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ESPEN Guidelines on Parenteral Nutrition: Surgery

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SUMMARY

In modern surgical practice it is advisable to manage patients within an enhanced recovery protocol and thereby have them eating normal food within 1–3 days. Consequently, there is little room for routine perioperative artificial nutrition. Only a minority of patients may benefit from such therapy. These are predominantly patients who are at risk of developing complications after surgery. The main goals of perioperative nutritional support are to minimize negative protein balance by avoiding starvation, with the purpose of maintaining muscle, immune, and cognitive function and to enhance postoperative recovery.

Several studies have demonstrated that 7–10 days of preoperative parenteral nutrition improves postoperative outcome in patients with severe undernutrition who cannot be adequately orally or enterally fed. Conversely, its use in well-nourished or mildly undernourished patients is associated with either no benefit or with increased morbidity.

Postoperative parenteral nutrition is recommended in patients who cannot meet their caloric requirements within 7–10 days orally or enterally. In patients who require postoperative artificial nutrition, enteral feeding or a combination of enteral and supplementary parenteral feeding is the first choice.

The main consideration when administering fat and carbohydrates in parenteral nutrition is not to overfeed the patient. The commonly used formula of 25 kcal/kg ideal body weight furnishes an approximate estimate of daily energy expenditure and requirements. Under conditions of severe stress requirements may approach 30 kcal/kg ideal body weights.

In those patients who are unable to be fed via the enteral route after surgery, and in whom total or near total parenteral nutrition is required, a full range of vitamins and trace elements should be supplemented on a daily basis.

Preliminary remarks

In modern surgical practice it is advisable to manage patients within an enhanced recohave them eating normal food within 1–3 days. Consequently, there is little room for routine perioperative artificial nutrition. Only a minority of patients may benefit from such therapy. These are predominantly patients who are at risk of developing complications after surgery, namely patients who have suffered substantial weight loss, have very low body mass index (BMI) (under 18.5–22 kg/m^2 depending on age) or exhibit inflammatory activity. Once patients have developed infectious complications artificial nutritional support is generally required. It is difficult, if not ethically unacceptable, to randomize this subgroup into those that do or do not receive nutritional support.

The main goals of perioperative nutritional support are to minimize negative protein balance by avoiding starvation, with the purpose of maintaining muscle, immune, and cognitive function and to enhance postoperative recovery.

Energy substrates can be given either by the enteral or parenteral route. Several studies[1–24] have suggested a better outcome when at least part of the patient's requirement is met by the enteral route. There is some agreement that parenteral nutrition, when administered to patients who also tolerate enteral nutrition or who are not malnourished causes more harm than benefit. It has been suggested that this cannot be fully explained by the facts that in the older studies patients were often hyperalimented, only received carbohydrates as energy source, or did not receive proper glucose control. However, one meta-analysis rigidly controlling for the items mentioned, did not confirm a deleterious effect of parenteral nutrition (PN).[25] In cases of prolonged gastrointestinal dysfunction,

