Summary of Statements; Intensive Care

<table>
<thead>
<tr>
<th>Subject</th>
<th>Recommendations</th>
<th>Grade</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Starvation or underfeeding in ICU patients is associated with increased morbidity and mortality</td>
<td>B</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Patients who are not expected to be on oral nutrition within 3 days should receive PN if EN is contraindicated or if they do not tolerate EN. Electrolytes (P, Mg, K) monitoring as needed. Particular caution in malnourished if suspected</td>
<td>C</td>
<td>1, 3</td>
</tr>
<tr>
<td>Requirements</td>
<td>ICU patients receiving PN should receive a complete formulation to fully cover their needs</td>
<td>C</td>
<td>1, 3</td>
</tr>
<tr>
<td></td>
<td>Provide energy as close as possible to the measured energy expenditure to decrease negative energy balance. In absence of IC, ICU patients should receiving copy past and increased to target over next 3 days.</td>
<td>B</td>
<td>2, 3, 9</td>
</tr>
<tr>
<td>Complementary PN with EN</td>
<td>All the patients receiving less than their targeted enteral feeding after 3 days should be considered for complementary PN.</td>
<td>C</td>
<td>3</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>The minimal amount required is about 2g/kg/day</td>
<td>B</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Hyperglycemia contributes to complications and death in the critically ill patient</td>
<td>A</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Hyperglycemia should be avoided to prevent infectious complications. Mortality may be decreased in surgical ICU patients if blood glucose is maintained between 4.5 and 6.1 mmol/L and if appropriate calories are delivered. Whether a target below 8.3 mmol/L is equally effective and perhaps safer remains unknown.</td>
<td>A</td>
<td>4</td>
</tr>
<tr>
<td>Lipids</td>
<td>Lipids are an integral part of PN for energy provision and ensure essential fatty acids in long term ICU patients. IV lipids can be administered safely at a rate of 0.7 up to 1.5 g/kg/d</td>
<td>B</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>LCT/MCT, olive oil and fish oil enriched emulsions show clinical advantages on Omega 6 fatty acids emulsions, (except in terms of survival)</td>
<td>B</td>
<td>6</td>
</tr>
<tr>
<td>Amino Acids</td>
<td>When PN is indicated, a balanced amino acids mixture should be infused at 1.3 – 1.5 g/kg ideal</td>
<td>B</td>
<td>7</td>
</tr>
<tr>
<td>body weight/day in patients receiving adequate energy supply</td>
<td>The amino acid solution should include 0.2 to 0.4 g/kgBW/day of glutamine (0.3 to 0.6 g/kg/day alanyl-glutamine)</td>
<td>A</td>
<td>7</td>
</tr>
<tr>
<td>------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------</td>
<td>---</td>
<td>----</td>
</tr>
<tr>
<td>Micronutrients</td>
<td>Any prescription of PN includes 1 daily dose of multivitamins and 1 daily dose of trace elements.</td>
<td>C</td>
<td>9</td>
</tr>
<tr>
<td>Route</td>
<td>Central line is required to administer high osmolarity PN mixture designed to cover the nutritional needs</td>
<td>C</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Peripheral line could be considered to administer low osmolarity (&lt; 800 mOsmol/L) mixture design to cover a fraction of the nutritional needs and mitigate a negative energy balance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mode</td>
<td>PN admixture should be administered as a complete all-in-one bag</td>
<td>B</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations:

- PN: parenteral nutrition. General term used to describe nutrition through either a central or peripheral venous catheter. ICU: Intensive Care Unit, IC: Indirect calorimetry
- EN: enteral nutrition. General term used to include both oral nutritional supplements (ONS) and tube feeding.
- IV: intravenous, LCT: long chain triglycerides, MCT: medium chain triglycerides
- ICU patients: For the use of PN in patients who have a complicated course during their ICU stay, focusing particularly on those who develop a severe inflammatory response, i.e. patients who failure of at least one organ during their ICU stay. (SOFA > 4). These guidelines are not for patients admitted for monitoring only (ICU stay below 3 days).
- The body weight used is the body weight before acute illness in case of fluid retention or obesity.
- P: phosphore, Mg: Magnesium, K: potassium, Ca: calcium, CH: carbohydrates, EPA:
- eicosapentaenoic acid, DHA: Docosahexaenoic Acid
Introduction:

Nutrition 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 of early delivery and gastrointestinal use efficiency. Parenteral nutrition (PN) represents an
alternative or additional approach when other routes are not succeeding (not necessarily failed
completely) or when it is not possible or unsafe to use other routes. The main goal of PN is to deliver
safely a nutrient mixture related to requirements and to avoid complications. This nutritional
approach has been a subject of debate in the last decades. Since there is a wide range of
interpretation regarding the content of PN, our guidance will reflect largely these different views. PN
carries the considerable risk of overfeeding which can be as deleterious as underfeeding. Therefore
the authors will present the evidence available regarding the indications, the implementation, the
calories required, the possible complementary use with enteral nutrition, but also the relative
importance of the macro and micronutrients mixed in the formula proposed to the critically ill
patient. Data on long term survival expressed as 6 month survival will also be considered a relevant
outcome measure

1. Should we use Parenteral Nutrition (PN)? When should we start PN?

1.1 Statement: Starvation or underfeeding in ICU patients results into increased morbidity
and mortality.

Comments: ICU patients 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 during 14 days or exclusive glucose (250-300 g/d) iv
administration. Those on PN had 10 times less mortality that those on glucose (1). In their meta-
analysis of PN versus 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 nor early initiated EN. Despite
an association with increased infectious complications, a grade B evidence-based recommendation
can be generated for PN use in patients in whom EN cannot be initiated within 24 h of ICU
admission or injury. Giner M et al. have shown that nutritional support influences positively
morbidity and mortality rates in critically ill patients (3). In a prospective study involving 129 ICU
patients, they found that 43% were malnourished. Length of hospital stay (p = n.s.), incidence of
complications (p < 0.01), and number of patients not 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 sicker patients.

