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Nutrition in critical care

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Learning objectives

By reading this article, you should be able to:

- Describe how to assess the nutritional risk of the critically ill patient.
- Discuss the risks and benefits of starting enteral nutrition (EN) in critical illness.
- Recall the indications for supplemental or total parenteral nutrition (PN).

Key points

- Nutritional status should be assessed clinically for all patients on admission to ICU, though the value of scoring tools remains controversial.
- If haemodynamically stable, enteral nutrition (EN) is recommended as first-line and should be started within 48 h of admission.
- Where EN is contraindicated or insufficient, parenteral (PN) should be used for supplementation or replacement.
- New evidence suggests PN may be no riskier than EN.
- Most studies of supplementation with micronutrients or using specific nutrient blends have shown either no benefit or harm, except in specific subgroups.

The optimal approach to nutrition in critical illness is unknown despite numerous RCTs over the past decade. This article is an update on previous articles in this journal on nutrition (2007) and parenteral nutrition (2013).[1,2]

So why feed?

The aim of nutritional support is to attenuate the detrimental effects of critical illness on nutritional state, such as increased energy deficit and catabolism; it may favourably influence outcomes and prevent or reverse malnutrition,[3,4] Currently, it is unknown how long starvation in critical illness can last without harmful consequences, but most guidance agrees that nutritional therapy should be started as soon as possible and certainly within the first week of critical illness.

Nutritional assessment

The UK's National Institute for Health and Care Excellence (NICE) recommends the screening on admission to hospital and regular reassessment of adult nutritional intake, using a validated tool such as the Malnutrition Universal Screening Tool (MUST).[5] A five-step tool, MUST identifies adults who are obese, malnourished, or at nutritional risk. MUST uses BMI, weight loss, and an acute disease effect score to give an overall malnutrition risk.

In 2016, the American Society of Parenteral and Enteral Nutrition (ASPEN) and Society of Critical Care Medicine (SCCM) guidelines recommended that if high risk (score $\geq$2) and where insufficient oral intake is anticipated, a dietician or nutrition team perform a formal nutritional risk assessment, using a scoring system such as the Nutritional Risk Screening (NRS-2002) or Nutrition Risk in the Critically Ill (NUTRIC) score.[3] NUTRIC stratifies patients as low (score 0–4) or high (score 5–9) risk, based on comorbidities and clinical condition to help individualise nutrition to current circumstances and disease state.[3]

However, the most recent European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines contest this.[4] MUST and NRS-2002 are not specific for critical illness and

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although NUTRIC was designed for such patients, NUTRIC has not been validated in the ICU and does not improve mortality,[4,6] ESPEN recommends a general clinical assessment (looking for a history of and examination, pre-ICU weight loss or a decline in physical performance decline before admission to ICU, and examination of, muscle mass, body composition and strength); and that patients admitted to ICU for >48 h should be considered at high risk for malnutrition.[4]

During acute illness, the aim is to meet patient energy expenditure (EE), thus decreasing negative energy balance. Ideally, EE should be determined using indirect calorimetry (IC), which measures oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$). ESPEN recommends that if IC is unavailable, $\dot{V}CO_2$ only (derived from the ventilator) or $\dot{V}O_2$ only (derived from a pulmonary artery [PA] catheter) will estimate EE more accurately than feeding equations.[4] However, obtaining such values routinely in UK practice may be difficult, particularly with the declining use of the PA catheter.

If unavailable, feeding equations (e.g. Harris-Benedict, Schofield)—using sex, weight, height, age, and activity level—approximate EE but vary up to 60%.[4] Failing these assessments, patients should receive 25 kcal kg^{-1} day^{-1} of feed, increasing to target over 2–3 days.[3] The Tight Calorie Control Study (TICACOS) compared nutrition guided by resting EE (intervention) with a weight-based regimen (control: 25 kcal kg^{-1} day^{-1}) during critical illness. The results were slightly conflicting, with longer durations of ICU stay and artificial ventilation but lower mortality in the intervention group.[7]

In the Early Goal-Directed Nutrition in ICU Patients (EAT-ICU) study, early-goal directed nutrition (EGDN) (with enteral nutrition [EN] and supplemental parenteral nutrition [PN]) and using measurements from IC and 24 h urinary urea excretion was compared with standard care (EN within 24 h and supplemental PN after 7 days if less than a 25 kcal kg^{-1} day^{-1} target was achieved) in a single-centre RCT.[8] EGDN resulted in greater energy and protein delivery with more episodes of hyperglycaemia episodes (blood glucose $\geq$15 mmol L^{-1}), greater use of insulin, and increased plasma urea. There was, however, no increase in renal replacement therapy (RRT) need and no differences found in any clinical outcome at 6 months.

