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ESPEN Guidelines on Parenteral Nutrition: Intensive care

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SUMMARY

Nutritional support in the intensive care setting represents a challenge but it is fortunate that its delivery and monitoring can be followed closely. Enteral feeding guidelines have shown the evidence in favor of early delivery and the efficacy of use of the gastrointestinal tract. Parenteral nutrition (PN) represents an alternative or additional approach when other routes are not succeeding (not necessarily having failed completely) or when it is not possible or would be unsafe to use other routes. The main goal of PN is to deliver a nutrient mixture closely related to requirements safely and to avoid complications. This nutritional approach has been a subject of debate over the past decades.

PN carries the considerable risk of overfeeding which can be as deleterious as underfeeding. Therefore the authors will present not only the evidence available regarding the indications for PN, its implementation, the energy required, its possible complementary use with enteral nutrition, but also the relative importance of the macro- and micronutrients in the formula proposed for the critically ill patient. Data on long-term survival (expressed as 6 month survival) will also be considered a relevant outcome measure.

Since there is a wide range of interpretations regarding the content of PN and great diversity in its practice, our guidance will necessarily reflect these different views. The papers available are very heterogeneous in quality and methodology (amount of calories, nutrients, proportion of nutrients, patients, etc.) and the different meta-analyses have not always taken this into account. Use of exclusive PN or complementary PN can lead to confusion, calorie targets are rarely achieved, and different nutrients continue to be used in different proportions. The present guidelines are the result of the analysis of the available literature, and acknowledging these limitations, our recommendations are intentionally largely expressed as expert opinions.

Abbreviations: PN, parenteral nutrition. General term used to describe nutrition through either a central or peripheral venous catheter; EN, enteral nutrition. General term used to include both oral nutritional supplements (ONS) and tube feeding; ICU, Intensive Care Unit; IC, Indirect calorimetry; IV, intravenous; LCT, long chain triglycerides; MCT, medium chain triglyceride; The body weight used, the body weight before acute illness in the case of fluid retention or obesity; P, phosphorus; Mg, magnesium; K, potassium; Ca, calcium; CHO, carbohydrates; PaO_2/FiO_2, ratio of arterial to inspired oxygen; GPX, glutathione peroxidases; EPA, eicosapentanoic acid; DHA, docosahexanoic acid.

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Summary of statements: Intensive Care			
Subject	**Recommendations**	**Grade**	**Number**
Indications	Patients should be fed because starvation or underfeeding in ICU patients is associated with increased morbidity and mortality	C	1.1
	All patients who are not expected to be on normal nutrition within 3 days should receive PN within 24 to 48 h if EN is contraindicated or if they cannot tolerate EN.	C	1.2
Requirements	ICU patients receiving PN should receive a complete formulation to cover their needs fully.	C	1.3
	During acute illness, the aim should be to provide energy as close as possible to the measured energy expenditure in order to decrease negative energy balance.	B	2.1
	In the absence of indirect calorimetry, ICU patients should receive 25 kcal/kg/day increasing to target over the next 2–3 days.	C	2.1
Supplementary PN with EN	All patients receiving less than their targeted enteral feeding after 2 days should be considered for supplementary PN.	C	3
Carbohydrates	The minimal amount of carbohydrate required is about 2 g/kg of glucose per day.	B	4
	Hyperglycemia (glucose >10 mmol/L) contributes to death in the critically ill patient and should also be avoided to prevent infectious complications.	B	5
	Reductions and increases in mortality rates have been reported in ICU patients when blood glucose is maintained between 4.5 and 6.1 mmol/L. No unequivocal recommendation on this is therefore possible at present.	C	5
	There is a higher incidence of severe hypoglycemia in patients treated to the tighter limits.	A	5
Lipids	Lipids should be an integral part of PN for energy and to ensure essential fatty acid provision in long-term ICU patients.	B	6.1
	Intravenous lipid emulsions (LCT, MCT or mixed emulsions) can be administered safely at a rate of 0.7 g/kg up to 1.5 g/kg over 12 to 24 h	B	6.8
	The tolerance of mixed LCT/MCT lipid emulsions in standard use is sufficiently documented. Several studies have shown specific clinical advantages over soybean LCT alone but require confirmation by prospective controlled studies.	C	6.4
	Olive oil-based parenteral nutrition is well tolerated in critically ill patients.	B	6.5
	Addition of EPA and DHA to lipid emulsions has demonstrable effects on cell membranes and inflammatory processes. Fish oil-enriched lipid emulsions probably decrease length of stay in critically ill patients.	B	6.6
Amino Acids	When PN is indicated, a balanced amino acid mixture should be infused at approximately 1.3–1.5 g/kg ideal body weight/day in conjunction with an adequate energy supply.	B	7
	When PN is indicated in ICU patients the amino acid solution should contain 0.2–0.4 g/kg/day of L-glutamine (e.g. 0.3–0.6 g/kg/day alanyl-glutamine dipeptide).	A	8
Micronutrients	All PN prescriptions should include a daily dose of multivitamins and of trace elements.	C	9
Route	A central venous access device is often required to administer the high osmolarity PN mixture designed to cover the nutritional needs fully..	C	1.3
	Peripheral venous access devices may be considered for low osmolarity (<850 mOsmol/L) mixtures designed to cover a proportion of the nutritional needs and to mitigate negative energy balance.	C	1.3
	If peripherally administered PN does not allow full provision of the patient's needs then PN should be centrally administered	C	1.3
Mode	PN admixtures should be administered as a complete all-in-one bag	B	1.4

1. Should we use parenteral nutrition (PN)? When should we start PN?

Recommendation: Patients should be fed because starvation or underfeeding in ICU patients is associated with increased morbidity and mortality. Grade C.

Comments: The ICU patient's[k] chance of survival without nutritional support is unknown but the increased metabolic needs related to stress are likely to accelerate the development of malnutrition, a condition associated with impaired clinical outcome. In a randomized study, 300 patients undergoing major surgery received continuous total PN or exclusively glucose (250–300 g/d) intravenous administration for 14 days. Those on PN had 10 times less mortality than those on glucose.[1] In their meta-analysis of PN vs. enteral nutrition (EN), Simpson and Doig[2] evaluated 9 trials with complete follow-up and found a mortality benefit in favor of PN compared with delayed but not early initiation of EN. Despite an association with increased infectious complications, a grade B evidence-based recommendation could be generated for PN use in patients in whom EN cannot be initiated within 24 h of ICU admission or injury. Giner et al.[3] have shown that nutritional therapy favorably influences morbidity and mortality rates in critically ill patients. In a prospective study involving 129 ICU patients, they found that 43% were malnourished. The incidence of complications ($p < 0.01$), and the number of patients who failed to be discharged from hospital ($p < 0.05$) were greater in the malnourished patients than in the well-nourished. In patients with less severe degrees of illness, the existence of malnutrition led to a worse outcome than in otherwise sicker patients.

The clinical outcome of 48 ICU patients was analyzed for the duration of mechanical ventilation, of ICU stay, and 30-day mortality.[4] The energy deficit after 7 days and that accumulated during the ICU stay ($-12{,}600 \pm 10{,}520$ kcal) correlated with both total and infectious complications ($p = 0.048$ and $p = 0.0049$, respectively). The correlations were also strong with the duration of mechanical ventilation, the number of days of antibiotics, and the length of ICU stay. Energy deficit however was not correlated with mortality. Villet et al.[4] concluded that there is as yet no answer to the question "how long can an ICU patient been starved without deleterious consequences".

2. Should we wait for recovery and the ability of the patient to take normal nutrition or should we start PN in patients who have not resumed normal intake within 10 days?

Recommendation: All patients who are not expected to be on normal nutrition within 3 days should receive PN within

[k] ICU patients: Patients developing an intensive inflammatory response with failure of at least one organ (SOFA > 4). These guidelines are not intended for patients admitted only for monitoring (ICU stay below 3 days) but for patients with an acute illness necessitating support of organ function during an ICU episode expected to be longer than 3 days.

24–48 h if EN is contraindicated or if they cannot tolerate EN. (Grade C).

Comments: The ESPEN guidelines on EN[5] state that "The insufficient provision of nutrients is likely to result in undernutrition within 8–12 days following surgery and/or ICU admission. In order to prevent undernutrition and related adverse effects, all ICU patients who are not expected to be on a full oral diet within three days should receive EN". EN is accordingly recommended as the first choice route for nutrition support in ICU patients. The use of PN is however reported to lie between 12% and 71%, and of EN between 33% and 92%, of critically ill patients who receive nutritional support.[6–11]

No study has evaluated the best timing for PN initiation in ICU patients. Nevertheless, the European (ESPEN)[5] and Canadian (CSCN)[11] clinical guidelines recommend the initiation of EN within 24 h or 24–48 h, respectively, after admission to ICU. By extension, PN, if indicated, should also be initiated within 24–48 h after ICU admission since it has been demonstrated that it does not increase mortality in comparison with EN. Ten to 20% of ICU patients have a contraindication to EN (bowel obstruction, short bowel syndrome, abdominal compartment syndrome, mesenteric ischemia, etc.) or have very limited tolerance to EN which precludes them receiving sufficient feed to cover their requirements. This condition is frequently limited to 3–5 days and serves as a relative indication for PN. In other patients, intolerance to EN lasts for much longer periods and corresponds to an absolute indication for PN as an absence of nutritional support would increase the risk of mortality and morbidity.[12] It can reasonably be claimed that all patients who are not expected to be on normal nutrition within 2 days should receive PN if EN is contraindicated or if they cannot tolerate EN, because no significant difference in clinical outcome has been shown between EN and PN in ICU patients.[13] Heyland's meta-analysis evaluated 26 randomized trials of 2211 patients in terms of clinical outcome for patients having received PN vs. standard care (conventional oral diets with intravenous dextrose) in surgical or critically ill patients. No influence of PN on mortality rate was found (risk ratio 1.03); nevertheless a trend towards fewer complications in patients with malnutrition was identified. Furthermore, many patients who had received suboptimal PN (insufficient coverage of energy and protein needs) were included and this may have reduced the true influence of PN on outcome. This insufficient coverage of energy and protein needs is found in most of the studies on this topic.

Another meta-analysis of PN vs. EN[2] also supports a grade B evidence-based recommendation for PN use in patients in whom EN cannot be initiated within 24 h of ICU admission or injury. However, in their meta-analysis of PN vs. EN, Gramlich et al.[14] evaluated 13 studies and found that the use of EN was associated with a significant decrease in infectious complications (relative risk 0.64–0.87, $p = 0.004$) albeit with no difference in mortality rate (relative risk = 1.08–1.65, $p = 0.7$). There was no difference in the length of hospital stay between groups receiving EN or PN ($p = 0.6$). PN was associated with a higher incidence of hyperglycemia. Data that compared days on a ventilator and the frequency of development of diarrhea were inconclusive. In their meta-analysis of PN vs. EN, Braunschweig et al.[15] found a higher risk of infection associated with PN, which could be partially explained by the higher number of patients with hyperglycemia in this population. These authors concluded that "standard care was associated with a higher risk of infection and mortality in the 3 trials of populations that had high percentages of malnutrition; however in the 4 trials of normally nourished populations, it was associated with a lower risk of infection". It is indeed probable that PN is associated with more hyperglycemia than EN, and hyperglycemia (inter alia) reduces neutrophil chemotaxis and phagocytosis and were found to be an independent risk factor for short-term infection in patients undergoing coronary artery surgery.[16] Thus hyperglycemia (whether or not induced by PN) could have been a significant confounding factor in most of the ICU studies comparing EN and PN in terms of clinical outcome, as tight glycaemic control has only been more recently introduced as routine approach in ICU.[17]

3. Should we use central venous assess for PN administration?

Statement: A central venous access device is often required to administer the high osmolarity PN mixture designed to cover the nutritional needs fully (Grade C).

Peripheral venous access devices may be considered for low osmolarity (<850 mOsmol/L) mixtures designed to cover a proportion of the nutritional needs and to mitigate negative energy balance (Grade C).

If peripherally administered PN does not allow full provision of the patient's needs then PN should be centrally administered (Grade C).