The clinical outcome of 48 ICU patients was analyzed for the duration of mechanical ventilation,
ICU stay, and 30-days mortality (4). Energy deficit after 7 days and cumulated during the stay
(−12,600±10,520 kcal) were correlated with both total and infectious complications (P=0.048 and
P=0.0049, respectively). The correlations were also strong with the length of mechanical ventilation,
the number of days of antibiotics, and the length of ICU stay. Energy deficit was not correlated with
mortality. Villet et al. concluded that there is yet no answer to the question “how long can an ICU
patient be starved without deleterious consequences.

1.2 Recommendation: All patients who are not expected to be on normal nutrition within
three days should receive PN to fully cover their needs if EN is contraindicated or if they
cannot tolerate EN (C). If peripherally administered PN does not allows to fully cover the
patients needs, then PN should be preferably centrally administered (C)

Comments:
There is no study to evaluate the best timing for PN initiation in ICU patients. Nevertheless, the recent European (ESPEN) (5) and Canadian (CSCN) (11) clinical guidelines recommend to initiate EN within 24 hours or 24 to 48 hours, respectively, after admission to ICU. By extension, PN, if indicated, should be initiated within 24 to 48 hours after ICU admission. The recently published ESPEN guidelines stated that “The insufficient provision of nutrients is likely to result in undernutrition within eight to twelve days following surgery and/or ICU admission. In order to prevent undernutrition and related adverse effects, all ICU patients who are not expected be on a full oral diet within three days should receive EN (5). EN is recommended as the first choice route for nutrition support in ICU patients. The use of PN is reported to be between 12% to 71% and EN between 33% to 92% of critically ill patients who receive nutritional support (6, 7, 8, 9, 10, 11). 10-20% of the ICU patients have a contraindication to EN (bowel obstruction, short bowel syndrome, abdominal compartment syndrome, mesenteric ischemia) or have very limited tolerance to EN which precludes them to receive a sufficient amount of feed to cover their requirements. This condition is frequently limited to 3 to 5 days. In other patients, intolerance to EN lasts for much longer period and corresponds to an indication for PN as an absence of nutritional support would probably increase their risk for mortality and morbidity (12). It can be claimed that all patients who are not expected to be on normal nutrition within three days should receive PN, if EN is contraindicated or if they cannot tolerate EN, because no significant impact on clinical outcome has been shown during comparison between EN and PN in ICU patients (13). Indeed Heyland’s meta-analysis has evaluated the 26 randomized trials of 2211 patients in terms of clinical outcome for patients having received PN versus 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 toward fewer complications in patients with malnutrition was identified. Furthermore, patients
having received suboptimal PN (insufficient coverage of energy and protein needs) were also included and may have reduced the influence of PN on outcome.

This claim has been further reinforced by a meta-analysis of PN versus EN (2) supporting 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. In their meta-analysis of PN versus EN, Gramlich et al. (14) evaluated 13 studies and found that the use of EN as opposed to PN was associated with a significant decrease in infectious complications (relative risk 0.64 to 0.87, P = 0.004) but not with any difference in mortality rate (relative risk = 1.08 to 1.65, P =0.7). There was no difference in the number of days on a ventilator or length of stay in the hospital between groups receiving EN or PN (Mean 0.07 to 0.33, P = 0.6). PN was associated with a higher incidence of hyperglycemia. Data that compared days on a ventilator and the development of diarrhea in patients who received EN versus PN were inconclusive. In their meta-analysis of PN versus EN, Braunschweig et al. (15) found an higher risk of infection associated with PN which could be partially explained by the higher number of patients with hyperglycemia in this population. As a side conclusion, Braunschweig et al claimed 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 reduces neutrophil chemotaxis and phagocytosis and was found to be an independent risk factor for short-term infection in patients undergoing coronary artery surgery (16). Thus hyperglycemia in ICU patients could have significantly influence most of the studies comparing EN and PN in terms of clinical outcome as tight glycemic control has only been recently introduced as a routine therapy in ICU (17).
Which venous access should be used for PN administration?

Comments: Central PN is usually administered into a large-diameter vein, usually the superior vena cava though the jugular or subclavian vein. Long-term use tunnel-catheter or implanted chamber are occasionally used as alternatives to standard central catheter. Central catheter generally have a single lumen but double or triple lumen are available to allow for simultaneous administration of PN and one or more therapeutic agents incompatible with PN admixture. Central administered PN can cover all nutritional needs as the vein tolerance to hyperosmolar solution is usually not a limitation.

Alternatively peripheral 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 often covers less than the overall needs in macro- and micronutrients as the vein tolerance limits the total amount and the flow rate of nutrients because of their hyperosmolarity.

The debate on the superiority of central versus peripheral PN (18), as well as the method for optimizing peripheral PN administration (19), has been ongoing for a long time. A recent review by Turcotte et al. have recently reviewed the studies in surgical patients on peripherally inserted catheters (PIC) versus central venous catheters (CVC) for the administration of PN (20). The number of infectious complications was similar, the thrombotic episodes appeared more frequent and occurred earlier with PIC, phlebitic complications accounted for premature catheter removal in approximately 6% of PIC and approximately 40% of PICCs were removed before completion of therapy.

The prospective study by Alonso-Echanove et al. (21) has analyzed the risk factors for central venous catheter (CVC)-associated bloodstream infections (BSI) among 8,593 CVC. They showed that antimicrobial-impregnated CVC reduced by 66% the risk for CVC-associated BSI only among
patients whose CVC was used to administer PN (2.6 CVC-associated BSIs per 1,000 CVC-days vs no PN, 7.5 CVC-associated BSIs per 1,000 CVC-days; \( P = .006 \)). In addition, peripherally inserted central catheters (PICCs) were associated with a lower risk for CVC-associated BSI (\( P = .0001 \)).

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. More comparative prospective studies in ICU patients are needed to document the potential advantages of PIC over CVC. ICU patients receiving PN should have their needs fully covered. Therefore, if peripherally administered PN does not allow to fully cover the patients needs, then PN should be preferably centrally administered (C).

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

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

**Comment:** PN regimens contain more than 40 different components, including water, macronutrients (carbohydrates, lipids, amino acids), micronutrients (electrolytes, trace elements, vitamins) and other additives (e.g. glutamine, insulin, heparin). They can be administered in either “separate bottles system” or “all-in-one bag system”. The separate bottles system requires numerous i.v. line manipulations associated with increased risk of administration errors, as well as septic and metabolic complications.