Certain disease subgroups (e.g. patients with extensive burns patients) may have greater nutritional requirements than in health. Though a one-size approach to energy and nutritional replacement probably does not fit all, individualised EE targets appear to confer no additional benefit.

When to start feeding?

Enteral nutrition

ESPEN and ASPEN both recommend that EN should start within 48 h of ICU admission, preferably once haemodynamic stability is achieved.[3,9] The trials we have reviewed defined 'early' as starting feed as soon as feasible, at most within 48 h. There are two approaches: trophic (increasing from 10 to 20 ml h^{-1}, 1 kcal ml^{-1}) or full feeding. Trophic feeding has been found to be safe, with fewer gastrointestinal complications and is recommended up to 6 days from admission to ICU.[3]

The Permissive Underfeeding or Standard Enteral Feeding in High- and Low-Nutritional-Risk Critically Ill Adults Trial (PERMIT) randomised 894 patients to permissive underfeeding (40–60% of caloric requirement) or standard feeding (70–100% caloric requirement) with similar protein intake targets (1.2–1.5 g kg^{-1} day^{-1}). There was no difference in 90 day mortality or other outcomes, regardless of nutritional risk.[6] The Initial Trophic *vs* Full Enteral Feeding in Patients With Acute Lung Injury trial (EDEN) recruited 1000 predominantly medical patients with acute lung injury (ALI) to either trophic (400 kcal day^{-1}) or full (1300 kcal day^{-1}) EN. Trophic EN for up to 6 days did not improve ventilator-free days, 60-day mortality, or infectious complications, but was associated with less gastrointestinal intolerance.[10]

First-line, EN should be delivered to the stomach via a nasogastric tube. There is no evidence that post-pyloric feeding is superior to nasogastric feeding.[3] In addition, post-pyloric feeding is more complex and requires input from the radiology or gastroenterology teams. However, in patients at high risk of pulmonary aspiration, switching from bolus to continuous feeding may be safer; and post-pyloric feeding may be indicated should this fail.[3] Administration of prokinetic drugs early in those at risk may improve tolerance and reduce the incidence of aspiration further[3]: erythromycin is recommended as the first-line agent, with metoclopramide a second-line addition or alternative.[4]

Gastric residual volumes (GRVs) of <500 ml do not correlate with the risk of aspiration.[3] One study suggests GRV monitoring makes no difference to the incidence of ventilator-associated pneumonia. EN should not be stopped because of diarrhoea unless no other aetiology for the diarrhoea is found, and the rate should only be reduced if GRVs exceed 500 ml.[3]

During haemodynamic instability, timing is problematic. Ideally, patients should be fully resuscitated and vasopressors stopped before EN is commenced. However, where prolonged vasopressor therapy is anticipated, EN should be started with cautious monitoring for signs of intolerance.[3]

Parenteral nutrition

The optimal timing for starting PN timing in critical illness remains unknown. ESPEN recommends starting PN after 3–7 days if the patient cannot tolerate EN.[4] However, early PN has not been found to alter mortality or other critical care outcomes. ESPEN recommends exhausting all EN strategies before considering supplemental PN, case by case. Compared with PN, no nutritional therapy for 14 days from ICU admission is associated with greater mortality (21 *vs* 2%, $P<0.05$) and longer hospital stay (36.3 *vs* 23.4 days, $P<0.05$).[11]

The Early *vs* Late Parenteral Nutrition in Critically Ill Adults (EPaNIC) trial compared early (day 3) and late (day 8) PN initiation in those at risk of malnutrition.[12] Late initiation was associated with improved ICU survival, shorter mechanical ventilation duration, and less need to RRT. The EPaNIC trial showed no benefits from additional PN in patients who could receive EN. The early PN group had higher infection rates and healthcare costs.[12]