Comments: PN is usually administered into a large-diameter vessel, normally the superior vena cava or right atrium, accessed via the jugular or subclavian vein. For longer-term ICU use, a tunneled-catheter or implanted chamber is occasionally used as alternatives to a standard central venous access device. Central venous access devices generally have a single lumen but double or triple lumen catheters are available to allow for simultaneous monitoring and the administration of PN and one or more therapeutic agents incompatible with PN admixtures. Centrally administered PN can cover all nutritional needs as vessel tolerance to hyperosmolar solutions is usually not a limitation.

Alternatively PN can be delivered into a peripheral vein, usually of the hand or forearm. Veins of the lower limb are occasionally used if those of the upper limbs are not accessible. Peripheral PN may however provide less than the overall needs for macro- and micronutrients as the amounts given may be limited by venous intolerance to the hyperosmolarity of the admixture, and by the more limited flow rates into a smaller vessel. Debate on the relative strengths of central and peripheral PN,[18] as well as on the methods for optimizing peripheral PN administration,[19] have been ongoing for a long time and the perceived disadvantages of peripheral approaches have led to the development and use of peripherally inserted central catheters (PICC). Turcotte et al. recently reviewed the studies comparing peripherally inserted central catheters (PICCs) and conventional central venous catheters (CVCs) for the administration of PN in surgical patients.[20] The number of infectious complications was similar, but thrombotic episodes appeared more frequent and occurred earlier with PICC, phlebitic complications accounting for premature catheter removal in approximately 6% of cases; approximately 40% of PICCs were removed before completion of therapy.

The prospective study by Alonso-Echanove et al. [21] analyzed the risk factors for central venous catheter (CVC)-associated bloodstream infections (BSI) among 8593 CVC. They showed that antimicrobial-impregnated CVC reduced the risk of CVC-associated BSI by 66% only among patients whose CVC was used to administer PN (2.6 CVC-associated BSIs per 1000 CVC-days vs. 7.5 CVC-associated BSIs per 1000 CVC-days in those not on PN; $p = 0.006$). In addition, in this study peripherally inserted central catheters (PICCs) were associated with a lower risk of CVC-associated BSI ($p = 0.0001$).

Peripheral PN is often used to complete insufficient EN, if central catheters are unavailable or contraindicated, although there is no conclusive trial to support this practice. Results appear relatively

poor in ICU. PICC lines perhaps offer a suitable middle way between peripheral catheters and conventional central lines. Additional prospective comparative studies in ICU patients are needed. ICU patients receiving PN should have their needs fully covered. Therefore, if peripherally or PICC administered PN does not allow the patient's needs to be met fully, then PN should be centrally administered (Grade C).

4. Should we use all-in-one bags for PN administration?

Recommendation: PN admixtures should be administered as a complete all-in-one bag (Grade B).

Comments: PN regimens contain more than 40 different components, including water, macronutrients (carbohydrates, lipids, amino acids), electrolytes, micronutrients (trace elements, vitamins) and other additives (e.g. glutamine, insulin, heparin). They can be administered either using separate containers, or from an "all-in-one bag system" prepared in the hospital pharmacy or by industry. The separate containers approach requires numerous IV line manipulations associated with an increased risk of administration errors, as well as of septic and metabolic complications.[22]

In a prospective, randomized, unblinded, controlled study,[23] separate containers, hospital-compounded bags and all-in-one bags were compared. PN-related activities of medical, nursing and pharmacy staff were timed. Use of the all-in-one bag was the least expensive PN system. Separate container application costs were significantly higher ($p < 0.01$). The recent ASPEN consensus[24] recommended a standardized process for PN administration in order to improve patient safety and clinical appropriateness, and to maximize resource efficiency. This process includes the use of standardized PN formulations but also aspects of ordering, labeling, screening, compounding, and administration of PN. A safe PN system must exist which minimizes procedural incidents and maximizes the ability to meet individual patient requirements. The availability of clinicians with expertise in nutrition support therapy is a strong factor in assuring this.

5. How much parenteral nutrition should critically ill patients receive?

Recommendation: During acute illness, the aim should be to provide energy as close as possible to the measured energy expenditure in order to decrease negative energy balance. (Grade B). In the absence of indirect calorimetry, ICU patients should receive 25 kcal/kg/day increasing to target over the next 2–3 days (Grade C).

No precise amount of energy can be recommended to be provided by partial or total parenteral nutrition, since no large prospective study has demonstrated an advantage to any measurement technique or predictive formula. Studies are under way to determine the potential advantages of targeting energy delivery according to measured energy expenditure.

Comments: Despite recommendations for early EN in critically ill patients,[3] many authors have described the difficulty in reaching the prescribed energy intake. This reflects many factors including cautious decision-making in the early phases of stress, and in the early postoperative state,[25] gastroparesis and lack of normal gastric emptying[26,27] related to sepsis or treatment with noradrenaline (norepinephrine) or morphine derivates, absence of protocols,[12] and indeed the trend for a decrease in PN prescription.[10,28] All pose challenges and may induce an energy deficit. In addition, accurate determination of resting energy expenditure is not always feasible. Equations give only an approximate evaluation,[29–31] and indirect calorimetry is not available or used in many units.[32] Moreover, evidence-based studies to demonstrate the usefulness of measuring energy expenditure in the critically ill are lacking. Bartlett in 1985,[33] in a retrospective study showed that surgical ICU patients with a total energy balance lower than −10,000 kcal during their entire ICU stay, had a mortality of more that 85%. Mault et al.[34] in a prospective multicenter study compared patients with positive and negative total energy balance and showed that those with positive energy balance had shorter durations of ventilation and shorter ICU stays. Rubinson[35] studied patients with low oral or enteral intake in the ICU and demonstrated that those who intake fell below 25% of their requirements had a significant increase in the prevalence of bacteremia. Villet et al.[4] showed that negative energy balance was associated with increased infectious complications following open heart surgery, and Dvir et al.[36] observed prospectively an increase in all complications in a general intensive care unit population. Petros et al.[37] retrospectively compared patients who reached their calorie targets with those who did not reach it and showed that the latter had increased SOFA scores and increased mortality.

A pilot prospective study[38] compared calorie administration guided by indirect calorimetry to that following a 25 kcal/kg/day rule in 50 patients. Tight calorie control guided by indirect calorimetry apparently decreased hospital stay and hospital mortality by more than 50%. This first prospective randomized study in this field used both enteral and parenteral routes to achieve the caloric target, and has led Heiddeger et al.[39] to promote wider use of supplementary PN feeding associated with EN in the early days of ICU admission.

A note of caution must however be added to the given data suggesting hazard from more generous calorie provision. Kirshman et al.[40] showed prospectively that patients (fed enterally or parenterally) had better outcomes from 9 to 18 kcal/kg/day than those receiving higher amounts. In another prospective observational study of 415 patients of whom 20% received EN, 35% received PN and 35% mixed nutrition, those receiving PN had higher mortality but APACHE II scores were also higher.[41]

6. Is there an indication for parenteral nutrition supplementary to enteral nutrition?

Recommendation: All patients receiving less than their targeted enteral feeding after 2 days should be considered for supplementary parenteral nutrition (Grade C).

Table 1 summarizes the conflicting results regarding PN used with or without EN and explains why recommendations are grade C.

Comments: There are two serious drawbacks with EN: the number of patients who can receive it and the often low amount of energy delivered. The implementation of an evidence-based algorithm can increase the number of patients fed by the enteral route. However the ACCEPT study[42] showed that even in the intervention group the mean proportion of patients receiving EN on day 4 was only 60%. The ANZICS Clinical trials group succeeded in providing earlier feeding but still at a level far from nutritional adequacy.[43] This may be the reason why clinical outcomes were not improved. It is therefore not surprising that Simpson and Doig's meta-analysis of 11 high quality studies comparing enteral and parenteral nutrition, revealed a significant effect in favor of PN when it was compared to late enteral nutrition (see Table 1).[2]

The limitations of EN often lead to negative cumulative energy balance. Two papers[4,36] have shown that this is associated with an increasing number of complications. This makes it very tempting to supplement insufficient EN with PN. Yet, there is still little evidence to support such an approach. The meta-analysis by Dhaliwal et al.[44]

Table 1
Conflicting meta-analysis results regarding the benefits of PN in different ICU populations.

	Number of studies included	Type of nutrition studied and Specific population	RR (95% CI)	Conclusions
Simpson [2]	11	vs. EN		PN improves outcomes
Gramlich [14]	13	vs. EN in terms of infection	0.64 (0.46–0.87)	EN better but no difference in mortality, length of ventilation, or diarrhea
Dhaliwal[44]	5	Combination of PN and EN vs. EN alone		No effect of PN on mortality, infection, length of ventilation or length of stay
Brauschweig[15]	27	vs. EN	0.64 (0.54–0.76)	Standard better than PN
Brauschweig[15]	7	vs. standard nutritional care in the malnourished		
		Mortality	3.0 (1.09–8.6)	PN improves
		Infection	1.17 (0.88–1.56)	PN might improve

included five trials[45–50] comparing the supplementation of EN with PN. One of these trials[48] is apparently an expansion of a former study,[49] so the number is reduced to four. Three of them[46–48] supplemented parenteral nutrition in patients with an obviously functioning gastrointestinal tract and two of these included some odd results. Dunham et al.[47] described 37 patients randomized into three arms: total parenteral nutrition (TPN), total enteral nutrition (TEN), and mixed nutrition (PN/EN). They reported a mortality of 6.6% in the TPN and 8.3% in the TEN, but 30.0% in the PN/EN arm; this is presumably an effect of small numbers. Herndon et al.[48] evaluated 39 patients with burns covering >50% surface area and found a mortality of 63% with PN compared to 26% in the control group (who also received between 1086 and 2454 kcal/24 h parenterally). This study suggested net harm from excess parenteral nutrition (and may have ended the "hyperalimentation" concept).

Thus, the study described by Bauer et al.[45] is the only trial that can really be used to elucidate the value of mixed enteral/parenteral nutrition. They reported on two groups of 60 patients each who received either enteral plus parenteral nutrition (treatment group) or EN plus placebo (control group). The energy delivery was adjusted daily so the sum from both routes would achieve the target of 25 kcal/kg/day. After 7 days of feeding retinol binding protein and prealbumin were significantly ($p < 0.05$) improved in the treatment group compared to the control group. There was no difference in 90-day mortality or in the incidence of infections. The hospital length of stay was significantly reduced (from 33.7 ± 27.7 days to 31.2 ± 18.5 days) but this is clearly only a minor benefit and further and larger trials are certainly warranted to evaluate the concept of mixed parenteral and enteral nutrition.

7. Carbohydrates: what are the requirements?

Recommendation: The minimal amount of carbohydrate required is about 2 g/kg of glucose per day (Grade B).

Comments: *There is* no persuasive evidence to indicate that carbohydrates (CHO) are essential nutrients for humans comparable to the case for several amino acids, fatty acids and the micronutrients.[50] The powerful endogenous capacity for glucose synthesis (gluconeogenesis) from lactate, glycerol and amino acids in the liver, but also in the kidneys[51] and perhaps in other tissues such as muscle and the gut,[52] is probably sufficient to ensure complete autonomy. Nonetheless glucose constitutes a convenient and safe source of calories for use in PN.

Metabolism: The specificity of glucose among other hexoses in animal metabolism is due to its very high affinity to specific cellular plasma-membrane glucose transporters (e.g. GLUT) and to its phosphorylating enzymes (the hexokinases). Hexokinases form the single family of enzymes able to catalyze glucose metabolism, and conversely glucose-6-phosphatase is the single catalyst for the production of glucose from glucose-6-phosphate.