In a prospective randomized unblinded controlled study (22), the 3 currently available PN separate systems “Separate Bottle” and “All-in-one Bag” were compared. PN-related activities of medical, nursing and pharmacy staffs were timed for PN administration. "All-in-one Bag” was the least expensive PN system. Separate bottle application costs were significantly higher (\( p < 0.01 \)). ASPEN
recent consensus (23) claimed that a standardized process for PN administration must be explored 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 includes 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 expertise of clinicians with nutrition support therapy is a strong factor in assuming safe PN system.

2. How much Parenteral Nutrition should critically ill patients receive?

2.1 Recommendation: During acute illness, the aim should be to provide energy as close as possible to measured energy expenditure in order to decrease negative energy balance (Grade B).

No precise amount of calories can be recommended to be provided by partial or total parenteral nutrition, since no prospective study can demonstrate an advantage in any measured technique or predicted formula. Studies are under way to show the advantages of targeting energy delivery according to measured energy expenditure.

Comment: Despite recommendations for early EN in critically ill patients (24), many authors have described the difficulty to reach the prescribed calorie intake because of cautious decision making in the early phase of stress or the early postoperative state (25), gastric paresis and lack of normal gastric emptying (26, 27) related to sepsis or treatment with noradrenaline or morphine derivates, absence of protocols (28) and a trend for a decrease in PN prescription (29). This approach is in contradiction with the recommendations of the American College of Chest Physicians (ACCP) (30) and may induce an energy deficit.
In addition, accurate determination of resting energy expenditure is not easily feasible. Equations give an approximate evaluation (31, 32, 33), and indirect calorimetry is not a tool available or used in all units (34). Moreover, evidence-based studies are lacking to demonstrate the usefulness of measuring energy expenditure in the critically ill. Barlett in 1985 (35), in a retrospective study showed that surgical ICU patients with a total energy balance lower that – 10,000 kCal during their entire ICU stay, had a mortality of more that 85%. Mault et al (36) in a prospective multicenter study compared patients with positive and negative total energy balance and showed that those with positive energy balance had a shorter length of ventilation and a shorter ICU stay. Rubinson (37) studied patients with low oral or enteral intake in the ICU and demonstrated that those with below 25% 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 in post open heart surgery patients and Dvir et al (38) observed prospectively an increase in all complications in a general intensive care unit population. Finally Petros et al (39) compared retrospectively patients who reached the calorie target to those who did not reach it and showed that the latest had an increased SOFA score and an increased mortality. A pilot of a prospective study (40) comparing calorie administration guided by indirect calorimetry to that guided by a 25 kCal/kg/day rule in 50 patients showed in an abstract (18) that tight calorie control guided by indirect calorimetry could significantly decrease hospital stay and hospital mortality by more than 50%. This first prospective randomized study in this field used the enteral and the parenteral routes to achieve the calorie target. This complementary nutritional support has been suggested by Heiddeger et al to propose the use of more enteral feeding associated with PN mainly in the first days of ICU admission.
3. Is there an indication for parenteral nutrition complementary to enteral nutrition?

Recommendation: All patients who are not expected to be on a full oral diet within 3 days and who do not receive sufficient enteral nutrition for > 24h should receive complementary parenteral nutrition (C).

Comment: There are two serious drawbacks in 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. But the ACCEPT study (41) showed that even in the intervention group the mean proportion of patients receiving EN on day 4 was only 60%. It is not surprising that the meta analysis by Simpson and Doig (2), which compiled 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).

EN also often delivers only a small amount of calories and leads to a negative cumulative energy balance. Two papers (4, 38) have shown that a cumulative energy deficit 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 the approach of mixed enteral and parenteral nutrition. The meta-analysis by Dhaliwal et al. (42) included five trials (43-47) comparing the supplementation of EN with PN. One of these trials (46) is apparently an expansion of a former study (47), so the number is reduced to four. Three of them (44-46) supplemented parenteral nutrition in patients with an obviously functioning GI tract while two of them had some odd results: Dunham et al. (45) described 37 patients who were randomized into three arms: total parentral 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. Herndon et al. (46) evaluated 39 patients with burns covering >50% TBSA and found under parenteral hyperalimentation a mortality of 63% compared to 26% in the control group (which also received between 1086±138 kcal/24h (survivors) and 2454±408 kcal/24h parenterally administered). This study suggested a net harm of excess in parenteral nutrition and even ended the "hyperalimentation" concept.

So, the study described by Bauer et al. (43) 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 daily adjusted so the sum of both routes would achieve the target of 25 kcal/kg BW/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 days mortality or in the incidence of infections. Yet, the hospital length of stay was significantly reduced from 33.7 ± 27.7 days to 31.2 ± 18.5 days.

This is only a minor benefit and certainly further and larger trials are warranted to evaluate the concept of mixed parental and enteral nutrition.

Table 1 summarizes the conflicting results regarding the PN used with or without EN and explains why recommendations are grade C.
4. **Carbohydrates: Which are the requirements?**

**Recommendation:** The minimal requirements for glucose are about 2g/kg BW/day (Grade B) and they should not exceed 5-6 g/kg/day.

**Comments:**

There is no real evidence indicating that carbohydrate are essential nutrients for Humans as it is the case for several amino acids, fatty acids and micronutrients (48). The powerful endogenous capacity of glucose synthesis (gluconeogenesis) from lactate, glycerol and amino acids in the liver but also the kidney (49) and may be in some other tissues such as muscle and gut (50), is probably sufficient to ensure a complete autonomy.

Metabolism. The specificity of glucose among other hexoses is due to its very high affinity to specific cellular plasma-membrane glucose transporters (GLUT) and phosphorylating enzymes (hexokinase). Hexokinases are the single family of enzymes able to catalyze glucose, and conversely glucose-6-phosphatase is the single way to produce glucose back 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 CH are the source of energy used for ATP synthesis. As compared to fatty acids, CH (glucose, pyruvate) has three unique properties related to energy metabolism: (i) it may provide ATP in the absence of oxygen; (ii) it offers the highest oxidative efficiency (ATP/O ratio) and (iii) it allows an anaplerotic flux providing Krebs-cycle intermediates and other compounds (51). These features evidence 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 whenever it comes from glucose, lactate or alanine, does not affect the result (52, 53).