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Summary of statements: Surgery			
Subject	**Recommendations**	**Grade**	**Number**
Indications	Preoperative fasting from midnight is unnecessary in most patients	A	Preliminary remarks
	Interruption of nutritional intake is unnecessary after surgery in most patients	A	Preliminary remarks
Application	Preoperative parenteral nutrition is indicated in severely undernourished patients who cannot be adequately orally or enterally fed	A	1
	Postoperative parenteral nutrition is beneficial in undernourished patients in whom enteral nutrition is not feasible or not tolerated	A	2
	Postoperative parenteral nutrition is beneficial in patients with postoperative complications impairing gastrointestinal function who are unable to receive and absorb adequate amounts of oral/enteral feeding for at least 7 days	A	2
	In patients who require postoperative artificial nutrition, enteral feeding or a combination of enteral and supplementary parenteral feeding is the first choice	A	2
	Combinations of enteral and parenteral nutrition should be considered in patients in whom there is an indication for nutritional support and in whom >60% of energy needs cannot be met via the enteral route, e.g. in high output enterocutaneous fistulae or in patients in whom partly obstructing benign or malignant gastro-intestinal lesions do not allow enteral refeeding. In completely obstructing lesions surgery should not be postponed because of the risk of aspiration or severe bowel distension leading to peritonitis	C	2
	In patients with prolonged gastrointestinal failure parenteral nutrition is life-saving	C	2
	Preoperative carbohydrate loading using the oral route is recommended in most patients. In the rare patients who cannot eat or are not allowed to drink preoperatively for whatever reasons the intravenous route can be used	A	3
Type of formula	The commonly used formula of 25 kcal/kg ideal body weight furnishes an approximate estimate of daily energy expenditure and requirements. Under conditions of severe stress requirements may approach 30 kcal/kg ideal body weight	B	4
	In illness/stressed conditions a daily nitrogen delivery equivalent to a protein intake of 1.5 g/kg ideal body weight (or approximately 20% of total energy requirements) is generally effective to limit nitrogen losses	B	4
	The Protein:Fat:Glucose caloric ratio should approximate to 20:30:50%	C	4
	At present, there is a tendency to increase the glucose:fat calorie ratio from 50:50 to 60:40 or even 70:30 of the non-protein calories, due to the problems encountered regarding hyperlipidemia and fatty liver, which is sometimes accompanied by cholestasis and in some patients may progress to non-alcoholic steatohepatitis	C	5
	Optimal nitrogen sparing has been shown to be achieved when all components of the parenteral nutrition mix are administered simultaneously over 24 hours	A	6
	Individualized nutrition is often unnecessary in patients without serious co-morbidity	C	7
	The optimal parenteral nutrition regimen for critically ill surgical patients should probably include supplemental *n*-3 fatty acids. The evidence-base for such recommendations requires further input from prospective randomised trials	C	8
	In well-nourished patients who recover oral or enteral nutrition by postoperative day 5 there is a little evidence that intravenous supplementation of vitamins and trace elements is required	C	9
	After surgery, in those patients who are unable to be fed via the enteral route, and in whom total or near total parenteral nutrition is required, a full range of vitamins and trace elements should be supplemented on a daily basis	C	9
	Weaning from parenteral nutrition is not necessary	A	10

PN should be given until enteral function returns. The most important situations where enteral nutrition is contraindicated (thereby suggesting mandatory total parenteral nutrition), are intestinal obstruction, malabsorption, multiple fistulas with high output, intestinal ischemia, severe shock with impaired splanchnic perfusion, and fulminant sepsis.[24]

To devise a nutritional support regimen for patients undergoing surgery, the basic changes in body metabolism that occur as a result of injury should be understood. In addition, recent studies have shown that not only surgery itself influences the response to nutritional support, but also many of the perioperative routine practices have a major impact on how well nutritional support is tolerated by the postoperative patient.[26]

Surgery, like any injury to the body, elicits a series of reactions including release of stress hormones and inflammatory mediators. This release of mediators to the circulation has a major impact on body metabolism. They cause catabolism of glycogen, fat and protein with release of glucose, free fatty acids and amino acids into the circulation, so that substrates are in part diverted from the purposes they serve in the non-stressed state (i.e. physical activity) to the task of raising an adequate healing response. For optimal rehabilitation and wound healing, the body needs to be well nourished to mobilise adequate substrates, largely derived from muscle and adipose tissue, with nutritional support to allow synthesis of acute phase proteins, white cells, fibroblasts, collagen and other tissue components of the wounded area.

Recent studies have shown that measures to reduce the stress of surgery can minimize postoperative insulin resistance, possibly improving the ability to tolerate normal nutrition, but also allowing patients to recover faster, even after major surgical operations. The effects on morbidity and mortality still need to be studied. Such programmes for enhanced recovery after surgery[26] involve multiple components that combine to minimize stress and to facilitate the return of function. These include preoperative preparation and medication, fluid balance, anaesthesia and postoperative analgesia regimens, perioperative nutrition, and mobilization.[26]

Traditionally, many patients undergoing major gastrointestinal resections receive large volumes of crystalloids intravenously during and after surgery. It was suggested that fluids and electrolytes were given in excess, resulting in substantial weight gain and oedema. It was also suggested that this overload was a major cause of postoperative ileus and delayed gastric emptying.[27–29] When fluids were restricted to the amount needed to maintain salt and water balance, gastric emptying returned sooner and patients were capable of tolerating normal food and had bowel movements several days earlier than those in positive balance. However, this claim has not been consistently supported by later studies.[26,30] The adverse effects of opioids used for pain relief can be avoided or substantially minimized by applying epidural analgesia in combination with general anaesthesia. This especially improves cognitive function and bowel peristalsis.