Glucose-6-phosphate has three main fates: (i) glycolysis (leading to glycerol-3-phosphate, pyruvate and other intermediates), (ii) glycogen synthesis and (iii) the pentose phosphate pathway, a mandatory pathway leading to NADPH synthesis, a key component in the oxidative stress homeostasis. Fatty acids and CHOs are the sources of energy used for ATP synthesis. As compared to fatty acids, CHOs (as glucose and pyruvate) have three unique properties related to energy metabolism: (i) they may provide ATP in the absence of oxygen; (ii) they offer a higher oxidative efficiency (ATP/oxygen ratio) and (iii) they allow an anaplerotic flux providing Krebs-cycle intermediates and other compounds.[53] These features demonstrate the mandatory role of carbohydrate in cellular energy economy. However, if a supply of pyruvate to the mitochondria is mandatory, the way it is supplied is not unique, and whether it comes from glucose, lactate or alanine, does not affect the result.[54,55]

Besides a major role in energy metabolism, CHOs are also tightly connected to protein metabolism. While fatty acids are not adequate precursors for carbohydrate synthesis (conversely to pyruvate there is no anaplerotic flux from acetyl-CoA), the pool of amino acids released from protein (muscle) breakdown represents a major source of endogenous substrates together with the glycerol released from triglyceride hydrolysis. CHO metabolism, in turn, provides the carbon skeleton required for non-essential amino acid synthesis.

Requirement: The powerful pathways allowing de novo synthesis and interconversion of CHO complicate the issue of exogenous CHO requirements. There are several reports of low or very low carbohydrate diets being used in humans with no apparent side effects.[56] However, basal requirement of glucose is estimated to be roughly 2 g/kg/day for an adult. The basis of this evaluation is weak and as has been said: "carbohydrate could be theoretically eliminated from the diet, but it is probably safe(r) to give 150 g/day"!.[57] Three situations can be differentiated regarding organ dependence on glucose.

- Tissues completely or largely deprived of mitochondria (very poor or no oxidative metabolism): ATP can be provided only by glycolysis (or glycogenolysis). These tissues completely depend on glucose supply and include: red blood cells, probably many immune cells, all transparent tissues of the eyes, the renal medulla, and muscle during anaerobic contraction. However this does not necessarily mean a requirement for an exogenous glucose supply, since recycling pathways can supply these tissues with endogenous glucose, at the expense of liver fatty acid oxidation fuelling the gluconeogenesis.
- Tissue strongly, but not totally, dependent on glucose: the brain. Brain metabolism represents the majority of whole body glucose oxidation (100–120 g/day) and a rapid drop in plasma

glucose results in coma, with the potential for irreversible neurological sequelae. However, ketones and lactate [58] have been shown to fuel the brain safely when blood glucose is low. Hence the brain's dependency on glucose oxidation appears to be relative, accordingly to the metabolic surroundings. Again, this glucose may be of exogenous or endogenous origin. However, unlike the above situation where glucose is only converted to lactate (glycolysis), in the case of the brain glucose is fully oxidized and must then be replaced by newly formed molecules coming either from amino acids or glycerol.

- Tissues not directly depending on glucose: all remaining tissues. ATP supply in these tissues can be entirely provided from fat oxidation, given that the need of CHO for purposes other than energy metabolism (anaplerosis, nucleic acids, signaling molecules, etc.) remains. Indeed, in some cases of extreme glucose depletion, as seen in massive insulin intoxication for instance, the dramatic defect in brain function contrasts with a lack of major consequences on other key physiological functions.

Pathological considerations: High glucose concentration is an inflammatory and pro-oxidant signal and the tight homeostasis of glucose that results from its very complex regulation has probably been a crucial acquisition through evolution. In stress, by preventing the use of glucose in muscle and adipose tissue (low priority pathways), insulin resistance may allow sparing of glucose molecules for less dispensable purposes located in injured tissues or vital organs. Interestingly in trauma, non-injured muscle is insulin resistant, while injured muscle from the same individual is not! Insulin resistance could thus be an example of an appropriate response of the body to a difficult challenge: to spare glucose as an extremely valuable substrate only provided from muscle protein breakdown and simultaneously to secure a sufficient supply to vital organs and injured tissues. It can be seen that delivering large amounts of exogenous glucose to such a patient could compromise this delicate adaptation which re-orientates the fate of glucose at minimal consequence to blood glucose and muscle breakdown intensity, by inducing damaging hyperglycemia. However it is also well known that sustained muscle protein catabolism is deleterious, this being potentially prevented by exogenous glucose administration! Currently we try to resolve this challenge by providing both carbohydrate and insulin to our patients.[17] While there is no doubt that both fasting and hyperglycemia are deleterious, the best metabolic management of these patients is still a matter for further investigation.

8. Carbohydrates: which level of glycemia should we aim to reach?

Recommendation: Hyperglycemia (glucose >10 mmol/L) contributes to death in the critically ill pt and should also be avoided to prevent infectious complications (Grade B). Reductions and increases in mortality rates have been reported in ICU patients when blood glucose is maintained between 4.5 and 6.1 mmol/L. No unequivocal recommendation on this is therefore possible at present. There is a higher incidence of severe hypoglycemia in patients treated to the tighter limits (Grade A).

Comments: Carbohydrates are the main source of calories in almost all PN formulations. Glucose is the main metabolic fuel for the human body. The brain and peripheral nerves, the renal medulla, leukocytes, erythrocytes and bone marrow use glucose as the main source of oxidative energy. To meet the needs of the brain, the minimum daily amount of glucose is estimated to be 100–120 g. If this amount is not exogenously provided via nutrition, it will be generated via gluconeogenesis using amino acid precursors provided by skeletal muscle proteolysis. In starvation, parenteral provision of glucose has a protein sparing effect, as it decreases the need for skeletal muscle breakdown. Whether this also effectively happens in the critically ill has remained unclear.

A major study is currently ongoing to address the question of whether or not it is beneficial to add parenteral feeding early to enteral feeding in order to reach the nutritional target in ICU patients.[59] This study, which will run until 2011, assesses the impact of early PN, starting with IV glucose and progressively adding proteins and lipids, supplementing any early EN in order to achieve the calculated caloric needs.

While awaiting these further results, a theoretical consideration is that in the stressed patient the maximum oxidation rate of glucose is 4–7 mg/kg/min (or 400–700 g/day for a 70 kg patient). Hence, in order to decrease the risk of metabolic alterations, the maximum rate of glucose infusion should probably not exceed 5 mg/kg/min[60]; on average current regimens contain much less.

In the critically ill, insulin resistance is the reason why parenteral glucose infusion, and parenteral nutrition in general, further increase the level of circulating glucose. There is evidence that hyperglycemia in the critically ill patient contributes to and aggravates complications such as severe infections, organ dysfunction, and death. Insulin infusion to maintain normoglycemia (targeted between 4.5 and 6.1 mmol/L) during intensive care stay was shown to prevent such complications in 2 studies performed in surgical and medical adult ICU patients,[61] but not in a subsequent and substantial multicenter study, in which mortality was increased by this strategy.[62] The NICE SUGAR study compared the effects of the two blood glucose targets on 90 day all-cause mortality in ICU patients.[62] Within 24 h of admission, adults who were expected to require ICU treatment for 3 or more consecutive days were randomly assigned to undergo either intensive glucose control, with a target blood glucose range of 4.5–6.0 mmol/L, or more conventional control, with a target of 10.0 mmol/L or less. Of the 6104 patients 3054 were assigned to intensive, and 3050 to conventional control. The two groups had similar characteristics at baseline. Day 90 data were available for 3010 and 3012 patients, respectively. Some 829 patients (27.5%) in the intensive-control group died compared with 751 (24.9%) in the conventional-control group died. The odds ratio for increased mortality in the intensive-control group was 1.14 (95% confidence interval: 1.02–1.28; $p = 0.02$). The treatment effect did not differ significantly between surgical patients and non-operated patients. Severe hypoglycemia (blood glucose <2.2 mmol/L) was reported in 6.8% of the intensive-control group and 0.5% of the conventional-control group ($P < 0.001$). There was no significant difference between the two groups in the median number of days in the ICU, in the hospital, or in the median number of days of ventilation or renal-replacement therapy. These new results are already generating discussion, not least since it is suggested that the patients included were relatively starved of nutrients, but they certainly preclude a firm recommendation in favor of strict glycaemic control in the present guidelines. Further analyses of the earlier studies suggested that preventing hyperglycemia was the major factor dominating any direct effect of insulin[63–66] and that preventing hyperglycemia had benefits independent of the amount of intravenous glucose/calories infused.[63] A small multicenter study in patients with severe sepsis was stopped early for risk of hypoglycemia and was not statistically powered to confirm the benefits of blood glucose control.[67] Another multicenter study was stopped early for unintended protocol violation and risk of hypoglycemia.[68]

In order to investigate the impact on clinical outcome of parenterally administered glucose (alone or in combination with

lipids and protein) in the critically ill, studies should be done in the presence of a comparable level of glucose control. Indeed, additional hyperglycemia ensuing from the parenteral glucose load is likely to counteract potential benefit of the nutritional intervention. Further optimization of guidelines on parenteral glucose infusion will be informed by the results of studies such as the EPaNIC study (ClinicalTrial.gov Identifier: NCT 00512122).[59]

9. Should we use lipid emulsions in the parenteral nutrition of critically ill patients?

Statement. Lipid emulsions should be an integral part of PN for energy and to ensure essential fatty acid provision in long-term ICU patients. (Grade B).

9.1. Introduction: classification

Fatty acids are classified according to structural characteristics including the length of the carbon chain, presence and position of double bonds in the chain, and their configuration (i.e. cis vs. trans). Generally speaking they may be classified as saturated (no double bonds) or unsaturated (one or more double bonds), with the latter sub-classified as monounsaturated (one double bond) or polyunsaturated (two or more double bonds). According to chain length, fatty acids are termed short chain (<8 carbons), medium chain (8–14 carbons) or long chain (16 or more carbons); fatty acids with chains of 20 or more carbons are sometimes referred to as very long chain. With regard to the position of the double bond within the fatty acid chain three families are typically distinguished: omega-3, omega-6 and omega-9 (also referred to as *n*-3, *n*-6 and *n*-9). The omega terminology describes the position of the double bond closest to the methyl end of the chain. Fatty acids serve many functions including acting as energy sources, contributing towards the structure and physical properties of cell membranes, acting as precursors of bioactive lipid metabolites such as prostaglandins, and regulating cell responses including gene expression. Many fatty acids can be synthesized within the human body, but two (linoleic acid, an 18 carbon omega-6 fatty acid, and alpha-linolenic acid, an 18-carbon omega-3 fatty acid) cannot. These fatty acids must be supplied to humans and are referred to as the essential fatty acids. The typical ICU patient requires 9–12 g/day of linoleic acid and 1–3 g/day of alpha-linolenic acid. The essential fatty acids are synthesized in plants and are found in high amounts in plant oils (e.g. corn, sunflower, soybean). Their importance is emphasized by their further metabolism to key, longer chain, less saturated fatty acids such as arachidonic acid (omega-6), and eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA) (both omega-3). Fish oils contain EPA and DHA. Olive oil contains the omega-9 monounsaturated fatty acid oleic acid.

9.2. Energy

IV lipids are an integral part of three-in-one PN regimens, in which they provide an energy source and the essential fatty acids, as are needed in the long-term ICU patient. They allow low energy provision from carbohydrates which facilitates better glucose control. When infused at 1–2 g/kg/day lipid emulsions are safe and well tolerated and provide the required energy (e.g. 10 kcal/d).[69] Aberg et al.[70] explored the metabolic (by hypertriglyceridemic clamp) and thermogenic (by indirect calorimetry) responses to exogenous fat in relation to age (young and elderly patients) and found that lipid infusion was increasing energy expenditure by 6–9%. Fat oxidation was increased by 15–24% during infusion when compared to baseline and associated with increased lipoprotein lipase activity (4-to-5-fold). Tappy et al. showed[71] that administration of lipids decreased the fractional de novo lipogenesis when compared to glucose-based PN, induced a comparatively lower increase (7% vs. 26%) in the plasma glucose, in the insulin levels (40% vs. 284%) and did not increase CO_2 production while PN glucose based increased CO_2 by 15%. Lipids were not able to inhibit endogenous glucose production and net protein oxidation. The same group[72] also found that the use of omega-3 fatty acids was associated with decreased energy expenditure. Glucose and lipid oxidation were similar whether *n*-6 or *n*-3 based lipids were used. Others compared the use of olive oil-based nutrition to glucose-based PN in multiple trauma patients[73] and found this to be as safe and efficacious as glucose. Olive oil-based lipid emulsions were also associated with a lower blood glucose.