Besides a major role in energy metabolism, CH 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 the major source of endogenous substrates together with the glycerol released from triglyceride hydrolysis. On the other hand, CH metabolism provides the carbon skeleton required for non-essential amino acid synthesis.

Regulation and homeostasis. Glucose turnover is largely increased in stress (e.g. burns), however glucose oxidation is mostly unchanged, indicating increased substrate recycling and exogenous needs are probably not much elevated. There are many substrate-recycling pathways including CH and three of them are recognized for their prominent role: (i) the glucose-lactate Cori’s cycle; (ii) the glucose-alanine Cahill & Felig’s cycle and (iii) the glutamine-glucose cycle. CH metabolism is under a tight endocrine control and insulin plays a key role among the various hormones involved. Insulin, which is the major anabolic hormone, affects directly carbohydrate, protein and lipid metabolism.

When considering glucose metabolism (i.e. glycoysis, gluconeogenesis and glycogen metabolism) insulin affects the liver, the muscles and the adipose tissue. Liver plays a prominent role in glucose homeostasis in relation to its unique capacity of glucose storage (glycogen), release and de novo synthesis (gluconeogenesis). However, it has been recently shown that a liver-specific deletion of the gene responsible for LKB1 synthesis, a protein involved in AMPK phosphorylation, was responsible for a very large increase in blood glucose in vivo associated to a strong insulin resistance (54). This finding highlights the leading role of the liver in insulin resistance.
Requirement. The powerful pathways allowing de novo synthesis and interconversion of CH₃07 complicate much the issue of exogenous CH requirement. There are several reports of low or very low carbohydrate diets in humans with no apparent side effects (55). However, basal requirement of glucose are estimated to be roughly 2 g/kg of glucose/day for an adult, although the basis of this evaluation are rather weak and as experts in the field said: “carbohydrate could be theoretically eliminated from the diet, but it is probably safe to give 150 g/day”! (56). Three situations can be differentiated regarding organ dependence on glucose.

Tissues completely or largely deprived in mitochondria (no or very poor oxidative metabolism): ATP can be provided only by glycolysis (or glycogenolysis). Theses tissues completely depend on glucose supply and include: red blood cells, probably many immune cells, all transparent tissues of the yes, kidney medulla and muscle during anaerobic contraction. However this does not mean a requirement of exogenous glucose supply since recycling pathways can supply these tissues with endogenous glucose, at the expense of liver fatty acid oxidation fueling the gluconeogenesis.

Tissue strongly, but not totally, depending on glucose: the brain. Brain metabolism represent the majority of whole body glucose oxidation (100 to 120g/day) and a rapid drop in plasma glucose results in a coma, which might be accompanied by irreversible neurological sequellae. However, ketones and lactate (57) have been shown to safely fuel the brain when blood glucose is low. Hence the brain dependency toward glucose oxidation appears to be relative, accordingly to the metabolic surroundings. Again, whether this glucose is exogenous or endogenous is another issue. However, conversely to the above situation where glucose is only concerted to lactate (glycolysis), in the case of the brain, glucose is fully oxidized and then newly formed molecules coming from either amino acids or glycerol must replace it.
Tissues not directly depending on glucose: all remaining tissues. ATP supply in these tissues can be entirely provided from fat oxidation, given the fact that the need of CH for other purposes than energy metabolism (anaplerosis, nucleic acids, signaling molecules, etc.) remains. Actually, in some cases of extreme glucose depletion, as it can be seen in massive insulin intoxication for instance, the dramatic defect in brain function contrasts with the lack of major consequence or the other physiological main functions.

Pathological considerations. High glucose is an inflammatory and pro-oxidant signal and the tight physiological regulation of glucose resulting for a very complex regulation is probably an important acquisition through Evolution. In stress, by preventing the use of glucose in muscle and adipose tissue (low priority pathways), insulin resistance may allow sparing the glucose molecules to more indispensable purposes located in injured tissues or vital organs. Interestingly trauma, non-injured muscle is insulin resistant, while injured muscle from the same organism is not! Insulin resistance could be the 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. Obviously, delivering large amounts of exogenous glucose to this patient would compromise such delicate adaptation aiming reorienting the fate of glucose at minimal consequence on blood glucose and muscle breakdown intensity, by inducing a large hyperglycemia. However it is also well known that sustained muscle protein catabolism is deleterious, this being potentially prevented by exogenous glucose administration! We try to solve presently this challenge by providing both carbohydrate and insulin to our patients (58). 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 investigations.
5. **Carbohydrates : Which level of glycemia should we reach?**

**Recommendation:** Hyperglycemia should be avoided to prevent infectious complications.

Mortality may be decreased in surgical ICU patients if blood glucose is maintained between 4.5 and 6.1 mmol/L and if appropriate calories are delivered. Whether a target below 8.3 mmol/L is equally effective and perhaps safer remains unknown. (Grade A)

**Comment:** 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 to 150 grams. 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 remains unclear.

One 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-attempted EN in order to achieve the calculated caloric needs. While awaiting the results of this study, a theoretical consideration is that in the stressed patient maximum oxidation rate of glucose is 4 to 7 mg/kg/min (for a 70 kg patient 400 to 700 grams per day). Hence, in order to decrease the risk for metabolic alterations, the maximum rate of glucose infusion should probably not exceed 5 mg/kg/min (60) and current regimens on average contain much less.
In the critically ill, insulin resistance is the reason why parenteral glucose infusion, and parenteral nutrition in general, further increases the level of circulating glucose. There is recent 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 80 and 110 mg/dl) during intensive care stay has shown to prevent such complications in 2 studies performed in surgical and medical adult ICU patients (61-62). Further analyses of these studies suggested that preventing hyperglycemia is the major factor dominating any direct effect of insulin (63-66) and that preventing hyperglycemia has 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). One large (over 6000 patients) multicenter study is still ongoing (69).