The Early PN Trial compared early PN in critically ill adults with relative contraindications to early EN with a standard regimen of EN, PN, or no early feeding, and found no difference in 60 day mortality or ICU infection rates.[13]

Enteral *vs* parenteral nutrition

The Trial of the Route of Early Nutritional Support in Critically Ill Adults (CALORIES) aimed to answer whether EN was superior to PN.[14] It randomised 2388 adults within 36 h of unplanned ICU admission to EN or PN. Early PN was found to be

neither harmful nor beneficial compared with EN. EN was found to increase episodes of vomiting and hypoglycaemia (but without evidence of harm), infectious complications, and 30 day mortality (33.15% PN *vs* 34.2% EN, P=0.57). One criticism was most patients in both groups did not achieve the 25 kcal kg^{-1} day^{-1} target.

The Enteral *vs* Parenteral Early Nutrition in Ventilated Adults with Shock trial (NUTRIREA-2) found neither early (within 24 h) isocaloric (20–25 kcal kg^{-1} day^{-1}) EN nor PN improved mortality or secondary infection risk.[15] Early EN was associated with more severe gastrointestinal complications and a four-times increase in bowel ischaemia. Both NUTRIREA-2 and CALORIES found no benefit of EN over PN and reveal EN is not as harmless as previously thought.

EN remains recommended as the first-line strategy in critical illness, with total or supplemental PN considered where EN is contraindicated, complications develop, or energy targets are unmet. Early EN during haemodynamic instability may not be beneficial and may cause harm. Early nutritional support (EN or PN) does not appear to improve ICU mortality. An aid to nutritional support in critical illness can be found in Fig. 1.

PN prescription and formulation

PN must be prescribed by those trained in its use. Standard PN formulations are now available in preformulated combination bags with an admixture of solutions containing lipid (about 40% of non-protein calories), carbohydrate/glucose (60% of non-protein calories), amino acids, electrolytes, vitamins, minerals, and trace elements. Basal requirements for nutrients are summarised in Table 1.[5,16] The exact compositions and infusion rates can be tailored to the patient's needs. PN should be delivered via a dedicated central venous catheter (CVC) or peripherally inserted central catheter (PICC) lumen. PN lasting fewer than 3 months does not require a tunnelled line (e.g. Hickman); PICCs are equally safe.[17]

Table 1 Basal nutritional requirements in critical illness.[3,5] Note that these are basal requirement and may need to be increased in certain patients such as those with burns. Please see text for more details

Nutritional requirement	Per day (maintenance)
Water	30 ml kg^{-1}
Sodium (Na^+), Chloride (Cl^-)	1–2 mmol kg^{-1}
Potassium (K^+)	0.8–1.2 mmol kg^{-1}
Calcium (Ca^{2+}), Magnesium (Mg^{2+})	0.1 mmol kg^{-1}
Phosphate	0.2–0.5 mmol kg^{-1}
Energy	25 kcal kg^{-1}
Carbohydrate	2 g kg^{-1}
Protein	0.8–1.2 g kg^{-1}
Fat	1 g kg^{-1}