9.3. Metabolic effects of IV lipids

In the diet, in the bloodstream, in cells and tissues and in lipid emulsions, fatty acids are mainly found in esterified form, typically linked to glycerol, to form triglycerides and phospholipids, or with cholesterol, to form cholesteryl esters. Esterified fatty acids circulate in the bloodstream as components of lipoproteins. The protein components of lipoproteins are important in determining interactions with cellular lipoprotein receptors and lipoprotein metabolism and clearance from the bloodstream. Some non-esterified fatty acids do circulate; these are non-covalently bound to albumin. The blood concentrations of lipids and lipoproteins are regulated by a variety of hormones and cytokines, and alter according to physiological and pathological changes including those of inflammation.

Critical illness involves activation of inflammatory processes including the production of eicosanoids, cytokines, and reactive species. Although the inflammatory response is part of the normal host defense, overzealous production of inflammatory mediators can be damaging to host tissues and may be associated with worse patient outcomes. High circulating concentrations of inflammatory mediators are seen in the most critically ill patients[74] and have been associated (not necessarily causally) with poor outcomes.[69] In association with activation of inflammatory processes, patients may display an impairment of cell-mediated immunity including suppressed activity of antigen presenting cells and of T cells.[75] This diminishes the ability to control infection thus exacerbating the already poor clinical state and inducing further inflammation.[76] Fatty acids can influence inflammatory and immune processes through effects on cell membrane structure and function, modification of inflammatory mediator profile and alterations in gene expression.[77–80] Thus, the nature and quantity of lipid supplied to critically ill patients may have an important role in determining clinical outcome.[80] Experimental data and clinical studies do not yet provide a clear picture of the differential effects of lipid formulations currently available for use in parenteral nutrition,[80] although it is generally considered that omega-3 fatty acids act in a less inflammatory and possibly in an anti-inflammatory manner.[79,80] Omega-3 fatty acids can counter the actions of omega-6 fatty acids, which may promote inflammatory processes (arachidonic acid being the substrate for synthesis of inflammatory eicosanoids).

Lipid formulations used in parenteral nutrition are composed of triglycerides with phospholipids as emulsifiers. There are several different formulations of parenteral lipids available commercially:

- Soybean oil-based ; these are often referred to (incompletely) as long chain triglycerides (LCT)
- "Pharmaceutical" mixtures (usually 50:50) of soybean LCT and medium chain triglycerides from coconut oil (MCT)
- "Pharmacological" mixtures; these are triglyceride mixtures in which each glycerol molecule has a random or predetermined distribution of fatty acids with different chain lengths
- Mixtures (20:80) of soybean and olive oil

- Mixtures of lipids including fish oil (e.g. 30:30:25:15 mixtures of soybean, MCT, olive oil and fish oil; 40:50:10 mixture of soybean, MCT and fish oil)
- Fish oil is also available separately to be used as a supplement combined with other emulsions.

A meta-analysis using data from both surgical and critically ill patients suggested that the use of lipid emulsions is associated with higher complication rates.[79] However the total of calories and/or total carbohydrate administered was not always well controlled in the different groups or in the different studies, and we conclude that the evidence for a detrimental effect of lipids is not strong. Two large reviews summarizing the effects of different lipid emulsions on immune function[80,81] do not find significant advantages for any one specific emulsion. In any case, the immune parameters studied are numerous and subject to between-laboratory differences; overall it is currently difficult to summarize the effects of each specific emulsion so as to guide a specific prescription choice.

10. Do LCT/MCT lipid emulsions offer clinical advantage over LCT alone?

Recommendation: The tolerance of mixed LCT/MCT lipid emulsions in standard use is sufficiently documented. Several studies have shown specific clinical advantages over soybean LCT alone but require confirmation by prospective controlled studies (Grade C).

Comments: Soybean oil-based lipid emulsions high in linoleic acid have been widely used in the ICU and remain the reference emulsion in most studies. Glucose control can be achieved using a balanced supply of glucose in combination with such lipids.[80] Several studies have indicated the superiority of LCT/MCT mixtures over soybean LCT alone. They appear to improve nutritional status in comparison to solely LCT emulsions.[82] In a group of cancer patients undergoing surgery, LCT/MCT significantly improved plasma pre-albumin concentration [83] and (in another group) yielded better nitrogen balance.[84] LCT/MCT mixtures demonstrate lesser immunosuppressive effects in laboratory studies[85] and fewer clinical infections.[86] In a group of 72 severely malnourished surgical patients, those in the LCT/MCT group had a significantly lower incidence of intra-abdominal abscesses. Patients without cancer in the same study treated with LCT/MCT had a significantly lower mortality rate.[87] The LCT/MCT mixture was superior for ICU patients, and especially those on mechanical ventilation. In 21 ICU patients treated with either LCT or LCT/MCT, cardiac output, oxygen consumption and oxygen delivery increased significantly only in the LCT group.[88] In another study, LCT infusion increased the mean pulmonary artery pressure and pulmonary venous admixture and decreased the ratio of arterial to inspired oxygen (PaO_2/FiO_2), (i.e. it worsened oxygenation). Smyrniotis et al.[89] demonstrated that the infusion of LCT/MCT emulsions increased oxygen consumption (VO_2), cardiac output and CO_2 production (VCO_2), and it has been demonstrated that LCT/MCT can increase the PaO_2/FiO_2 when compared to LCT emulsion alone.[90]

One study found lower lipoprotein X (LpX) in a MCT/LCT treated group vs. LCT alone.[91] In a group of post-orthotopic liver transplantation patients, reticular endothelial system function recovery was significantly better in the LCT/MCT group.[92] These beneficial effects can be observed while maintaining essential fatty acid status.[93]

11. Is there evidence that olive oil-based parenteral nutrition is well tolerated in critically ill patients?

Recommendation: Olive oil-based parenteral nutrition is well tolerated in critically ill patients. (Grade B).

Comments: In an observational retrospective, single centre, cohort study comparing olive oil-based with soybean oil-based emulsions in 39 critically ill patients, Mateu de Antonio et al.[94] did not find any difference in infection rate, acute-phase proteins, or major health outcomes. The peak leukocyte count and the fibrinogen level at the end of the study were higher in the olive oil group. In burned patients, Garcia-de Lorenzo et al.[95] compared, in a prospective double blind randomized study, the tolerability and metabolic effects of parenteral nutrition containing LCT/MCT with those of an olive oil-based emulsion. No difference was found in the levels of acute-phase proteins. Liver function tests were better preserved in the olive-oil group. These findings could be explained by a diminution in the inflammatory cytokine tumor necrosis factor (TNF)-alpha. Sala-Vila et al.[96] have summarized the literature on olive oil-based emulsions and concluded that they are safe, well tolerated and presented advantages in the liver function of burned patients. Reasonable data exist also for their safe long-term use in patients on home parenteral nutrition for intestinal failure.[97] No prospective studies are available to guide use in other disease states such as ARDS or septic shock.

12. Does the addition of EPA and DHA to lipid emulsions have an effect on inflammatory processes, morbidity or mortality?

Recommendation: Addition of EPA and DHA to lipid emulsions has demonstrable effects on cell membranes and inflammatory processes (Grade B). Fish oil-enriched lipid emulsions probably decrease length of stay in critically ill patients. (Grade B).

Comments: Intravenous fish oil, providing EPA and DHA, results in a higher proportion of EPA and DHA in the cell membrane and a lower proportion of arachidonic acid,[98] decreasing the synthesis of inflammatory eicosanoids and cytokines, including TNF-alpha, IL-6 and IL-8 . The stress response to IV endotoxin is blunted by fish oil.[99] In post-abdominal surgery patients iv fish oil reduced TNF-alpha and IL-6 when compared to LCT/MCT.[100] Mechanisms of action have been described recently.[101] An unblinded, multi-centre dose-related study enrolled 661 patients (SAPS II score 32) and showed that intravenous fish oil supplementation had favorable effects on survival, infection rate, antibiotic requirements and length of stay when administered in doses between 0.1 and 0.2 g/kg/day.[102] The greatest influences were observed in abdominal sepsis, in which a decrease in resting energy expenditure without any other detectable effects has also been shown.[72] Wichmann et al.[103] randomized 256 surgical patients requiring intensive care to receive 5 days of PN including soybean oil or a mixed soybean LCT/MCT/fish oil emulsion. The latter group had significant increases in EPA, LTB_5 production and antioxidants, as well as a significantly shorter length of hospital stay (17.2 vs. 21.9 days, $p = 0.006$). Use of fish oil in PN for severe pancreatitis also resulted in a decreased inflammatory response and improved respiratory function.[104] On the contrary, Friesecke et al.[105] reported that use of a mixed soybean LCT/MCT/fish oil lipid emulsion in critically ill ICU patients had no effect on inflammatory markers, or on clinical outcomes including infections, ventilation requirement, or ICU or hospital stay compared with MCT/LCT without fish oil. A recent review of the effect of including fish oils in PN in ICU patients[106] concluded that there is a significant reduction in the length of stay when the Heller,[102] Wichmann,[103] Tappy,[72] Wang[104] and Friesecke[105] studies are analyzed together; no significant difference was found in terms of mortality.

13. Mixed lipid emulsions and concentration issues

In addition to the above justifications for the inclusion of fish oil in lipid emulsions, there is some evidence that they improve the

pharmacological profile of such mixtures.[107–109] Mixed lipid emulsions including fish oil were used in two trials, one in healthy volunteers and one in ICU patients; both studies used soybean oil (LCT) as the control. The mixed emulsions were shown to be better than LCT in terms of elimination and tolerance in healthy volunteers[110] and provided better anti-oxidant status in stressed patients in the ICU.[111]

In more general terms, lipid formulations are produced in different concentrations, usually ranging from 10 to 30%. It is postulated that the deleterious effect on the lipid profile of patients given parenteral lipid solutions is due to the emulsifier – phospholipid. In a solution with a higher lipid concentration, the ratio of the emulsifier to the oil is lower, therefore ensuring a lower plasma concentration of triglycerides, phospholipids and free fatty acids. When a lower concentration of lipids (10%) is used, there is an increase in the pathological LpX.[112,113] It can reasonably be assumed that this also applies to lipid mixtures and that high concentrations should be selected whenever possible.

14. Is it safe to administer lipid emulsions (LCT without or with MCT, or mixed emulsions) and at which rate?

Recommendation: intravenous lipid emulsions (LCT, MCT or mixed emulsions) can be administered safely at a rate of 0.7 g/kg up to 1.5 g/kg over 12–24 h (Grade B)

Comments: Wichmann et al.[103] compared the safety of lipid emulsions, enriched or not with *n*-3 fatty acids from fish oil, in patients after major abdominal surgery and showed that a rate of administration up to 1.5 g/kg was safe. It is current practice to administer lipid emulsions at a rate of up to 2 g/kg/day in Australia.[114] Indeed Carpentier and Hacquebard [115] have shown that even faster rates such as 0.10–0.20 g triglycerides/kg/h, mixtures comprising MCT, fish oil and soybean LCT may lead to the incorporation of *n*-3 fatty acids into white blood cell and platelet phospholipids within hours.

15. How much should be administered to meet protein requirements?

Recommendation: When PN is indicated, a balanced amino acid mixture should be infused at approximately 1.3–1.5 g/kg ideal body weight per day in conjunction with an adequate energy supply (Grade B)

Comments: The principal goal of protein/amino acid administration in critical illness is to provide precursors for protein synthesis in tissues with high turnover and to protect skeletal muscle mass and function. While energy requirements can be directly assessed by indirect calorimetry, the optimal protein/amino acid intakes in critical illness are hard to quantify because whole body nitrogen balance is not a reliable index of adequate protein synthesis in the liver, gut mucosa and immune system.