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 optimisation of guidelines on parenteral glucose infusion therefore awaits the results of studies such as the EPaNIC study (ClinicalTrial.gov Identifier: NCT 00512122).
6. How should we choose lipid emulsions in the parenteral nutrition regimen of critically ill patients?

6.1 Introduction: Classification and efficiency

Fatty acids are classified according to structural characteristics including chain length, presence of double bonds in the chain, position of double bonds, and configuration (i.e. cis vs. trans) of double bonds. Generally speaking they may be classified as saturated (no double bonds in the chain) or unsaturated (one or more double bonds in the chain), with the latter subclassified as monounsaturated (one double bond in the chain) or polyunsaturated (two or more double bonds in the chain).

According the chain length, fatty acids are termed short chain (< 8 carbons), medium chain (8 to 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-9, omega-6 and omega-3 (sometimes referred to as n-9, n-6 and n-3). 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 fatty acids (linoleic acid, an 18 carbon omega-6 fatty acid, and alpha-linolenic acid, an 18-carbon omega-3 fatty acid) cannot. These fatty acids are required to be supplied to humans and are referred to as essential fatty acids. The ICU patient requires 9 to 12 g/day of linoleic acid and 1 to 3 g 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). They can be further metabolized to longer chain, more unsaturated fatty acids including arachidonic acid (omega-6), and eicosapentaenoic acid.
(EPA) and docosahexaenoic acid (DHA) (both omega-3). Fish oil contains EPA and DHA. Olive oil contains the omega-9 monounsaturated fatty acid oleic acid.

6.2 Energy:

IV Lipids are an integral part of PN as energy source and provide essential fatty acids in long term ICU patients. They allow low calorie intake from dextrose origin for a better glucose control. Level B Experts (70) have shown that lipid emulsions when infused at 1 to 2 g/kg body weight/day rates, are safe and well tolerated and provide the required energy (10 kCal/d). Aberg W et al (71) explored the metabolic (hypertriglyceridemic clamp) and thermogenic response (by indirect calorimetry) to exogenous fat in relation to age (young and elderly patients) and found that lipid infusion was increasing energy expenditure by 6 to 9%. Fat oxidation was increased by 15 to 24% during infusion when compared to baseline and associated to increased lipoprotein lipase activity (4 to 5 fold). Tappy et al finally showed (72) in several elegant studies that administration of lipids decreased the fractional de novo lipogenesis when compared to PN –glucose based, induced a less lower increase (7% versus 26%) in the plasma glucose, in the insulin levels (40% versus 284%) and did not increase CO2 production while PN glucose based increased CO2 by 15%. Lipids were not able to inhibit endogenous glucose production and net protein oxidation. The same group found also (73) that the use of omega 3 fatty acids was energy sparing. Glucose and lipid oxidation were similar if 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 (74) and found this lipid emulsion safe and able to provide energy as glucose. Olive oil based lipid emulsions were also associated with a decrease in blood glucose.

6.3 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 to glycerol, to form triglycerides and phospholipids, or to
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 interaction with cellular lipoprotein receptors and lipoprotein metabolism and clearance from the bloodstream. Some non-esterfied 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, cytokines etc. and alter according to many physiological and pathological changes including inflammation.

Critical illness involves activation of inflammatory processes including production of eicosanoids, cytokines, and reactive species. Although the inflammatory response is part of normal host defense overzealous production of inflammatory mediators can be damaging to host tissues and may be associated with poor patient outcome. High circulating concentrations of inflammatory mediators are seen in the most critically ill patients (75) and have been associated with poor outcome (76). In association with activation of inflammatory processes, patients may display an impairment of cell-mediated immunity including suppressed antigen presenting cell activity and T cell reactivity (77). This predisposes to inability to control infection so exacerbating the poor clinical state and inducing further inflammation. 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 (78-80). Thus, the nature of lipid supplied to critically ill patients may have a role in determining clinical outcome (81). However experimental data and clinical studies do not provide a clear picture of the differential effects of lipid formulations currently available for use in parenteral nutrition (81), although it is generally considered that omega-3 fatty acids act in an anti-inflammatory manner (80, 81). The principal mechanism of action of omega-3 fatty acids is to counter the actions of omega-6 fatty acids, which may promote inflammatory processes (arachidonic acid is the substrate for synthesis of inflammatory eicosanoids).
Lipid formulations used in parenteral nutrition are composed of triglycerides with phospholipids as emulsifiers. There are a number of different formulations of parenteral lipids:

Soybean oil-based (e.g., Intralipid, Livolipid, etc); these are often referred to as long chain triglycerides (LCT)

Mixtures (usually 50:50) of LCT and medium chain triglycerides (MCT) (e.g., Lipofundin)

Mixtures (20:80) of LCT and olive oil (Clinoleic)

Structured lipids (these are triglyceride mixtures with predetermined-structured chain length formed by enzymatic manipulation of LCT and MCT)

Mixtures of lipids including fish oil (e.g. 30:30:25:15 mixture of LCT, MCT, olive oil and fish oil (SMOFLipid); 40:50:10 mixture of LCT, MCT and fish oil (Lipoplus, also known as Lipidem)

Fish oil for use as a supplement to be diluted with soybean oil (Omegaven).