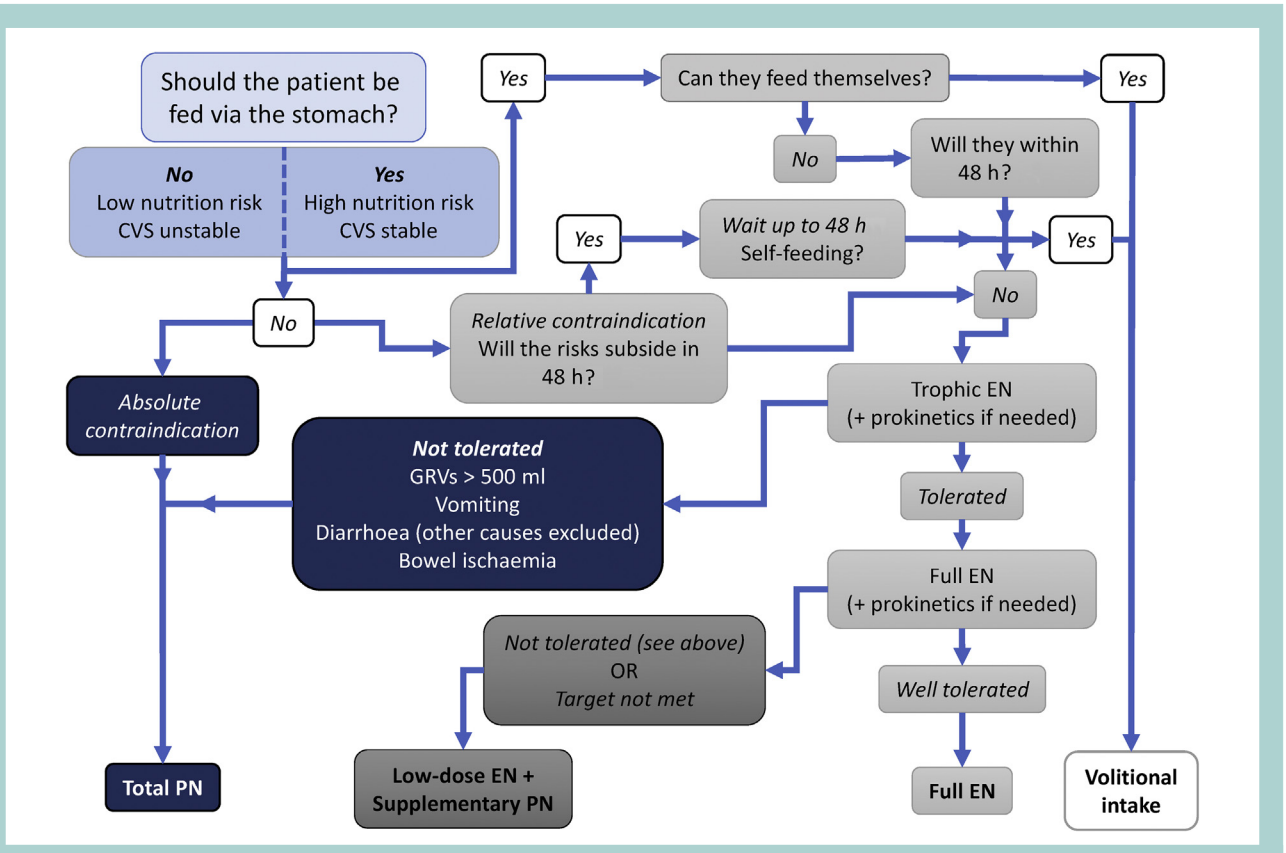

Fig 1 Aid to decision-making for nutritional support during critical illness. This should be used as a guide and specific decisions regarding nutrition should be made on an individual basis. CVS, cardiovascular system.

Carbohydrate

Glucose is the main carbohydrate in PN with concentrations of 40%, 50%, and 70%. ESPEN recommends <5 mg kg^{-1} min^{-1}.[4]

Protein

Optimal protein intake during critical illness is unknown, although ESPEN recommends 1.3 g kg^{-1} day^{-1} delivered progressively.[4] The Timing of PROTein INtake and clinical outcomes of adult critically ill patients on prolonged mechanical VENTilation (PROTINVENT) study demonstrated a time-dependent association between protein intake and ICU mortality.[18] A low protein intake (<0.8 g kg^{-1} day^{-1}) before day 3 combined with a high protein intake (>0.8 g kg^{-1} day^{-1}) after day 3 was associated with lower 6 month mortality (adjusted hazard ratio [HR], 0.609; 95% confidence interval [CI], 0.480–0.772, $P<0.001$) compared with patients with overall low (<0.8 g kg^{-1} day^{-1}) or high protein intake (>1.2 g kg^{-1} day^{-1}). PN must provide all essential amino acids, for example histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine.

In critical illness, synthesis of certain amino acids may be insufficient through increased demand. These are 'conditional' amino acids: arginine, cysteine, glutamine, tyrosine, glycine, ornithine, proline, and serine. It is unclear whether these should be replaced.

Glutamine facilitates nitrogen transport and may reduce protein catabolism. Low plasma glutamine is associated with poorer outcomes. One small trial ($n=45$) reviewed by ASPEN suggested some benefit of glutamine supplementation in burns although insufficient to justify a recommendation. Other trials have shown either harm or no benefit; one found early glutamine administration in critical illness with multi-organ failure increased in-hospital and 6 month mortality.[3] Routine glutamine supplementation is not recommended.

