must be actively sought on a regular basis and aggressively treated at an early stage, by removal of the infective stimulus and specific antimicrobial therapy.

A recent NCEPOD report on current UK practice and standards observed surrounding the administration of PN showed that ‘good practice’ was observed in only 19% of cases. Deficiencies in monitoring and assessment of patients on PN were observed in 54% of cases and metabolic complications related to PN occurred in 40% of cases, in which 49% of these complications were deemed ‘avoidable’. Hence, there is much room for improvement.

### Stopping PN

There has been interest in the idea of ‘topping up’ EN with PN in those who are not meeting daily calorie targets. Early signs are that this may improve patient outcomes.

There are no guidelines regarding when to cease PN; however, in view of what is known regarding the deleterious effects of malnutrition, and the large energy deficits that can accumulate in critical care patients, perhaps the best strategy would be to stop it when delivery of the patient’s daily energy needs are consistently achieved through enteral means.

### Conclusion

Malnutrition in critical care patients is associated with poor outcomes and patient harm. Initiation of adequate nutritional support within 48 h of admission to ICU is therefore important. EN is the first-line route, but due to many factors, there is often a need to use PN. Prescriptions for PN need to be individualized to the patient based on premorbid status and current physiological needs and should involve a multidisciplinary team approach. Close daily laboratory monitoring is required along with strict line sterility precautions to prevent infection.

### Declaration of interest

None declared.

### References


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**Table 1** Example PN prescriptions. For an average 70 kg patient without significantly complicating factors such as renal failure

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Please see multiple choice questions 1–4.