A meta-analysis using data from both surgical and critically ill patients suggested that use of lipid emulsions is associated with higher complication rates (82). However the amount of calories or of carbohydrates administered has not always been controlled in the different groups being compared or in different studies and therefore the evidence for a detrimental effect of lipids does not look to be strong. Two large reviews summarize the effects of different lipid emulsions on immune function (81, 83) and do not find significant advantages of one specific emulsion. However, the immune parameters studied are numerous and subject to between-laboratory differences and overall it is currently difficult to summarize the effects of each specific emulsion.
6.4 Recommendation: LCT/MCT lipid emulsions show a clinical advantage to LCT alone but no improvement in survival. Grade B

Comments: Soybean oil-based lipid emulsions high in linoleic acid are largely used in the ICU and remain the reference emulsion. Glucose control can be achieved using balanced supply of glucose associated to lipids as demonstrated in a retrospective database analysis including 70 enteral fed and 26 parenteral nourished ICU patients (84). Many studies have proven the superiority of the LCT/MCT lipid emulsion to LCT alone. It improves nutritional status in comparison to the LCT solution alone (85). In a group of cancer patients undergoing surgery, LCT/MCT significantly improved plasma pre-albumin concentration (86) and provided a better nitrogen balance in another group (87). The LCT/MCT solution demonstrated a lower immunosuppressive effect in laboratory studies (88, 89) and fewer clinical infections. 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 rate of mortality (90). The LCT/MCT solution was superior for patients in the ICU, 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 (91). In another study, LCT infusion increased the mean pulmonary artery pressure and pulmonary venous admixture and decreased arterial PO$_2$(PaO$_2$)/fractional inspired oxygen. Smyrniotis et al (92) demonstrated that the infusion of LCT/MCT emulsions increased oxygen consumption (VO$_2$), cardiac output and CO2 production (VCO2) (97). It was demonstrated that LCT/MCT increased the PaO2/fraction of inspired oxygen FIO2 when compared to LCT emulsion alone (94). One study found lower lipoprotein X in a MCT/LCT treated group vs LCT alone (94). In a group of post-orthotopic liver transplantation patients, RES function recovery was significantly better in the
LCT/MCT group (95). These beneficial effects were observed while maintaining essential fatty acid status (96).

6.5 **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 critically ill patients, Mateu de Antonio et al (97) included 39 patients and 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 (98) compared in a prospective double blind randomized study, the tolerability and metabolic effects of parenteral nutrition containing LCT/MCT to an olive oil-based emulsion. No difference was found in the levels of acute-phase proteins. Fibrinogen was also elevated at the end of the study. These findings could be explained by a diminution in the inflammatory cytokine TNF-alpha. Sala-Vila et al (99) summarized the literature about olive oil-based emulsions and concluded that it was safe, well tolerated and presented advantages in liver function of burned patients.

6.6. **Recommendation: Addition of EPA and DHA to lipid emulsions has an effect on cell membranes and inflammatory processes (Grade B). Until larger prospective randomized studies are available, fish oil enriched lipid emulsions could be proposed in abdominal sepsis and surgical patients requiring ICU.**

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 (100), decreasing the synthesis of inflammatory eicosanoids and cytokines, including TNF-alpha, IL-6 and IL-8 (105). The stress response to IV endotoxin is blunted by fish oil (101). In post-abdominal surgery patients iv fish
oil reduced TNF-alpha and IL-6 when compared to LCT/MCT (102). Mechanisms of action have been described recently (103). An unblinded, multicentre dose-related study enrolled 661 patients (SAPS II score 32) and showed that iv fish oil 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 (104). The best effects were observed in abdominal sepsis. A study in sepsis showed a decrease in resting energy expenditure with iv fish oil without any other detectable effects (105). Wichmann et al (106) included 256 surgical patients requiring intensive care and randomized them prospectively to receive 5 days of PN including soybean oil or an LCT/MCT/fish oil lipid emulsion. The latter group had a significant increase in EPA, LTB₅ production and antioxidants, as well as a significantly shorter length of hospital stay (17.2 vs. 21.9 days, p=0.006). Friesecke et al. (107) reported that use of a mixed 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. In contrast, use of fish oil in parenteral nutrition in severe pancreatitis patients resulted in a decreased inflammatory response and improved respiratory function (108).

6.7. Mixed lipid emulsions and concentration issues.

Although there is a theoretical basis for the inclusion of fish oil as a component of a lipid mixture such as seen in SMOFLipid, there is very little direct evidence of the efficacy of such mixtures (109-112). SMOFLipid was used in two trials, one in healthy volunteers and one in an ICU; both studies used soybean oil (LCT) as the control and this is likely less than optimal. SMOFLipid was shown to be better than LCT in terms of elimination and tolerance in healthy volunteers (113) and provided a better anti-oxidant status in stressed patients in the ICU (114).
Lipid formulations are produced in different concentrations, usually ranging from 10-30%. 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 fat is lower therefore ensuring a lower plasma concentration of triglycerides, phospholipids and free fatty acids. When a lower concentration of lipids (Intralipid 10%) was used, there was an increase in the pathological LpX (115, 116).

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

**Recommendation:** Lipid emulsion (LCT, MCT or mixed emulsions) should be administered safely at a rate of 0.7 g/kg up to 1.5 g/kg during 12 to 24 hours (Grade B)

**Comments**

Wichman et al (106) compared the safety of lipid emulsions enriched or with n-3 fatty acids from fish oil in patients after major abdominal surgery and showed that this administration was safe. It is a current practice to administer lipid emulsions at a rate of 2 g/kg/day in Australia (117). Carpentier and Hacquebard M (118) even showed that even at faster rates like 0.10-0.20 g triglycerides/kg/h mixtures containing both MCT and FO triglycerides together with soybean LCT may lead to a rapid incorporation of the n-3 fatty acids in white blood cell phospholipids or platelet phospholipids within hours. Mixture of lipids have variable hydrolyzation rates. All in one preparations are more used, decrease the rates of infection but allow also lower rate of lipid emulsions (22).
7. How much protein should be administered to meet protein requirements?

Recommendation: When parenteral nutrition is indicated a balanced amino acid mixture should be infused at approximately 1.3-1.5 g/kg ideal body weight/day in patients receiving 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 are 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 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 (119). 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 (120). Combined insulin, glucose and amino acid administration is associated to greater anabolic effects than administration of insulin or amino acids alone (121). Amino acid ability to stimulate muscle protein synthesis is positively correlated with level of physical activity being impaired in bed resting subjects (121, 122). In critical illness, stress hormones and inflammatory mediators inhibit insulin and amino acid anabolic efficiency. Lean tissue loss is unavoidable in patients with severe trauma or sepsis despite aggressive nutritional support (123) 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 were assessed in heterogeneous groups of severely traumatized (124) or septic (125) patients receiving total parenteral nutrition. The
optimal whole body protein sparing effects were achieved when amino acids were infused at the mean quantities of 1.3 and 1.5 g/kg/day in trauma (124) or septic patients (125, respectively. No further advantages were observed when amino acids were provided in greater amounts. 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 (126), these recommendation may not apply to all patients. In acute patients receiving hypocaloric feeding protein requirements were increased by about 25-30% (127, 128). Protein requirements in malnourished critically ill patients are also probably increased (129) but clinical data on this issue are not presently available.