In recent years the traditional guidelines to fast patients overnight before elective surgery have been abandoned. The traditional routine was not based on solid evidence,[31] while the evidence showing benefits and no harm when free intake of clear fluids was allowed until 2 h before anaesthesia was substantially stronger.[32] Consequently, many anaesthesiology societies have changed their

guidelines regarding fasting.[33] This change in guidelines was prompted by the absence of evidence that fasting reduced the risks of aspiration. Allowing patients to drink also relieves the feeling of thirst that many patients experience before surgery.

During the past decade, the metabolic effects of undergoing surgery in an overnight fasted state have been studied extensively and compared with the fed state.[34] The fed state may be induced prior to elective surgery by providing a carbohydrate load sufficiently large to elicit an insulin response similar to that occurring after a normal meal. Insulin sensitivity is increased when this treatment is given before the onset of the stress of the surgical trauma. This change in metabolism upon entering surgery has been shown to have several effects on the response to the operation. Studies have reported positive effects in the postoperative recovery period such as improved protein balance,[35] improved preservation of lean body mass[36] and muscle strength[37] and reduced length of hospital stay after the operation.[38,39]

In contrast with elective surgery where the emphasis is on early return to oral intake, much progress has been made during the last 20 years concerning the optimal design of PN to enhance recovery from critical illness. Firstly, it has been recognised that both the quality and quantity of lipid supplied may influence organ function, particularly that of the liver, and immune system.[40] This is especially relevant in patients that are critically ill for protracted periods of time. Secondly, the importance and the dangers of hyperglycaemia due to insulin resistance have been reported.[41] However, the initial enthusiasm for tight glucose control has been tempered by recognising the difficulty of maintaining low glucose levels without inducing periods of hypoglycaemia. Although convincing data shows that tight glucose control is of clinical benefit (fewer infectious episodes and lower mortality) in patients undergoing cardiovascular surgery, its clinical applicability at present appears only to be advantageous in intensive care settings where this tight control can be rigidly maintained.[42] Another modification of the PN regimen that may be of benefit consists of the addition of extra glutamine and arginine (see Section 9.2).

1. When is preoperative PN indicated?

In severely undernourished patients who cannot be adequately orally or enterally fed (Grade A).

Comments: The influence of nutritional status on postoperative morbidity and mortality has been well documented in both retrospective[43–46] and prospective studies.[47–59] Inadequate oral intake for more than 14 days is associated with a higher mortality.[60] Two multivariate analyses have shown, for hospitalised patients in general and for those undergoing surgery for cancer in particular, that undernutrition is an independent risk factor for the incidence of infectious complications, as well as increased mortality, length of hospital stay, and costs.[61]

Undernutrition frequently occurs in association with underlying disease (e.g. cancer) or with organ failure.[61–69] The risk of severe undernutrition is considered by the ESPEN working group to be present when at least one of the following criteria is present: weight loss $>$ 10–15% within 6 months; BMI $<$ 18 kg/m^2; subjective global assessment, Grade C; serum albumin $<$ 30 g/L (with no evidence of hepatic or renal dysfunction).

On the basis of several reports in the literature and a large cohort study,[70] the working group considers hypoalbuminaemia to reflect inflammatory activity and as such to be a risk indicator of postoperative infectious complications and mortality rather than of nutritional status itself.

Several studies have demonstrated that 7–10 days of preoperative parenteral nutrition improves postoperative outcome in patients with severe undernutrition.[10,71–73] Conversely, its use in well-nourished or mildly undernourished patients is associated with either no benefit or with increased morbidity.[71] Moreover, preoperative parenteral nutrition is costly and can generally only be applied in the hospital setting, prolonging length of stay in the hospital. Significant improvements in postoperative outcome have been reported by using preoperative oral nutritional supplements enriched with specific immune-modulating substrates regardless of baseline nutritional status.[74–82] This approach is cheaper than PN and patients can be treated at home. It requires extra attention to ensure that oral supplements or nutritional drinks are actually taken by the patients.

2. When is postoperative PN indicated?

Parenteral nutrition is beneficial in the following circumstances: in undernourished patients in whom enteral nutrition is not feasible or not tolerated (Grade A); in patients with postoperative complications impairing gastrointestinal function who are unable to receive and absorb adequate amounts of oral/enteral feeding for at least 7 days (Grade A).