Only one trial has examined the effects of arginine supplementation. In patients with severe sepsis and APACHE (acute physiology and chronic health evaluation) II scores between 10 and 15, arginine supplementation reduced bacteraemia and nosocomial infection incidence. However, supplementation made no difference to mortality in other groups when administered alongside other immune-modulating formulas. Routine arginine supplementation is not recommended.[3]

Non-essential amino acids which are produced in the body include alanine, asparagine, aspartic acid, and glutamic acid.

Lipids

The high calorific content of lipids makes them fundamental in nutritional support. They also provide essential fatty acids such as linoleic acid (LA), omega-6 (n-6) polyunsaturated fatty acid (PUFA), and omega-3 (n-3) PUFA α-linolenic acid (ALA) and their derivatives have important biological functions. LA is the metabolic precursor of arachidonic acid (ARA) and ALA is the precursor of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).[19]

Lipids are essential for cell membrane synthesis and assist delivery of fat-soluble vitamins (i.e. A, D, E, K). Lipids for nutritional support tend to be delivered as triglycerides. These may be as medium-chain fatty acids (medium-chain triglycerides [MCTs]; e.g. capric, caprylic, myristic, or lauric acids), long-chain (long-chain triglycerides [LCTs]; e.g. α-linolenic, linoleic, oleic, and palmitic acids), or very long-chain fatty acids (e.g. DHA and EPA).

Different fatty acids, their blend, and administration route (e.g. EN *vs* PN) can influence many physiological, immune, and metabolic processes. The ideal lipid emulsion (LE) blend and route has yet to be determined, but should be tailored to type of patient, critical illness severity and overall nutritional needs. Many different LEs are now available, including vegetable soybean oil (SO; rich in both n-6 PUFA and LA), MCTs (usually from coconut oil), olive oil (OO; containing oleic acid), and fish oils (FO; which contain EPA and DHA). ESPEN recommends that immune-modulating EN formulae be enriched with arginine and omega-3 fatty acids. Nucleotides may be superior to standard EN formulations in only certain subgroups (e.g. surgery and trauma).[9] In severe sepsis, immune-modulating EN may be harmful and is not recommended.

Omega-3-polyunsaturated fatty acids have many anti-inflammatory properties. However, despite this the Enteral Omega-3 Fatty Acid, α-Linolenic Acid, and the Antioxidant Supplementation in Acute Lung Injury (OMEGA) trial found patients given omega-3 fatty acids had fewer ventilator-free days and longer ICU stays.[19] In 2014, a multicentre trial performed by Koekkoek and colleagues[18] compared standard high-protein EN with standard high-protein EN enriched with glutamine, omega-3 PUFAs, selenium, and anti-oxidants with no effect on clinical endpoints. On subgroup analysis, medical ICU patients had a higher 6 month mortality.[19]

ESPEN recommends lipids as an essential part of PN but in doses not exceeding 1.5 g kg^{-1} day^{-1}.[4] PN with pure SO may worsen surgical-related stress and inflammatory response. ASPEN recommends SO-based PN be withheld in the week after PN initiation or limited to 100 g $week^{-1}$ if there are concerns over fatty acid deficiency with other groups recommending against pure SO-based PN.[3,19] OO-based LEs appear safe and well tolerated in critical illness, although there is no consistent evidence they are superior to SO-based LEs. The combination of mixed SO/MCT-based LEs instead of pure SO may be better than SO alone. FO-enriched EN and PN (with EPA and DHA) seems well tolerated and confers further benefits (e.g. reduced complications and shorter ICU and hospital stay) in surgical ICU patients.[19] Research on FO-enriched nutrition in medical ICUs is inconclusive, and further trials are needed.

Vitamins and trace elements

Micronutrients (trace elements and vitamins) appear to modulate the immune and inflammatory response ('immunonutrition') and need consideration during nutritional support. Many micronutrients are antioxidants. PN does not contain trace elements or vitamins because of instability. It requires separate prescribing and adding under controlled aseptic pharmaceutical conditions. Micronutrients are often omitted in more than half of ICU patients. Trace elements and vitamins include: thiamine (B_1), ascorbic acid/vitamin C, vitamin B_{12}, folate, fat-soluble vitamins (vitamins A, D, E, and K), copper, selenium, zinc, chromium, cobalt, fluoride, iron, iodine, manganese, molybdenum, and vanadium. Several trials have examined micronutrient supplementation beyond minimum requirements.