Protein synthesis stimulation requires adequate availability of all essential amino acids. Standard amino acid solutions are defined as "balanced" when their relative composition in essential amino acids is similar to individual amino acid requirements in healthy subjects.[116] In physiological conditions, intravenous amino acid administration leads to stimulation of whole body and muscle protein synthesis, while insulin and glucose infusions preferentially inhibit proteolysis.[117] Combined insulin, glucose and amino acid administration are associated with greater anabolic effects than administration of insulin or amino acids alone.[118] The ability of amino acids to stimulate muscle protein synthesis is positively correlated to the level of physical activity which is clearly impaired in individuals confined to bed.[118,119] In critical illness, stress hormones and inflammatory mediators inhibit insulin and amino acid anabolic efficiency, and lean tissue loss is unavoidable in patients with severe trauma or sepsis despite aggressive nutritional support.[120] Acceleration of muscle proteolysis plays a pivotal role in the catabolic response to critical illness.

The anticatabolic effects of different rates of amino acid infusion have been assessed in heterogeneous groups of severely traumatized[121] or septic[122] patients receiving total parenteral nutrition. The optimal whole body protein sparing effects were achieved when amino acids were infused at mean rates of 1.3 and 1.5 g/kg/day in trauma[121] or sepsis[122] respectively. No further advantages were observed when more amino acids were provided in these groups of patients in both studies, adequate energy was given parenterally as fat and glucose. Despite the fact that similar results were obtained when proteins were given enterally,[123] these recommendation may not apply to all patients. In anuric and non-oliguric acute renal failure critically ill ventilated patients, Scheinkestel et al.[124,125] and Singer[126] demonstrated that positive nitrogen balance can be achieved with high nitrogen input (0.4 g nitrogen/kg/day) when patients were treated using continuous renal-replacement therapy or hemodialysis respectively. In acutely ill patients receiving hypocaloric feeding, nitrogen requirements were increased by about 25–30%.[127,128] Nitrogen requirements in malnourished critically ill patients are also probably increased[123] but reliable clinical data on this issue are not presently available.

16. Is there an indication for specific amino acids?

Recommendation: When PN is indicated in ICU patients the amino acid solution should contain 0.2–0.4 g/kg/day of L-glutamine (e.g. 0.3–0.6 g/kg/day alanyl-glutamine dipeptide) (Grade A).

Comments: In the 1960s with the advent of crystalline L-amino acid solutions the intravenous nitrogen source moved away from a general mix of amino acids from a protein hydrolysate. Individual amino acids have different solubility and heat stability such that the eventual mixtures of amino acids have been a pharmaceutical compromise permitting practicability and stability. L-glutamine was omitted completely because crystalline L-glutamine is poorly soluble and degrades during heat sterilization. Glutamine participates in many metabolic processes. It is, for example, involved in protein and glucose metabolism, as a carrier for nitrogen and carbon between organs, is intimately connected with many other amino acids and with protein synthesis as a precursor for nucleotides, and cellular protection through glutathione and heat shock proteins, and it is a regulator of ammonia and acid base balance.[129] It is the most abundant free amino acid. Under normal conditions it is not an essential amino acid but has an endogenous production rate (predominantly in skeletal muscle) in the range 50–80 g/24 h for an adult.[130,131] In the critically ill however it appears that an increased demand for its utilization (increased immune activity and repair) is not adequately met over a sustained critical illness, and plasma levels fall.[129,132] A low plasma level is associated with a worse outcome.[133] Glutamine containing dipeptides (alanyl–glutamine or glycyl-glutamine is more stable and soluble) and now provide the opportunity to restore or even enhance the content of PN amino acid solutions.[129] Over the last 10 years an extensive evidence base for safety and beneficial clinical outcome has been built, such that its parenteral use can now be considered a standard of care.[134] No study of intravenous L-glutamine or dipeptide has shown harmful effects in the critically ill, with doses in the range 10–30 g glutamine/24 h being safely tolerated and seen to restore plasma levels.[135] Concerns that glutamate toxicity might result have not

been borne out, and cerebral glutamate is not affected even in head trauma patients.[136] Continuous renal-replacement therapy may increase glutamine loss by 4–7 g/day further enhancing the case for glutamine supplementation in this context.[137]

The various clinical outcome studies to date have each recruited modest numbers of patients but have indicated reduced mortality[138,139] or improved morbidity[140,141] with reduced infections or improved glycaemic control. The accumulated data from three level 1 and four level 2 studies involving 530 critically ill patients indicates a reduced mortality risk with PN containing glutamine (RR 0.67 CI 0.48 −0.92, $p = 0.01$).[142] Doses used in these studies ranged from 0.2 to 0.57 g/kg/day of glutamine. Results from a large multi-centre study involving critically ill patients on PN are awaited with interest.[143] Reductions in length of stay and reduced morbidity (infections or complications) have also been shown in patients with pancreatitis (see accompanying ESPEN guidelines). Where the dipeptide cannot be incorporated within the PN itself it has been shown safe to administer it through a peripheral line.[139]

Arginine while putatively advantageous in situations of stress are already present in standard amino acid solutions. However there is no firm clinical outcome evidence to support additional supplementation in the critically ill. Furthermore the endogenous production of arginine from citrulline is supported in the presence of a sufficient supply of its substrate glutamine.[144]

17. Are micronutrients required in ICU patients?

Recommendations: All PN prescriptions should include a daily dose of multivitamins and of trace elements. (Grade C).

Comments: Providing micronutrients to include the full range of trace elements and vitamins is an integral part of nutritional support.[145] In addition many trace elements and vitamins are essential in antioxidant defense. The latter being especially challenged in the critically ill patient there is in fact an increase in the specific micronutrient requirements. Parenteral and enteral feeding preparations differ in that commercially available PN solutions contain only amino acids, glucose, lipids and some electrolytes, but (for stability reasons) no trace elements or vitamins: this mandates their separate prescription. Micronutrients are however omitted from PN in as many as 50% of patients even in a university teaching hospital setting.[146] It is possible that as the use of PN is less frequent and is provided in an apparently complete format many clinicians simply "forget" the micronutrients, having become familiar with the more truly complete nature of enteral feeding mixtures.

17.1. Trace elements

Most of the commercial trace element preparations available in 2009 were developed in the 70s and 80s, and were conceived for stable patients, to a considerable extent in line with the American recommendations made in 1979.[147] These solutions have proved suitably balanced for long-term patients with regard to the majority of trace elements, as shown for example by a study investigating the levels in autopsy tissues of iron, zinc, copper, manganese, chromium and selenium of 8 people with short bowel syndrome who died after prolonged PN.[148] Most present-day ICU patients are however far from stable, suffer from multiple organ failure, and are frequently hypermetabolic with elevated nutritional requirements.

The FDA-approved trace element formulation results in relatively high levels of copper and manganese, which may be associated with toxicity during prolonged home PN (see ESPEN guidelines on home parenteral nutrition). Manganese toxicity has also been described during its acute administration in critically ill patients where it has led to neurotoxicity.[149]

Table 2
Clinical features of the commoner acute trace element and vitamin deficiency states which may become apparent during ICU care.

Micronutrient	Clinical signs	References
Thiamine (B1)	Congestive cardiac failure, lactic acidosis	163
Ascorbic acid	Scurvy	164
Copper	Arrhythmias, altered immunity, pseudo-scurvy	165,166
Selenium	Acute cardiomyopathy	167
Zinc	Delayed wound healing, Infections	168

The European population and that of some parts of Australasia are prone to low background (premorbid) selenium status due to the low soil content in those parts of the world. Combined with acute illness this characteristic exposes patients to a very high sensitivity to oxidative stress, as has been shown in an animal model of selenium deficient rodents submitted to experimental burn injury[150]: pre-morbid deficiency worsens oxidative stress and related damage. Indeed critically ill patients are characterized by increased oxidative stress which is proportional to the severity of the condition[151] and worse in uncorrected selenium deficiency.[152]

Consequences of acute trace element deficiencies are not immediately detected as the full clinical picture requires weeks to develop. While biochemical alterations appear within 3–5 days, the biological deficiency syndrome occurs earlier still. ICU patients are generally hypermetabolic, with increased macro-nutrient, trace element and vitamin requirements (the micronutrients being required for substrate metabolism). There are numerous reports on the consequences of deficiencies (examples in Table 2), and there are, for obvious ethical reasons, no randomized trials available testing PN with or without micronutrients.

Energy and protein substrates are adapted to metabolic levels in ICUs utilizing indirect calorimetry but nothing similar exists for micronutrients, which are invariably prescribed as "1 daily dose", whatever the body weight or metabolic rate. The doses of micronutrients should indeed probably be adapted in proportion to the other substrates and with regard to the underlying disease etiology (see below) (Grade C). In presence of major weight difference, adaptation of the daily dose should be considered (Grade C) (Table 3).

When PN is prolonged, and if the patient remains critically ill, determination of plasma concentrations on a monthly basis enables detection of gross deficiencies, which should be corrected by the individual trace element: selenium and zinc deficiency are particular risks.

Table 3
Trace element availability in standard formulations and modified requirements in ICU patients.

Trace element	Range present in commercially available preparations	Modified requirements in the critically ill
Chromium/mcg	10–15	↑
Cobalt/mcg	0–1.47	–
Copper/mg	0.48–1.27	↓[a]
Fluoride/mg	0.57–1.45	–
Iron/mg	1–1.95	–↓
Iodine/mcg	10–130	↓
Manganese/mg	0.2–0.55	↓
Molybdenum/mcg	10–25	?
Selenium/mcg	20–70	↑
Vanadium/mcg	0	?
Zinc/mg	3.27–10	↑

[a] reduced except in major burns where it should be increased 5-fold for the duration of open wounds.

Selenium is an essential component of the most important extra- and intra-cellular antioxidant enzyme family, the glutathione peroxidases (GPX). Plasma GPX levels are strongly depressed with increasing severity of septic condition.[152] Several randomized supplementation trials have tested the hypothesis that outcome in sepsis might be modulated by doses between 350 and 4000 mcg/day.[153–158] In the trial using the largest dose, no beneficial effects on mortality or infections were observed, but a trend to more respiratory complications was seen. However clear benefits were apparent in the lower dose trials (350–1000 mcg/day) where an initial bolus was followed by continuous infusion.

Selenosis has been observed in the healthy population with chronic intakes $>$ 750 mcg/day: therefore doses of 750–1000 mcg/day should probably not be exceeded in the critically ill, and administration of supraphysiological doses should perhaps be limited to 2 weeks.[158] These considerations indicate that high dose supplementation is not a true part of PN, but should be considered a therapeutic intervention to reinforce antioxidant defenses in defined conditions, such as severe SIRS and septic conditions.

Major burns should be addressed separately given the large exudative losses of copper, selenium and zinc: randomized trials have shown clinical benefit [153] from doses calculated to compensate these losses (typically 3–3.5 mg copper, 30–35 mg zinc, and 350 mcg selenium per day for 2–3 weeks in burns of greater than 20% body surface area).

Continuous renal-replacement therapy is another condition in which there is a continuous effluent loss of water soluble micronutrients, varying between the equivalent of 1–2 extra adult doses of selenium, zinc and thiamine each day[159]: additional daily supplements should accordingly be given (Grade C).

Recognizing the potential for toxicity with multiple vials of the available multiple trace element products (e.g. presenting excess manganese delivery in attempting to provide more selenium) it has been advocated that each trace element is ordered separately.[148] This adds time and cost and has great potential for increasing compounding errors; moreover in many countries it is not currently possible to compose a balanced regimen from single agent products. A compromise solution may be the development of new basic multiple trace element preparation to which additional trace elements can be added for patients with increased losses such as of selenium and zinc.

17.2. Vitamins

The commercially available vitamin solutions have been upgraded during the last decade, and there have been few recent publications on deficiency occurring in the ICU setting. In general the assiduous daily delivery of a comprehensive modern vitamin regimen will suffice. Thiamine and Vitamin C deficits do pose special risks however, not least since thiamine deficiency is widespread in the population admitted to emergency units.[160] Thiamine supplements (to the level of 100–300 mg/day) should be provided during the first 3 days in the ICU in patients with possible thiamine deficiency, and especially when alcohol abuse is suspected, in order to prevent neurological side effects associated with glucose delivery from PN (Grade B).