In patients who require postoperative artificial nutrition, enteral feeding or a combination of enteral and supplementary parenteral feeding is the first choice (Grade A).

Combinations of enteral and parenteral nutrition should be considered in patients in whom there is an indication for nutritional support and in whom $>$60% of energy needs cannot be met via the enteral route, e.g. in high output enterocutaneous fistulae (Grade C) or in patients in whom partly obstructing benign or malignant gastrointestinal lesions do not allow enteral refeeding (Grade C).

In completely obstructing lesions surgery should not be postponed because of the risk of aspiration or severe bowel distension leading to peritonitis (Grade C).

In patients with prolonged gastrointestinal failure PN is lifesaving (Grade C).

Comments: Patients having major surgery for head-neck, and abdominal cancer (larynx, pharynx or oesophageal resection, gastrectomy, pancreatoduodenectomy) often exhibit nutritional depletion before surgery[47,51,54–56,63,65,67,68] and run a higher risk of developing septic complications.[47,51,54–56,68] Postoperatively, oral intake is often delayed due to swelling, obstruction, impaired gastric emptying or paralytic ileus, making it difficult to meet nutritional requirements. In these patients surgeons should consider the placement of a feeding jejunostomy at the time of surgery. Nutritional support reduces morbidity and immune-modulating formulae appear to be especially efficacious.[81] Morbidity, length of hospital stay, and mortality are considered principal outcome parameters when evaluating the benefits of nutritional support. After discharge from the hospital or when palliation is the main aim of nutritional support, improvement in nutritional status and in quality of life is the main evaluation criteria.[83–93]

Other current guidelines recommend postoperative artificial nutrition for patients who cannot meet their caloric requirements within 7–10 days.[24,94] In patients who require postoperative artificial nutrition, enteral feeding or a combination of enteral and supplementary parenteral feeding is the first choice. The routine use of postoperative parenteral nutrition has not proved useful either in well-nourished patients or in those with adequate oral intake within a week after surgery.[24,94]

New anaesthetic techniques for pain control and the development of early postoperative recovery protocols allow the majority of patients to return to oral feeding very shortly after surgery. Consequently, the number of patients requiring postoperative nutritional support is progressively declining.

3. Is preoperative metabolic preparation of elective patients using carbohydrate treatment useful?

For most patients preoperative carbohydrate loading using the oral route is recommended (Grade A). In the rare patients who cannot eat or are not allowed to drink preoperatively for whatever reasons the intravenous route can be used.

Comments: For patients who qualify for free intake of fluids according to modern guidelines, carbohydrate drinks that have been tested properly can be safely used. This treatment has been shown to minimise insulin resistance, postoperative hyperglycaemia, loss of protein, lean body mass and muscle function, reduce anxiety and postoperative nausea and vomiting in general and orthopaedic surgery, and to be cardioprotective in cardiac surgery. This is therefore the primary mode of treatment to be recommended to most patients. For those who cannot eat or are not allowed to drink preoperatively for whatever reason, a glucose infusion at a rate of 5 mg/kg per min will have very similar effects, not only with regard to the main metabolic outcome variable – insulin resistance – but also to protein metabolism[35] and cardiac protection.[95–98]

The overwhelming majority of the data available in this field is based on studies in non-diabetic patients, with only one exception.[95] When given orally, the drink is a mixture of complex carbohydrates, i.e. maltodextrins, in a concentration of about 12.5%.[99] When given intravenously, carbohydrate loading is achieved using a glucose solution with a higher concentration, usually 20%, to administer a sufficient quantity in a low volume to ensure a sufficient insulin response.[100] Studies where i.v. glucose loading alone or in combination with other nutrients or insulin have been reviewed in more detail in recent years.[34,38,101–108] It is uncertain to what extent the addition of other substrates or insulin adds to the effects of glucose alone. In the healthy non-diabetic patient with normal glucose tolerance, glucose administration will induce insulin release and this will also ensure glucose control when greater quantities of glucose are infused.