Selenium supplementation in the Randomised Trial of Glutamine and Selenium Supplemented Parenteral Nutrition for Critically Ill Patients (SIGNET) demonstrated no benefits in terms of infectious complications or mortality.[3]

Although vitamin D deficiency is associated with poorer patient outcomes, the Effect of High-Dose Vitamin D_3 on

Hospital Length of Stay in Critically Ill Patients With Vitamin D Deficiency (VITdAL-ICU) study in 2014, found routine supplementation with high-dose vitamin D did not improve hospital length of stay or 6 month mortality; however, patients with severe deficiency may benefit. ESPEN recommends single high-dose vitamin D_3 administration (500 000 IU) within a week of admission where 25-hydroxy-vitamin D plasma concentrations <12.5 ng ml^{-1}.[4]

Overall, despite evidence showing certain nutrients modulate inflammatory and immune responses, routine supplementation is mostly associated with harm.

Complications of PN

Although the CALORIES and NUTRIREA-2 trials concluded that complications from PN with good CVC care may be less problematic than previously thought,[14,15] they are still significant. The incidence of CVC-associated infection (bacterial/fungal) was higher in patients who receive PN compared with those who did not. Infection is also higher when hygiene is poor, with emergency CVC insertion, increasing illness severity and duration of CVC use. Metabolic complications of PN include hyperglycaemia, electrolyte abnormalities, Wernicke's encephalopathy, nutrient excess or deficiency, liver dysfunction, and refeeding syndrome. Although these are rare, routine monitoring of glucose, fluids, and electrolytes is warranted.

Special groups of patients

ASPEN's most recent guidelines make specific recommendations for certain groups of patients. These include patients with: acute respiratory distress (ARDS), acute kidney injury (AKI), hepatic failure, acute pancreatitis, sepsis, trauma, traumatic brain injury (TBI), spinal cord injury, open abdomen, burns, postoperative major surgery, critical illness recovery, and those who have chronic critical illness, obesity, and those at the end of life.[3] Detailed discussion of each subgroup is beyond the scope of this article. However, some are briefly discussed below.

Refeeding

Refeeding syndrome is a clinical condition that results from restarting nutrition after starvation. Increased phosphate uptake by cells on starting feed can result in a marked reduction in serum phosphate, causing severe hypophosphataemia, low potassium, and magnesium. Severe hypophosphataemia may manifest as confusion, delirium, seizures, respiratory failure, rhabdomyolysis, and cardiovascular collapse warranting prompt recognition and management. The refeeding syndrome trial found that a protocol for restricting caloric intake over the first few days compared with no restriction in those with refeeding syndrome (serum phosphate <0.65 mmol L^{-1}) improved 60 day mortality and was associated with fewer respiratory infections.[3]

Acute pancreatitis

In severe acute pancreatitis, early EN feeding failed to improve outcomes in comparison with on-demand feeding delayed to 72 h. Allowing patients 3–4 days to start volitional oral intake appeared safe and effective.[3] The respective roles and benefits of EN compared with vs PN remains an areas of contention.

Summary

Overall, providing nutrition within a week of admission appears to convey benefit for patients in ICU. When there is cardiovascular stability, nutrition should be started as soon as possible and ideally within 48 h of admission. If the patient is haemodynamically unstable, there is no clear answer to the timing of feeding; the risks of starvation must be weighed against the risk of adverse effects.

Feeds should be increased to target over 2–3 days (slower if at refeeding risk) and GRVs <500 ml should not be used to assess tolerance to feeding. Although EN remains first-line, the CALORIES and NUTRIREA-2 studies have shown that PN may be less risky than previously thought; if monitored and administered correctly, PN is safe as an alternative to EN.

With few exceptions, most attempts at modulating standard formulations have been of no benefit or harmful. In general, first-line nutritional support in ICU should be standard formulation EN within 48 h of admission with PN replacement where necessary. Supplemental PN should be considered on a case-by-case basis.

Declaration of interest

The authors declare that they have no conflicts of interest.

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MCQs

The associated MCQs (to support CME/CPD activity) will be accessible at www.bjaed.org/cme/home by subscribers to *BJA Education*.

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