Vitamin E, and particularly the isoform alpha-tocopherol is contained in all lipid emulsions used for PN, even if its concentration is highly variable (varying between 16 and 505 mmol/l), depending on the lipid source and the storage lifetime of the emulsion.[161] Additional supplementation is therefore not generally required.

Some patients have specific substitution requirements that should be considered separately from PN requirements, such as those with major burns and patients on continuous renal-replacement therapy. The latter increases requirements above basal recommendations mainly by causing loss of water soluble micronutrients especially ascorbic acid and thiamine [162]: 2 or 3 vials of existing standard multivitamin preparations can be administered daily to achieve an adequate dose (Grade C).

17.3. Electrolytes

Critically ill patients are prone to fluid and sodium overload, and renal dysfunction is frequent. Therefore it is neither adequate nor appropriate to propose guidelines for the use of electrolytes on the basis of body weight or as a fixed element of parenteral nutrition. The highly variable requirements should instead be determined by plasma electrolyte monitoring.

Conflict of interest

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

References

1. Sandström R, Drott C, Hyltander A, et al. The effect of postoperative intravenous feeding (TPN) on outcome following major surgery evaluated in a randomized study. *Ann Surg* 1993;**217**:185–95.
2. Simpson F, Doig GS. Parenteral vs. enteral nutrition in the critically ill patient: a meta-analysis of trials using the intention to treat principle. *Intensive Care Med* 2005;**31**:12–23.
3. Giner M, Laviano A, Mequid MM, Gleason JR. In 1995 a correlation between malnutrition and poor outcome in critically ill patients still exists. *Nutrition* 1996;**12**:23–9.
4. Villet S, Chiolero RL, Bollmann MD, et al. Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. *Clin Nutr* 2005;**24**:502–9.
5. Kreymann KG, Berger MM, Deutz NE, et al. ESPEN Guidelines on enteral nutrition: intensive care. *Clin Nutr* 2006;**25**:210–23.
6. Payne-James JJ, de Gara CJ, Grimble GK, et al. Artificial nutrition support in hospitals in the United Kingdom – 1991: second national survey. *Clin Nutr* 1992;**11**:187–92.
7. Hill SA, Nielsen MS, Lennard-Jones JE. Nutrition support in intensive care units in England and Wales: a survey. *Eur J Clin Nutr* 1995;**49**:371–8.
8. De Jonghe BC, Appere-De Vecchi, et al. A prospective survey of nutritional support practices in intensive care units patients: what is prescribed? what is delivered? *Crit Care Med* 2001;**29**:8–12.
9. Preiser JC, Berré J, Carpentier Y, et al. Management of nutrition in European intensive care units: results of a questionnaire. *Intensive Care Med* 1999;**25**:95–101.
10. Lipman TO. Grains or veins: is enteral nutrition really better than parenteral nutrition? A look at the evidence. *J Parenter Enteral Nutr* 1998;**22**:167–82.
11. Heyland DK, Schroter-Noppe D, Drover JW, et al. Nutrition support in the critical care setting: current practice in Canadian ICUs – opportunities for improvement? *J Parenter Enteral Nutr* 2003;**27**:74–83.
12. Jolliet P, Pichard C, Biolo G, et al. Enteral nutrition in intensive care patients: a practical approach. *Intensive Care Med* 1998;**24**:848–59.
13. Heyland DK, MacDonald S, Keefe L, Drover JW. Total parenteral nutrition in the critically ill patient: a meta-analysis. *JAMA* 1998;**280**:2013–9.
14. Gramlich L, Kichian K, Pinilla J, Rodych NJ, Dhaliwal R, Heyland DK. Does enteral nutrition compared to parenteral nutrition result in better outcomes in critically ill adult patients? A systematic review of the literature. *Nutrition* 2004;**20**:843–8.
15. Braunschweig CL, Levy P, Sheean PM, Wang X. Enteral compared with parenteral nutrition: a meta-analysis. *Am J Clin Nutr* 2001;**74**:534–42.
16. Golden SH, Peart-Vigilance C, Kao WH, Brancati FL. Perioperative glycemic control and the risk of infectious complications in a cohort of adults with diabetes. *Diabetes Care* 1999;**22**:1404–8.
17. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001;**345**:1359–67.
18. Kohlhardt S. A new peripheral vein catheter makes central intravenous nutrition unnecessary. *Nutrition* 1991;**7**:66.
19. Madan M, Alexander DJ, Mellor E, Cooke J, McMahon MJ. A randomised study of the effects of osmolarity and heparin with hydrocortisone on thrombophlebitis in peripheral intravenous nutrition. *Clin Nutr* 1991;**10**:309–14.
20. Turcotte S, Dubé S, Beauchamp G. Peripherally inserted central venous catheters are not superior to central venous catheters in the acute care of surgical patients on the ward. *World J Surg* 2006;**30**:1605–19.
21. Alonso-Echanove J, Edwards JR, Richards MJ, et al. Effect of nurse staffing and antimicrobial-impregnated central venous catheters on the risk for bloodstream infections in intensive care units. *Infect Control Hosp Epidemiol* 2003;**24**:916–25.
22. Durand-Zaleski I, Delaunay L, Langeron O, Belda E, Astier A, Brun-Bruisson C. Infection risk and cost-effectiveness of commercial bags or glass bottles for total parenteral nutrition. *Infect Control Hosp Epidemiol* 1997;**18**:183–8.

23. Pichard C, Schwarz G, Frei A, et al. Economic investigation of the use of three-compartment total parenteral nutrition bag: a prospective randomized unblinded controlled study. *Clin Nutr* 2000;**19**:245–51.
24. Kochevar M, Guenter P, Holcombe B, et al. ASPEN statement on parenteral nutrition standardization. *J Parenter Enteral Nutr* 2007;**31**:441–8.
25. McClave SA, Sexton LK, Spain DA, et al. Enteral tube feeding in the intensive care unit: factors impeding adequate delivery. *Crit Care Med* 1999;**27**:1252–6.
26. Barr J, Hecht M, Flavin KE, et al. Outcomes in critically ill patients before and after the implementation of an evidence-based nutritional management protocol. *Chest* 2004;**125**:1446–57.
27. Montejo JC. Enteral nutrition-related gastrointestinal complications in critically ill patients: a multicenter study. The nutritional working group of the Spanish society of intensive care medicine and coronary units. *Crit Care Med* 1999;**27**:1447–53.
28. Frankenfield DC, Coleman A, Alam S, Cooney RN. Analysis of estimation methods for resting metabolic rate in critically ill adults. *J Parenter Enteral Nutr* 2009;**33**:27–36.
29. White MS, Shepherd RW, McEnery JA. Energy expenditure in 100 ventilated, critically ill children: improving the accuracy of predictive equations. *Crit Care Med* 2000;**28**:2307–12.
30. MacDonald A, Hildebrandt L. Comparison of formulaic equations to determine energy expenditure in the critically ill patient. *Nutrition* 2003;**19**:233–9.
31. Sirvo M, Boshi V, Falconi C. Which REE prediction equation should we use in normal-weight, overweight and obese women? *Clin Nutr* 2003;**22**:193–204.
32. Singer P, Cohen JD. Clinical indications of indirect calorimetry in the intensive care setting. Year book of intensive care and emergency medicine. In: Vincent JL, editor. Berlin: Springer; 2003. p. 912–22.
33. Bartlett RH, Dechert RE, Mault JR, et al. Measurement of metabolism in multiple organ failure. *Surgery* 1982;**92**:771–9.
34. Mault J. Energy balance and outcome in critically ill patients: results of a multicenter, prospective, randomized trial by the ICU Nutrition Study Group. *J Parenter Enteral Nutr* 2000;**24**:S24.
35. Rubinson L, Diette GB, Song XS, Brower RG, Krishman JA. Low calorie intake is associated with noscomial bloodstream infections in patients in the medical intensive care unit. *Crit Care Med* 2004;**32**:350–7.
36. Dvir D, Cohen J, Singer P. Computerized energy balance and complication in critically ill patients: an observational study. *Clin Nutr* 2006;**25**:37–44.
37. Petros S, Engelmann L. Enteral nutrition delivery and energy expenditure in medical intensive care patients. *Clin Nutr* 2006;**25**:51–9.
38. Anbar R, Theilla M, Fisher H, Lev S, Madar Z, Singer P. Decrease in hospital mortality in tight calorie balance control study: the preliminary results of the TICACOS study. *Clin Nutr Suppl* 2008;**27**:S11.
39. Heideger CP, Romand JA, Treggiari MM, Pichard C. Is it now time to promote mixed enteral and parenteral nutrition for the critically ill patient? *Intensive Care Med* 2007;**33**:963–5.
40. Kirshman JA, Parce PB, Martinez A, Diette GB, Brower RG. Caloric intake in medical ICU patients. Consistency of care with guidelines and relationship to clinical outcomes. *Chest* 2003;**124**:297–305.
41. Elke G, Schadler D, Engel L, et al. Current practice in nutritional support and its association with mortality in septic patients. Results from a national prospective, multicenter study. *Crit Care Med* 2008;**36**:1762–7.
42. Martin CM, Doig GS, Heyland DK, Morrison T, Sibbald WJ. Multicentre, cluster-randomized clinical trial of algorithms for critical-care enteral and parenteral therapy (ACCEPT). *CMAJ* 2004;**170**:197–204.
43. Doig GS, Simpson F, Finfer S, et al. Effect of evidence-based feeding guidelines on mortality of critically ill adults: a cluster randomized controlled trial. *JAMA* 2008;**300**:2731–41.
44. Dhaliwal R, Jurewitsch B, Harrietha D, Heyland DK. Combination enteral and parenteral nutrition in critically ill patients: harmful or beneficial? A systematic review of the evidence. *Intensive Care Med* 2004;**30**(8):1666–71.
45. Bauer P, Charpentier C, Bouchet C, Nace L, Raffy F, Gaconnet N. Parenteral with enteral nutrition in the critically ill. *Intensive Care Med* 2000;**26**:893–900.
46. Chiarelli AG, Ferrarello S, Piccioli A, Abate A, Chini G, Berioli MB, et al. Total enteral nutrition versus mixed enteral and parenteral nutrition in patients at an intensive care unit. *Minerva Anestesiol* 1996;**62**:1–7.
47. Dunham CM, Frankenfield D, Belzberg H, Wiles C, Cushing B, Grant Z. Gut failure predictor of or contributor to mortality in mechanically ventilated blunt trauma patients? *J Trauma* 1994;**37**:30–4.
48. Herndon DN, Barrow RE, Stein M, Linares H, Rutan TC, Rutan R, et al. Increased mortality with intravenous supplemental feeding in severely burned patients. *J Burn Care Rehabil* 1989;**10**:309–13.
49. Herndon DN, Stein MD, Rutan TC, Abston S, Linares H. Failure of TPN supplementation to improve liver function, immunity, and mortality in thermally injured patients. *J Trauma* 1987;**27**:195–204.
50. Westman EC. Is dietary carbohydrate essential for human nutrition? *Am J Clin Nutr* 2002;**75**:951–3.
51. Joseph SE, Heaton N, Potter D, Pernet A, Umpleby MA, Amiel SA. Renal glucose production compensates for the liver during the anhepatic phase of liver transplantation. *Diabetes* 2000;**49**:450–6.
52. Mithieux G. New data and concepts on glutamine and glucose metabolism in the gut. *Curr Opin Clin Nutr Metab Care* 2001;**4**:267–71.
53. Leverve XM. Energy metabolism in critically ill patients: lactate is a major oxidizable substrate. *Curr Opin Clin Nutr Metab Care* 1999;**2**:165–9.
54. Leverve X. Mitochondrial function and substrate availability. *Crit Care Med* 2007;**35:9**(Suppl.):S454–60.
55. Leverve X, Batandier C, Fontaine E. Choosing the right substrate. *Novartis Found Symp* 2007;**280**:108–21.
56. Palgi A, Read JL, Greenberg I, Hoefer MA, Bistrian BR, Blackburn GL. Multidisciplinary treatment of obesity with a protein-sparing modified fast: results in 668 outpatients. *Am J Public Health* 1985;**75**:1190–4.
57. Bier DM, Brosnan JT, Flatt JP, et al. Report of the IDECG Working Group on lower and upper limits of carbohydrate and fat intake. *Eur J Clin Nutr* 1999;**53**(Suppl.):S177–8.
58. Maran A, Cranston I, Lomas J, Macdonald I, Amiel SA. Protection by lactate of cerebral function during hypoglycemia. *Lancet* 1994;**343**:16–20.
59. Impact of early parenteral nutrition completing enteral nutrition in adult critically Ill patients (EPaNIC). ClinicalTrial.gov Identifier: NCT 00512122.
60. Wilmer A, Van den Berghe G. Parenteral nutrition. In: Goldmand L, Ausiello D, editors. *Cecil textbook of medicine*. 23rd ed. PA, USA: Elsevier; 2008.
61. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy of medical intensive care patients. *N Engl J Med* 2006;**354**:449–61.
62. Finfer S, Chittock DR, Su SY, et al. NICE-SUGAR study investigators, intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009;**360**:1283–97.
63. Van den Berghe G, Wilmer A, Milants I, et al. Intensive insulin therapy in mixed medical/ surgical ICU – benefit versus harm. *Diabetes* 2006;**55**:3151–9.
64. Van den Berghe G, Wouters PJ, Bouillon R, et al. Outcome benefit of intensive insulin therapy in the critically ill – insulin dose versus glycemic control. *Crit Care Med* 2003;**31**:359–66.
65. Vanhorebeek I, De Vos R, Mesotten M, Wouters PJ, De Wolf-Peeters C, Van den Berghe G. Protection of hepatocyte mitochondrial ultrastructure and function by strict blood glucose control with insulin in critically ill patients. *Lancet* 2005;**365**:53–9.
66. Langouche L, Vanhorebeek I, Vlasselaers D, et al. Intensive insulin therapy protects the endothelium of critically ill patients. *J Clin Invest* 2005;**115**:2277–86.
67. Brunkhorst FM, Engel C, Bloos F, et al. German Competence Network Sepsis (SepNet). Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008;**358**:125–39.
68. Glucontrol Study: Comparing the Effects of Two Glucose Control Regimens by Insulin in Intensive Care Unit Patients. ClinicalTrial.gov Identifier: NCT 00107601.
69. Waitzberg DL, Torrinhas RS, Jacintho TM. New parenteral lipid emulsions for clinical use. *J Parenter Enteral Nutr* 2006;**30**:351–67.
70. Aberg W, Thorne A, Olivecrona T, Nordenstrom J. Fat oxidation and plasma removal capacity of an intravenous fat emulsion in elderly and young men. *Nutrition* 2006;**22**:738–43.
71. Tappy L, Schwarz JM, Schneiter P, et al. Effects of isoenergetic glucose-based or lipid-based parenteral nutrition on glucose metabolism, de novo lipogenesis and respiratory gas exchanges in critically ill patients. *Crit Care Med* 1998;**26**:860–86.
72. Tappy L, Berger MM, Schwarz JM, et al. Metabolic effects of parenteral nutrition enriched with *n*-3 polyunsaturated fatty acids in critically ill patients. *Clin Nutr* 2006;**25**:588–95.
73. Huschak G, Zur Nieden K, Hoell T, Riemann D, Mast H, Stuttmann R. Olive oil based nutrition in multiple trauma patients: a pilot study. *Intensive Care Med* 2005;**31**:1202–8.
74. Arnalich F, Garcia-Palomero E, López J, et al. Predictive value of nuclear factor kappa B activity and plasma cytokine levels in patients with sepsis. *Infect Immun* 2000;**68**:1942–5.
75. Bozza FA, Salluh JI, Japiassu AM, et al. Cytokine profiles as markers of disease severity in sepsis: a multiplex analysis. *Crit Care* 2007;**11**:R49.
76. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. *N Engl J Med* 2003;**348**:138–50.
77. Calder PC. *N*-3 polyunsaturated fatty acids and inflammation: from molecular biology to the clinic. *Lipids* 2003;**38**:343–52.
78. Calder PC. Use of fish oil in parenteral nutrition: rationale and reality. *Proc Nutr Soc* 2006;**65**:264–77.
79. Calder PC. *n*-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. *Am J Clin Nutr* 2006;**83**:1505S–19S.
80. Wanten GJA, Calder PC. Immune modulation by parenteral lipid emulsions. *Am J Clin Nutr* 2007;**85**:1171–84.
81. Wirtitsch M, Wessner B, Spittler A, et al. Effect of different lipid emulsions on the immunological function in humans: a systematic review with meta-analysis. *Clin Nutr* 2007;**26**:302–13.
82. Garnacho-Montero J, Ortiz-Leyba C, Jimenez-Jimenez FJ, et al. Clinical and metabolic effects of two lipid emulsions on the parenteral nutrition of septic patients. *Nutrition* 2002;**18**:134–8.
83. Chen FM, Wang JY, Sun LC, Juang RF, Huang TJ, Hsieh JS. Efficacy of medium-chain triglycerides compared with long-chain triglycerides in total parenteral nutrition in patients with digestive tract cancer undergoing surgery. *Kaohsiung J Med Sci* 2005;**21**:487–94.
84. Ball MJ. Parenteral nutrition in the critically ill: use of a medium chain triglyceride emulsion. *Intensive Care Med* 1993;**19**:89–95.
85. Waitzberg DL, Bellinati-Pires R, Salgado MM, et al. Effect of total parenteral nutrition with different lipid emulsions of human monocyte and neutrophil functions. *Nutrition* 1997;**13**:128–32.
86. Iovinelli G, Marinangeli F, Ciccone A, et al. Parenteral nutrition in ventilated patients with chronic obstructive pulmonary disease: long chain vs medium chain triglycerides. *Minerva Anestesiol* 2007;**73**:65–76.
87. Grau T, Ruiz de Adana JC, Zubillaga S, Fuerte S, Giron C. Randomized study of two different fat emulsions in total parenteral nutrition of malnourished