Changing metabolism using enteral or intravenous carbohydrate treatment before elective surgery has therefore been shown to have several beneficial effects including less pronounced stress response, heightened insulin sensitivity, and the opportunity to allow earlier postoperative feeding without the development of hyperglycaemia.[109]

4. What are the energy and protein requirements in the perioperative period?

The commonly used formula of 25 kcal/kg ideal body weight furnishes an approximate estimate of daily energy expenditure and requirements (Grade B). Under conditions of severe stress requirements may approach 30 kcal/kg ideal body weight (Grade B).

In illness/stressed conditions a daily nitrogen delivery equivalent to a protein intake of 1.5 g/kg ideal body weight (or approximately 20% of total energy requirements) is generally effective to limit nitrogen losses (Grade B). The protein:fat:glucose caloric ratio should approximate to 20:30:50% (Grade C).

Comments: *Energy*. In acute and chronic disease the resting metabolic rate is elevated above the values calculated from the Harris–Benedict equations in both men and women. The degree of hypermetabolism differs but is on average not more than 110–120% of predicted.[110–113] In individual patients this value may be increased substantially to 160–180% for short periods. Examples include patients with open burn wounds, severe acute sepsis and those with head trauma.[111,114–116]

The figure of 25 kcal/kg ideal body weight may severely overestimate daily energy expenditure in obese patients.[112] In view of the increased prevalence of obesity it is therefore wise to consider ideal body weight when calculating energy requirements and to use calorimetry whenever possible.

The main consideration when administering fat and carbohydrates in parenteral nutrition is not to overfeed the patient.[113,117,118] Hyperalimentation is known to increase energy expenditure, oxygen consumption and carbon dioxide production.[119,120] Especially in frail patients with low cardiac, ventilatory and respiratory reserve these effects may be deleterious.[121] In addition, hyperalimentation may induce fatty liver and lead to hypertriglyceridaemia with harmful effects on immune function.[40] Patients on long term parenteral nutrition are especially prone to develop fatty liver and cholestasis.[122] Several factors may be held responsible. Sepsis, but also milder chronic inflammatory states interfere with the hydrolysis of triglycerides leading to hypertriglyceridaemia and fatty liver. Patients requiring long term parenteral nutrition often have a short bowel leading to disturbances in enterohepatic cycling of bile acids. Bile acid loss in the stools diminishes the size of the bile acid pool, which makes the liver more vulnerable for toxic influences. Bacterial overgrowth may lead to the formation of secondary bile acids which have hepatotoxic effects, leading to cholestasis. Many patients now have underlying or concomitant metabolic syndrome – an additional factor leading to disturbed fat clearance. A proportion of patients with fatty liver go on to develop a non-infective hepatitis – steatohepatitis – which may ultimately progress to liver cirrhosis and liver failure. The lipid emulsion itself can aggravate hypertriglyceridaemia and liver steatosis.[123]

Conversely, a calculated intake of 25 kcal/kg per 24 h may underestimate requirements in patients with very low body weights due to very low fat mass. Although there are no data in the literature suggesting that slight underfeeding has harmful effects, in truly cachectic patients careful monitoring of body weight and vital signs is necessary to assess the response to nutritional support and to allow such patients to gain weight without causing signs of hypermetabolism due to hyperalimentation. In such cachectic patients care should be taken to increase the amount of calories and protein slowly and to take care to prevent the refeeding syndrome. In extreme cachexia indirect calorimetry, if available, may help to assess energy requirements.

Protein/amino acids

Amino acid requirements in parenteral nutrition are higher when the patient is stressed/traumatized/infected than in the non-stressed state[124–126] as a consequence of the stressed body breaking down more protein and more essential amino acids than when non-stressed. One reason why this is a useful arrangement is that it allows the immune system to increase its activity. For this purpose, more glutamine and alanine are required. They are produced by transamination of carbon skeletons with amino groups from the branched-chain amino acids (BCAA) which are irreversibly degraded in this process and cannot be re-utilized for renewed protein synthesis. It is well established that muscle protein degradation is regulated by pro-inflammatory modulators like tumour necrosis factor-alpha, interleukin-6 and others, and therefore cannot be reversed by nutrition.[127] The value of nutritional support comes instead from its support of protein synthesis in muscle and most importantly in the liver, yielding acute phase proteins, and in the immune system, yielding white cells crucial in the response to trauma or disease, and thereby limits net whole body protein loss.[124,128] As for energy requirements protein/nitrogen requirements should be calculated on the basis of ideal body weight or adjusted body weight. There are no convincing data suggesting that overfeeding nitrogen has deleterious effects as long as patients are not generally hyperalimented,[113] but provision of excess amino acids is certainly wasteful in cost terms. Whether to include the