8. Is there an indication for specific amino acids?

8.1 Recommendation: When PN is indicated the amino acid solution should contain between 0.2-0.4 g/kg BW glutamine (e.g. equivalent to 0.3 to 0.6 g/kg BW of ala-gln dipeptide). Grade A

8.2 Comment: In the 1960’s with the advent of amino acid solutions the intravenous protein source moved away from the general mix of amino acids from a protein hydrolysate. Individual amino acids have different solubility’s and heat stability’s such that the eventual mixtures of amino acids were a pharmaceutical compromise to make them practical and stable. In recognition of these limitations for stressed patients different modifications have been proposed (such as branch chain amino acid enrichment) but clear benefit or harmful effects have not been reported. This is not the case for glutamine which was omitted completely because crystalline L-glutamine is poorly soluble and degrades during heat sterilisation.

Glutamine participates in many metabolic processes (e.g. involved in protein and glucose metabolism as an inter organ carrier for nitrogen and carbon, 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 as a regulator of ammonia and acid base balance) (135). It is the most abundant free amino acid that under normal conditions is not an essential amino acid with an endogenous production rate (predominantly in skeletal muscle) in the range 50-80 g/24h for an adult (136-37). In the critically ill however it appears that an increased demand for its utilisation (increased immune activity and repair) is not adequately met over a sustained critical illness and plasma levels fall (135, 138). A low plasma level is associated with a worse outcome (139).

Glutamine containing dipeptides (alanyl-glutamine or glycyl-glutamine are more stable and soluble) and now provide the opportunity to restore or even enhance the content of PN amino acid solutions (135). Over the last 10 years an extensive evidence base for safety and beneficial clinical outcome has been built such that its parenteral use is now considered a standard of care (140). No study of intravenous L-glutamine or dipeptide have shown harmful effects in the critically ill with doses in the range 10-30g glutamine/24 being safely tolerated and required to restore plasma levelsi (141).

Specifically even in head trauma patients cerebral glutamate is not affected (142). Continuous renal replacement therapy may increase glutamine loss by 4-7g/day enhancing the case for glutamine supplementation (143).

The various clinical outcome studies to date have each recruited modest numbers of patients but have indicated reduced mortality (144, 145) or improved morbidity (146, 147) with reduced infections or improved glycaemic control. Accumulated data from three level 1 and four level 2 studies involving 530 critically ill patients on meta-analysis suggests a reduced mortality risk with PN glutamine (RR 0.67 CI 0.48 -0.92, p=0.01) (87). Doses use in these studies range from 0.2 to 0.57 g/kg/day of glutamine. Results from a large multi-centre study involving critically ill patients on PN (148) and also others on enteral feeding are awaited. Reductions in length of stay and reduced morbidity (infections or complications) have also been shown in patients with pancreatitis or those undergoing
surgery (see accompanying ESPEN guidelines). Where the dipeptide cannot be incorporated within
the PN feed it has been shown safe to administer through a peripheral line (140).

Arginine while putatively advantageous in situations of stress is 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).

9. Are micronutrients required in ICU patients?

Recommendations: Any prescription of PN requires the prescription of 1 daily dose of
multivitamins and of trace elements. Grade C

Comments: Providing micronutrients i.e. trace elements and vitamins is an integral part of
nutritional support (145). In addition many trace elements and vitamins are essential in antioxidant
defence, the later being challenged in the critically ill patient: the oxidative stress contributes to
increase the specific micronutrient requirements. Parenteral and enteral feeding solutions differ in
that industrial PN solutions contain only proteins, glucose, lipids and some electrolytes, but no trace
elements or vitamins for stability reasons: this implies that they must be prescribed separately. An
abstract presented at ESPEN congress in 1997 showed that micronutrients were not prescribed in
nearly 50% of patients on PN in a University teaching hospital (146): indeed as PN is less frequent
and requires better metabolic knowledge, many clinicians just “forget” them as they consider the PN
bags to be analogue to the enteral complete feeding solutions.

9.1 Trace elements:

Most industrial preparations available in 2008 were developed in the 70s and 80s, and were
conceived for stable patients. The latter differ from most actual ICU patients who suffer multiple
organ failure including gut failure and are frequently hypermetabolic. The solutions are balanced for stable patients regarding the majority of trace elements as shown by a USA study investigating the levels in autopsy tissues of Fe, Zn, Cu, Mn, Cr, and Se of 8 people with short bowel syndrome on prolonged PN (147): of note the US recommendations were made in 1979 (148). The FDA-approved formulation result in high levels of copper and manganese, which is associated with a strong potential for copper and manganese toxicity during prolonged home PN. By contrast Mn toxicity has never been described during acute administration in critically ill patients.

The European population has some specificities with low to suboptimal selenium status due to the low soil content: when becoming acutely ill this exposes the patients to a very high sensitivity to oxidative stress as shown by an animal model using selenium normal and deficient rodents submitted to an experimental burn injury (149): pre-illness 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 (150).

Consequences of acute 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 is much ahead.

ICU patients are generally hypermetabolic, with increased nutrient requirements, and corollary increased trace element and vitamin requirements as the micronutrients are required for substrate metabolism. There are numerous reports about deficiencies (examples in table 2), and there are of course, for obvious ethical reasons, no randomised trial available testing a PN with or without micronutrients.

Energy and substrates are adapted to metabolic level in ICUs disposing of indirect calorimetry nothing similar existes for micronutrients. The micronutrients are invariably prescribed as “1 daily
dose”, whatever the bodyweight or metabolic rate. The doses of micronutrients should indeed probably be adapted in proportion to the substrates (Grade C). In presence of major weight difference, adaptation of the daily dose should be considered (Grade C).

When PN is prolonged, and if the patient remains critically ill, determination of plasma concentrations on monthly basis enables detection of gross deficiencies, that should be supplied by the individual trace element: selenium and zinc are particularly at risk.