surgical patients; effect of infectious morbidity and mortality. *Nutr Hosp* 2003;**18**:159–66.
88. Masclans JR, Iglesia R, Bermejo B, Pico M, Rodriguez-Roisin R, Planas M. Gas exchange and pulmonary haemodynamic responses to fat emulsions in acute respiratory distress syndrome. *Intensive Care Med* 1998;**24**:918–23.
89. Smyrniotis VE, Kostopanagiotou GG, Arkadopoulos NF, et al. Long-chain versus medium-chain lipids in acute pancreatitis complicated by acute respiratory distress syndrome: effects on pulmonary hemodynamics and gas exchange. *Clin Nutr* 2001;**20**:139–43.
90. Faucher M, Bregeon F, Gainnier M, Thirion X, Auffray JP, Papazian L. Cardiopulmonary effects of lipid emulsions in patients with ARDS. *Chest* 2003;**124**:285–91.
91. Hailer S, Jauch KW, Wolfram G. Influence of different fat emulsions with 10 or 20% MCT/LCT or LCT on lipoproteins in plasma of patients after abdominal surgery. *Ann Nutr Metab* 1998;**42**:170–80.
92. Kuse ER, Kotzerke J, Muller S, Nashan B, Luck R, Jaeger K. Hepatic reticuloendothelial function during parenteral nutrition including an MCT/LCT or LCT emulsion after liver transplantation – a double-blind study. *Transpl Int* 2002;**15**:272–7.
93. Chambrier C, Bannier E, Lauverjat M, Drai J, Bryssine S, Bouletreau P. Replacement of long chain triglyceride with medium-chain triglyceride/long-chain triglyceride lipid emulsion in patients receiving long-term parenteral nutrition: effects on essential fatty acid status and plasma vitamin K1 levels. *J Parenter Enteral Nutr* 2004;**28**:7–12.
94. Mateu-de Antonio J, Grau S, Luque S, Marin-Casino M, Albert I, Ribes E. Comparative effects of olive oil-based and soyabean oil-based emulsions on infection rate and leucocyte count in critically ill patients receiving parenteral nutrition. *Br J Nutr* 2008;**99**:846–54.
95. García-de-Lorenzo A, Denia R, Atlan P, et al. Parenteral nutrition providing a restricted amount of linoleic acid in severely burned patients: a randomised double-blind study of an olive oil-based lipid emulsion vs. medium/long-chain triacylglycerols. *Br J Nutr* 2005;**94**:221–30.
96. Sala-Vila A, Barbosa VM, Calder PC. Olive oil in parenteral nutrition. *Curr Opin Clin Nutr Metab Care* 2007;**10**:165–74.
97. Thomas-Gibson S, Jawhari A, Atlan P, Brun AL, Farthing M, Forbes A. Safe and efficacious prolonged of olive oil based lipid emulsion (ClinOleic) in chronic intestinal failure. *Clin Nutr* 2004;**23**:697–703.
98. Mayer K, Fegbeutel C, Hattar K, et al. Omega-3 vs. omega-6 lipid emulsions exert differential influence on neutrophils in septic shock patients: impact on plasma fatty acids and lipid mediator generation. *Intensive Care Med* 2003;**29**:1472–81.
99. Pluess TT, Hayoz D, Berger MM, et al. Intravenous fish oil blunts the physiological response to endotoxin in healthy subjects. *Intensive Care Med* 2007;**33**:789–97.
100. Wachtler P, Konig W, Snekal M, Kemen M, Koller M. Influence of a total parenteral nutrition enriched with omega-3 fatty acids on leukotriene synthesis of peripheral leukocytes and systemic cytokine levels in patients with major surgery. *J Trauma* 1997;**42**:191–8.
101. Singer P, Shapiro H, Theilla M, Anbar R, Singer J, Cohen J. Anti inflammatory properties of omega-3 fatty acids in critical illness: novel mechanisms and an integrative perspective. *Intensive Care Med* 2008;**34**:1580–9.
102. Heller AR, Rossler S, Litz RJ, et al. Omega-3 fatty acids improve the diagnosis-related clinical outcome. *Critical Care Med* 2006;**34**:972–9.
103. Wichmann MW, Thul P, Czarnetski HD, Morlion BJ, Kemen M, Jauch KW. Evaluation of clinical safety and beneficial effects of a fish oil containing lipid emulsion (Lipoplus MLF541): data from a prospective randomized multicenter trial. *Crit Care Med* 2007;**35**:700–6.
104. Wang X, Li W, Li N, Li J. Omega-3 fatty acids-supplemented parenteral nutrition decreases hyperinflammatory response and attenuates systemic disease sequelae in severe acute pancreatitis: a randomized and controlled study. *J Parenter Enteral Nutr* 2008;**32**:236–41.
105. Friesecke S, Lotze C, Kohler J, Heinrich A, Felix SB, Abel P. Fish oil supplementation in the parenteral nutrition of critically ill medical patients: a randomized controlled trial. *Intensive Care Med* 2008;**34**:1411–20.
106. Mayer K, Seeger W. Fish oil in critical illness. *Curr Opin Clin Nutr Metab Care* 2008;**11**:121–7.
107. Buenestado A, Cortijo J, Sanz MJ, et al. Olive oil-based lipid emulsion's neutral effects on neutrophil functions and leukocyte-endothelial cell interactions. *J Parenter Enteral Nutr* 2006;**30**:286–96.
108. Van Kempen AA, van der Crabben SN, Ackermans MT, Endert E, Kok JH, Sauerwein HP. Stimulation of gluconeogenesis by intravenous lipids in preterm infants: response depends on fatty acid profile. *Am J Physiol Metab* 2006;**290**:723–30.
109. Reimund JM, Rahmi G, Escalin G, et al. Efficacy and safety of an olive oil-based intravenous fat emulsion in adult patients on home parenteral nutrition. *Aliment Pharmacol Ther* 2005;**21**:445–54.
110. Schlotzer E, Kanning U. Elimination and tolerance of a new parenteral lipid emulsion (SMOF) a double cross-over study in healthy male volunteers. *Ann Nutr Metab* 2004;**48**:263–8.
111. Antebi H, Mansoor O, Ferrier C, et al. Liver function and plasma antioxidant status in intensive care unit patients requiring total parenteral nutrition: comparison of 2 fat emulsions. *J Parenter Enteral Nutr* 2004;**28**:142–8.
112. Kalfarentzos F, Kokkinis K, Leukaditi K, Maroulis J, Onoufriou A, Alexopoulos K. Comparison between two fat emulsions: intralipid 30 percent vs intralipid 10 percent in critically ill patients. *Clin Nutr* 1998;**17**:31–4.
113. Tashiro T, et al. Intravenous intralipid 10% vs. 20%, hyperlipidemia, and increase in lipoprotein X in humans. *Nutrition* 1992;**8**:155–60.
114. Ali AB, Chapman-Kiddell C, Reeves MM. Current practices in the delivery of parenteral nutrition in Australia. *Eur J Clin Nutr* 2007;**61**:554–60.
115. Carpentier Y, Hacquebard M. Intravenous lipid emulsions to deliver omega 3 fatty acids. *Prostaglandins Leukot Essent Fatty Acids* 2006;**75**:145–8.
116. Young VR, Borgonha S. Nitrogen and amino acid requirements: the Massachusetts Institute of Technology amino acid requirement pattern. *J Nutr* 2000;**130**:1841S.
117. Tessari P, Inchiostro S, Biolo G, et al. Differential effects of hyperinsulinemia and hyperaminoacidemia on leucine-carbon metabolism in vivo. Evidence for distinct mechanisms in regulation of net amino acid deposition. *J Clin Invest* 1987;**79**:1062–9.
118. Biolo G, Tipton KD, Klein S, Wolfe RR. An abundant supply of amino acids enhances the metabolic effect of exercise on muscle protein. *Am J Phys* 1997;**273**:E122–9.
119. Biolo G, Ciocchi B, Lebenstedt M, et al. Short-term bed rest impairs amino acid-induced protein anabolism in humans. *J Physiol* 2004;**558**:381–8.
120. Streat SJ, Beddoe AH, Hill GL. Aggressive nutritional support does not prevent protein loss despite fat gain in septic intensive care patients. *J Trauma* 1987;**27**:262–6.
121. Larsson J, Lennmarken C, Mårtensson J, Sandstedt S, Vinnars E. Nitrogen requirements in severely injured patients. *Br J Surg* 1990;**77**:413–6.
122. Shaw JH, Wildbore M, Wolfe RR. Whole body protein kinetics in severely septic patients. The response to glucose infusion and total parenteral nutrition. *Ann Surg* 1987;**205**:288–94.
123. Ishibashi N, Plank LD, Sando K, Hill GL. Optimal protein requirements during the first 2 weeks after the onset of critical illness. *Crit Care Med* 1998;**26**:1529–35.
124. Scheinkestel C, Adams F, Kar L, et al. Impact of varying parenteral protein loads on amino-acid balance in critically ill anuric patients on CAVHDF. *Nutrition* 2003;**19**:813–5.
125. Scheinkestel C, Kar L, Marshall K, et al. Prospective randomized controlled trial to access caloric and protein needs of critically ill, anuric ventilated patients requiring continuous renal replacement therapy. *Nutrition* 2003;**19**:909–16.
126. Singer P. High-dose amino acid infusion preserves diuresis and improves nitrogen balance in non-oliguric acute renal failure. *Wien Klin Woch* 2007;**119**:218–22.
127. Greenberg GR, Jeejeebhoy KN. Intravenous protein-sparing therapy in patients with gastrointestinal disease. *J Parenter Enteral Nutr* 1979;**3**:427–32.
128. Choban PS, Burge JC, Scales D, Flancbaum L. Hypoenergetic nutrition support in hospitalized obese patients: a simplified method for clinical application. *Am J Clin Nutr* 1997;**66**:546–50.
129. Griffiths RD. Evidence for glutamine use in the critically ill. *Proc Nutr Soc* 2001;**60**:403–10.
130. Furst P, Pogan K, Stehle P. Glutamine dipeptides in clinical nutrition. *Nutrition* 1997;**13**:731–7.
131. Kreider ME, Stumvoll M, Meyer C, et al. Steady-state and nonsteady state measurements of plasma glutamine turnover in humans. *Am J Phys* 1997;**272**:E621–7.
132. Bongers T, Griffiths RD, McArdle A. Exogenous glutamine; the clinical evidence. *Crit Care Med* 2007;**35**:S545–52.
133. Oudemans-van Straaten HM, Bosman RJ, Treskes M, et al. Plasma glutamine depletion and patient outcome in acute ICU admissions. *Intensive Care Med* 2001;**27**:84–90.
134. Wernerman J. Role of glutamine supplementation in critically ill patients. *Curr Opin Anaesthesiol* 2008;**21**:155–9.
135. Tjader I, Berg A, Wernerman J. Exogenous glutamine: compensating a shortage? *Crit Care Med* 2007;**35**:S553–6.
136. Berg A, Bellander BM, Wanecek M, et al. Intravenous glutamine supplementation to head trauma patients leaves cerebral glutamate concentration unaffected. *Intensive Care Med* 2006;**32**:1741–4.
137. Berg A, Norberg A, Marling CR, et al. Glutamine kinetics during intravenous glutamine supplementation in ICU patients on continuous renal replacement therapy. *Intensive Care Med* 2007;**33**:660–6.
138. Griffths RD, Jones C, Palmer TEA. Six month outcome of critically ill patients given glutamine supplemented parenteral nutrition. *Nutrition* 1997;**13**:295–302.
139. Goeters C, Wenn A, Mertes N, et al. Parenteral L-alanyl-L-glutamine improves 6-month outcome in critically ill patients. *Crit Care Med* 2002;**30**:2032–7.
140. Powell-Tuck J, Jamieson CP, Bettany GEA, et al. A double blind, randomised, controlled trial of glutamine supplementation in parenteral nutrition. *Gut* 1999;**45**:82–8.
141. Déchelotte P, Hasselmann M, Cynober L, et al. L-alanyl-L-glutamine dipeptide supplemented total parenteral nutrition reduces infectious complications and glucose intolerance in critically ill patients: The French controlled, randomized, double-blind, multicenter study. *Crit Care Med* 2006;**34**:598–604.
142. Canadian Critical Care Clinical Practice Guidelines Committee. Nutritional support in mechanically ventilated critically ill adult patients. 2009 update, available via, http://www.criticalcarenutrition.com/index.php?option=com_content&task=view&id=17&Itemid=40 [accessed 04.09].
143. Andrews PJ, Avenell A, Noble DW, et al. Randomized trial of glutamine and selenium supplemented parenteral nutrition for critically ill patients. Protocol version 9, 19th February 2007, known as SIGNET (Scottish Intensive care Glutamine or seleNium Evaluation Trial). *Trial* 2007;**8**:25.