amino acid in the total count of the calories depends on the perspective of the physician. The classic teaching of the physiology of nutrition states that having determined the total energy requirement of a healthy individual, the caloric needs are met by giving carbohydrates, fats and proteins in well-defined percentages. However, the assumption behind this statement is that the calorie:nitrogen ratio is always the same in healthy and ill conditions. This is not true in postoperative or many post-injury settings where protein requirements far exceed the increase in energy expenditure. On the other hand, there is increasing awareness of the adverse consequences of overfeeding the patients in critical conditions, hence the careful calculation of the calories administered to the patient has to take into account not only carbohydrates and fats but also the amino acids, even if their contribution to the total calorie load is relatively small.

5. Which is the optimal glucose:lipid ratio?

At present, there is a tendency to increase the glucose:fat calorie ratio from 50:50 to 60:40 or even 70:30 of the non-protein calories, due to the problems encountered regarding hyperlipidaemia and fatty liver, which is sometimes accompanied by cholestasis and in some patients may progress to non-alcoholic steatohepatitis (Grade C).

Comments: Exactly what disadvantages derive from fatty liver and hypertriglyceridaemia are unknown. In the vascular literature it is firmly established that hypertriglyceridaemia is a risk factor for the development of arteriosclerosis and acute infusion of long-chain triglyceride (LCT) containing lipid emulsion diminishes the ability of the arterial vascular bed to relax. The main concern that these conditions impair immune response is not supported by a recent meta-analysis.[129] However, most experts recommend avoiding a triglyceride level greater than 5 mmol/dL, although hard data supporting this are lacking. When this level is reached it is recommended by many experts in the field to diminish the fat content (especially *n*-6 poly-unsaturated fatty acids (PUFAs)) of the parenteral nutrition or temporarily to withdraw fat. In this event the energy deficit should not be replaced by adding more glucose because this may exceed the patient's oxidative capacity.

6. Which is the optimal PN mixture?

Optimal nitrogen sparing has been shown to be achieved when all components of the parenteral nutrition mix are administered simultaneously over 24 h (Grade A).

Comments: Three-in-one mixtures are convenient and allow continuous and stable administration of all necessary components. The importance and complexity of the mixing process however is underestimated and requires experience. The composition may influence emulsion stability and particle size. These characteristics are difficult to assess and only in extreme situations will "oiling out" become visible. The recommendations of the manufacturers and of specialist pharmacy units should therefore be followed when mixing is performed in the regular hospital pharmacy. Mixing on the wards is to be strongly discouraged. Commercially available "ready-made" nutrition mixtures should be kept refrigerated as recommended and only mixed (by opening compartmentalized bags) just before administration.

Endeavours to allow the cholecystokinin response to occur, thus aiming to prevent biliary sludge forming in the gallbladder by discontinuation of nutrition during 8–10 h per 24 h (cycling feeding) have not been shown to be beneficial in the perioperative context. Such practices also tend to increase metabolic instability, specifically with regard to glucose homeostasis. Little research has been done regarding the tapering of nutrition during the 24 h immediately surrounding the operation. Generally the infusion rate is reduced to half or less of requirements to minimize metabolic instability during and immediately after operation. Recent data suggest that glucose homeostasis is achieved within 1 h after abruptly discontinuing parenteral nutrition.

7. Standard versus individualized nutrition?

Individualized nutrition is often unnecessary in patients without serious co-morbidity (Grade C).

Comments: There are a number of situations in which standardized nutritional support cannot be applied:

- Patients who suffer from heart failure may benefit from more concentrated nutrition, in which requirements are fulfilled in a lower volume. These patients sometimes require a sodium restricted regimen.
- Patients with chronic renal failure and oliguria often require a restricted sodium and potassium regimen in low total volume. Protein/nitrogen restriction is generally not recommended, because it may aggravate the malnutrition which is often accompanying chronic renal failure.[125,130,131] The quality of renal replacement therapy has improved to such a degree that nitrogenous waste can efficiently be cleared even when liberal amounts of amino acids are included in the nutritional regimen.[130]
- Patients with hepatic failure have in the past been treated with low protein diets. This is obsolete.[13] Very few patients will develop hepatic encephalopathy when receiving nutrition with normal amounts of protein. In fact, restriction induces a vicious circle by down-regulating enzymes in the urea cycle. Most patients therefore benefit from normal or even liberal amounts of protein/amino acids.[132] In parenteral nutrition the induction of encephalopathy by amino acids in the nutritional mixture is even rarer and daily amounts up to 1.2–1.5 g protein/kg ideal body weight may be safely administered. There is still some support for the claim that BCAA enriched parenteral nutrition is of benefit in liver patients and specifically those with impending or existing neurological signs. However, such patients should not undergo surgery if this can be prevented, because liver failure strongly increases the risk of developing infectious complications.
- Patients with gut failure or high output fistulas may develop a multitude of metabolic and electrolyte disturbances, which make supplementation with several components of the normal nutrition mix necessary. Specifically trace elements, electrolytes (especially sodium and magnesium) and vitamins are prone to become deficient. Standardized nutrition may sometimes still be possible but the mix should be supplemented as required.

8. Should specific nutrients be added to standard PN to obtain a clinical benefit?

The optimal PN regimen for critically ill surgical patients should probably include supplemental n-3 fatty acids (Grade C). The evidence-base for such recommendations requires further input from prospective randomised trials.

Comments: *Lipids.* The inclusion of a lipid emulsion as part of the energy source in PN reduces the overall carbohydrate load and

osmolarity of the solution and this has generally been held to be good practice. However, replacing glucose-derived calories with lipid calories is not without metabolic effects. The standard lipid emulsions have for many years been soybean-based emulsions rich in *n*-6 PUFA. However, *n*-6 PUFAs tend to have a pro-inflammatory effect, and trials tend to show lower complication rates in patients receiving PN containing fewer of these fatty acids.[133]

In view of these considerations attempts have been made to reduce the long-chain PUFA content without a net loss of lipid calories. This has been done by replacing part of the lipid by medium-chain triglycerides (MCT), by administering synthetic lipids which consist of a glycerol backbone randomly esterified with MCT or LCT and which thus provide another route to the provision of LCT and MCT, or by a substantial replacement of PUFA by *n*-9 LCT (olive oil). All such emulsions contain lower amounts of *n*-6 fatty acids and appear to have fewer immunological effects.[134]

In comparison to *n*-6 PUFAs, *n*-3 PUFAs have a relatively anti-inflammatory effect and when included with gamma linolenic acid and given enterally in ICU, have been shown in prospective randomized trials to improve pulmonary inflammation, to shorten days on the ventilator and overall ICU stay.[135–137] When included in PN, *n*-3 fatty acids have been shown to blunt the physiological response to endotoxin in healthy subjects.[138] In open label cohort studies, increasing dosage of *n*-3 PUFAs has been associated with reduced ICU stay following major abdominal surgery,[139] and in a randomised trial inclusion of *n*-3 PUFAs in PN was associated with reduced overall hospital stay.[140] Thus, at present there is some evidence that inclusion of *n*-3 fatty acids in PN may benefit organ function and reduce length of stay in patients undergoing major surgery or admitted to the surgical ICU. However, these trends will need to be substantiated in adequately powered randomised trials.

Amino acids.: Many different modifications of the amino acid composition have been proposed for parenteral nutrition of stressed patients. BCAA enrichment has been proposed for severely traumatized or diseased patients. Neither clear clinical benefit nor harmful effects have been reported.

Glutamine and arginine are the two amino acids that have received significant evaluation as potential modulators of clinical outcome in surgical patients receiving PN. To circumvent the problem that glutamine is unstable in solution and not very soluble, glutamine peptides have been constructed with glycine and alanine. In stressed states the body "infuses itself" with an amino acid mixture which is richer in glutamine and alanine than the amino acid composition of the proteins that we eat normally.