Selenium supplementation: critically ill patients are characterized by increased oxidative stress and depressed antioxidant defences. Selenium is an essential component of the most important extra- and intracellular antioxidant enzyme family, the glutathione peroxidases (GPX): plasma levels are strongly depressed with increasing severity of septic condition (151). A series of randomised supplementation trials have been carried out testing the hypothesis that outcome in sepsis might be modulated by doses ranges between 350 and 4000 mcg per day(152-157). In the trial using the largest doses, no beneficial effects on mortality and infections were observed but a trend of more respiratory complications, while the benefits were present in the lower dose trials (350-1000).

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 their administration should be limited to 2 weeks according to actual data (158). Due to these limitations such a supplementation is not a true part of PN, but should be considered a pharmacological reinforcement of antioxidant defences in defined conditions, i.e. in severe SIRS and septic conditions.
9.2. Vitamins:

The industrial vitamin solutions have been upgraded during the last decade, with little recent publications of deficiency. Thiamine and Vitamin C are at highest risk of deficit. Thiamine deficit is widespread in the population admitted to emergency units (158).

Vitamin E, and particularly the isoform alpha-tocopherol is contained in all lipid emulsions used for PN: concentration is highly variable (varying between 16 and 505 mmol/l), and depends on the lipid source and the storage lifetime of the emulsion (159). Additional supplementation is therefore not required.

Some patients have specific substitution requirements that should be considered separately from PN requirements:

Continuous renal replacement therapy causes a continuous loss in the effluent varying between 1-2 adult doses of selenium, zinc and thiamine per day (160) that should be given in addition to basal requirements.

Major burns cause large exudative Cu, Se and Zn losses: randomised trials have shown clinical benefit (161) from doses calculated to compensate the exudates (3-3.5 mg Cu, 30-35 mg Zn, 350 mcg Se per day for 2-3 weeks in burn > 20% Body Surface Area).

A large proportion of patients having alcohol problems, thiamine supplements (100-300 mg/day) should be provided during the first 3 days in the ICU to prevent neurological side effects associated with PN glucose delivery.

There is no specific solution for these patients: it is therefore tempting to administer 2 or 3 vials of existing preparations to achieve an adequate dose. Recognizing the potential for toxicity with the available multiple trace element products of increasing the delivery of all trace element by giving
multiple vials, particularly for Mn, it has been advocated to order each trace element separately (147). This adds time and cost and has great potential for increasing compounding errors. 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 trace element losses such as selenium and zinc.

9.4 Electrolytes:

Critically ill patients generally suffer at some stage fluid and sodium overload, while kidney dysfunction is frequent. Therefore it is not adequate to propose guidelines pro kg body weight of any of the electrolytes as the requirements are extremely variable and should be determined by plasma electrolyte monitoring of Na, K, Mg, and P.
Table 1. Conflicting meta analysis results regarding PN in the ICU explaining the level C recommendations

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Specific population</th>
<th>RR</th>
<th>95% CI</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simpson (2)</td>
<td>11</td>
<td></td>
<td></td>
<td>PN improves</td>
</tr>
<tr>
<td>Gramlich (14)</td>
<td>13</td>
<td>0.64</td>
<td>0.46 0.87</td>
<td>EN better but no difference in mortality, LOV, diarrhea</td>
</tr>
<tr>
<td>Dhaliwal (45)</td>
<td>5</td>
<td></td>
<td></td>
<td>No PN effect on mortality, infection, LOV or LOS</td>
</tr>
<tr>
<td>Brauschwig (15)</td>
<td>27</td>
<td>0.64</td>
<td>0.54 0.76</td>
<td>Standard better than PN</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>3.0</td>
<td>10.9 8.6</td>
<td>PN improves</td>
</tr>
<tr>
<td></td>
<td>In Malnourished</td>
<td>1.17</td>
<td>0.88 1.56</td>
<td>PN improves</td>
</tr>
<tr>
<td></td>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infection</td>
<td></td>
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Table 2: Clinical symptoms of acute trace element and vitamin deficiencies

<table>
<thead>
<tr>
<th>Micronutrient</th>
<th>Clinical signs</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiamine (B1)</td>
<td>Congestive cardiac failure, lactic acidosis</td>
<td>(162)</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>Scurvy</td>
<td>(163)</td>
</tr>
<tr>
<td>Copper</td>
<td>Arrhythmias, altered immunity</td>
<td>(164, 165)</td>
</tr>
<tr>
<td>Selenium</td>
<td>Acute cardiomyopathy</td>
<td>(166)</td>
</tr>
<tr>
<td>Zinc</td>
<td>Delayed wound healing, Infections</td>
<td>(167)</td>
</tr>
</tbody>
</table>
Table 3: Trace element

<table>
<thead>
<tr>
<th>Trace element</th>
<th>Range present in industrial preparations</th>
<th>Modified requirements in critically ill</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromium mcg</td>
<td>10-15</td>
<td>↑</td>
</tr>
<tr>
<td>Cobalt mcg</td>
<td>0-1.47</td>
<td>-</td>
</tr>
<tr>
<td>Copper mg</td>
<td>0.48-1.27</td>
<td>↓ #</td>
</tr>
<tr>
<td>Fluoride mg</td>
<td>0.57-1.45</td>
<td>-</td>
</tr>
<tr>
<td>Iron mg</td>
<td>1-1.95</td>
<td>↓</td>
</tr>
<tr>
<td>Iodine mcg</td>
<td>0.01-0.13</td>
<td>↓</td>
</tr>
<tr>
<td>Manganese mcg</td>
<td>0.2-0.55</td>
<td>↓</td>
</tr>
<tr>
<td>Molybdenum mmol</td>
<td>10-25</td>
<td>?</td>
</tr>
<tr>
<td>Selenium mcg</td>
<td>20-70</td>
<td>↑</td>
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<tr>
<td>Vanadium mcg</td>
<td>0</td>
<td>?</td>
</tr>
<tr>
<td>Zinc mg</td>
<td>3.27-10</td>
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# reduced except in major burns where it is increased 5-fold for the duration of open wounds.
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