144. Vermeulen MAR, Van de Poll MCG, Ligthart-Mellis GC, et al. Specific amino acids in the critically ill patient exogenous glutamine/arginine: a common denominator? *Crit Care Med* 2007;**35**:S568–76.
145. ESPEN. *Basics in clinical nutrition*. 3rd ed. Prague: Galen; 2004.
146. Kyle U, Jetzer G, Schwarz G, Pichard C. Utilization of total parenteral nutrition (TPN) in a university hospital: a prospective quality control study in 180 patients. *Clin Nutr* 1997;**17**(Suppl. 1):48.
147. Shils ME, Burke AW, Greene HL, et al. American Medical Association, Guidelines for essential trace element preparations for parenteral use. *JAMA* 1979;**241**:2051–4.
148. Howard L, Ashley C, Lyon D, Shenkin A. Autopsy tissue trace elements in 8 long-term parenteral nutrition patients who received the current U.S. Food and drug administration formulation. *J Parenter Enteral Nutr* 2007;**31**:388–96.
149. Hardy IG, Gillanders L, Hardy G. Is manganese an essential supplement for parenteral nutrition? *Curr Opin Clin Nutr Metab Care* 2008;**11**:289–96.
150. Agay D, Sandre C, Ducros V, et al. Optimization of selenium status by a single intra-peritoneal injection of Se in Se deficient rat: possible application to burned patient treatment. *Free Radic Biol Med* 2005;**39**:762–8.
151. Alonso de Vega JM, Diaz J, Serrano E, Carbonell LF. Plasma redox status relates to the severity in critically ill patients. *Crit Care Med* 2000;**28**:1812–4.
152. Forceville X, Vitoux D, Gauzit R, Combes A, Lahilaire P, Chappuis P. Selenium, systemic immune response syndrome, sepsis, and outcome in critically ill patients. *Crit Care Med* 1998;**26**:1536–44.
153. Berger MM, Baines M, Raffoul W, et al. Trace element supplements after major burns modulate antioxidant status and clinical course by way of increased tissue trace element concentration. *Am J Clin Nutr* 2007;**85**: 1293–300.
154. Berger MM, Soguel L, Shenkin A, et al. Influence of early antioxidant supplements on clinical evolution and organ function in critically ill cardiac surgery, major trauma and subarachnoid hemorrhage patients. *Crit Care* 2008;**12**:R101.
155. Angstwurm MW, Engelmann L, Zimmermann T, et al. Selenium in Intensive Care (SIC): results of a prospective randomized, placebo-controlled, multiple-center study in patients with severe systemic inflammatory response syndrome, sepsis, and septic shock. *Crit Care Med* 2007;**35**:118–26.
156. Angstwurm MWA, Schottdorf J, Schopohl J, Gaertner R. Selenium replacement in patients with severe systemic inflammatory response syndrome improves clinical outcome. *Crit Care Med* 1999;**27**:1807–13.
157. Forceville X, Laviolle B, Annane D, et al. Effects of high doses of selenium, as sodium selenite, in septic shock: a placebo-controlled, randomized, double-blind, phase II study. *Crit Care* 2007;**11**:R73.
158. Berger MM, Shenkin A. Selenium in intensive care: probably not a magic bullet but an important adjuvant therapy. *Crit Care Med* 2007;**35**:306–7.
159. Berger MM, Shenkin A, Revelly JP, et al. Copper, selenium, zinc and thiamine balances during continuous venovenous hemodiafiltration in critically ill patients. *Am J Clin Nutr* 2004;**80**:410–6.
160. Jamieson CP, Obeid OA, Powell-Tuck J. The thiamine, riboflavin and pyridoxine status of patients on emergency admission to hospital. *Clin Nutr* 1999;**18**:87–91.
161. Wanten G, Beunk J, Naber A, Swinkels D. Tocopherol isoforms in parenteral lipid emulsions and neutrophil activation. *Clin Nutr* 2002;**21**:417–22.
162. Berger MM, Eggimann P, Heyland DK, et al. Reduction of nosocomial pneumonia after major burns by trace element supplementation: aggregation of two randomised trials. *Crit Care* 2006;**10**:R153.
163. Desport JC, Cazelles-Boudier C, Devalois B, Dolan P, Lotfi H. Evolution des concentrations de vitamine B1 chez des patients chirurgicaux en nutrition parentérale totale recevant les apports quotidiens recommandés par l'AMA. *Nutr Clin Métabol* 1995;**9**:79–86.
164. Perret JL, Lagauche D, Favier JC, Rey P, Bigois L, Adam F. Scurvy in intensive care despite vitamin supplementation. *Presse Med* 2004;**33**:170–1.
165. Sampson B, Constantinescu MA, Chandarana I, Cussons PD. Severe hypocupraemia in a patient with extensive burn injuries. *Ann Clin Biochem* 1996;**33**:462–4.
166. Hoyle GS, Schwartz RP, Auringer ST. Pseudoscurvy caused by copper deficiency. *J Pediatr* 1999;**34**:161–4.
167. de Berranger E, Colinet S, Michaud L, et al. Severe selenium deficiency secondary to chylous loss. *J Parenter Enteral Nutr* 2006;**30**:173–4.
168. Jeejeebhoy KN. Human zinc deficiency. *Nutr Clin Pract* 2007;**22**:65–7.