Glutamine has a major role as a substrate for the immune system and for the small bowel. Recent evidence also suggests it may act as a stress-signalling molecule and thus some of its benefits may be independent of its action as a metabolic fuel. Glutamine has been shown to aid preservation of small bowel anatomy and function in patients following major surgery[141] and to preserve T-lymphocyte responsiveness in similar patients.[142] A meta-analysis has shown that postoperative PN supplemented with glutamine dipeptide (20–40 g/24 h) improves nitrogen balance and short term outcome in patients who have undergone abdominal surgery.[143] However, a recent multicentre trial carried out in 427 well-nourished cancer patients did not show any advantage on short term outcome in subjects receiving perioperative i.v. glutamine.[144] Surgical patients in ICU receiving glutamine enriched PN or EN have been shown in a few studies to have reduced mortality, lower infection rates and reduced organ failure. However, definitive evidence is still lacking and several major randomised studies are in progress.[145]

Arginine has also received considerable attention, because it is known to stimulate T-cell function and is a precursor of nitric oxide. Recent studies showed that arginine when given along with other immunomodulatory nutrients reduced the incidence of postoperative infections and length of stay in cancer patients undergoing abdominal surgery.[146] The potentially beneficial effects in surgical patients of arginine, enterally given, cannot be dissected from the effects of ω-3 fatty acids and RNA in these formulas. Nor is it certain that these results can be extrapolated to parenteral nutrition. There is, however, controversy about the use of either enteral or parenteral arginine in critically ill septic patients[147] and further studies are awaited.

9. Should vitamins/trace elements be used in perioperative PN?

In well-nourished patients who recover oral or enteral nutrition by postoperative day 5 there is a little evidence that intravenous supplementation of vitamins and trace elements is required (Grade C).

In those patients after surgery who are unable to be fed via the enteral route, and in whom total or near total parenteral nutrition is required, a full range of vitamins and trace elements should be supplemented on a daily basis (Grade C).

Comments: Short-term standard micronutrient supplementation does not restore plasma antioxidant status after surgery.[148] It is possible that during surgical stress supra-normal amounts of ascorbate, alpha-tocopherol, and trace elements are required. While data from prospective randomized controlled trials support the supplementation of PN with vitamins and trace elements in critically ill patients (see ESPEN guidelines on PN in critical illness) no data exist for patients with an uncomplicated course, and nor are there studies in which the requirements for micronutrients are investigated in malnourished patients compared to well-nourished patients.

When early oral food intake/enteral nutrition is combined with parenteral nutrition, intravenous supplementation of vitamins appears to be unnecessary. In the case of total parenteral nutrition, a consensus exists that micronutrients/antioxidants should be supplemented on a daily basis.[149–152] In accordance with the USA Food and Drug Administration (FDA) the recommendations for micronutrients provision were recently updated[149,152] (see Table 1).

Table 1
Daily requirements for vitamins in adults when given parenterally (V1).

Vitamins	Requirement
Thiamin (B1)	6 mg
Riboflavin (B2)	3.6 mg
Niacin (B3)	40 mg
Folic acid	600 μg
Panthotenic acid	15 mg
Pyridoxine (B6)	6 mg
Cyanocobalamin (B12)	5 μg
Biotin	60 μg
Ascorbic Acid (C)	200 mg
Vitamin A	3300 IU
Vitamin D	200 IU
Vitamin E	10 IU
Vitamin K	150 μg

Daily requirements for trace elements in adults when given parenterally (V1)

Trace element	Standard intake
Chromium	10–15 μg
Copper	0.3–0.5 mg
Iron	1.0–1.2 mg
Manganese	0.2–0.3 mg
Selenium	20–60 μg
Zinc	2.5–5 mg
Molybdenum	20 μg
Iodine	100 μg
Fluoride	1 mg

10. Is weaning from PN necessary?

No (Grade A).

Comments: From the popularisation of PN by Dudrick until recently it has been recommended that PN is tapered prior to discontinuation so as to prevent hypoglycaemia. However, it has been shown that even after prolonged PN the beta-cells remain sensitive to changes in glucose levels and that adaptation of glucose levels and insulin secretion occur very quickly.[153]

Ad hoc studies have shown that after the abrupt discontinuation of PN containing glucose at about 3.7 g/kg per day, the plasma glucose returns to the pre-infusion baseline within 60 min without any symptom of hypoglycaemia.[154,155] There are no differences in mean glucose values or in key hormones (such as epinephrine, norepinephrine, insulin, glucagon, growth hormone, and cortisol) between abrupt and tapered discontinuation.[156]

No difference in the lowest blood glucose value was found in a randomized trial comparing abrupt discontinuation versus gradual tapering of PN. No patient had a significant change in hypoglycaemia questionnaire score.[157]

Conflict of interest

Conflict of interest on file at ESPEN (espenjournals@espen.org).

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