Nutritional Support in Intensive Care Unit (ICU) Patients

Module 18.3
Repletion, Supplementation and Pharmaco-nutrition

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Learning Objectives

- Knowledge of nutrients impacting favourably on the outcome of critically ill patients, such as some fatty acids, glutamine, antioxidants, etc;
- Concept of pharmaconutrition versus provision of balanced feeding solutions;
- Fat as substrates and fatty acid classification and main functions;
- Potential indications and controversies around the omega-3 PUFA and the various IV fat emulsions;
- Rationale and benefits of parenteral glutamine in ICU patients;
- Rationale and benefits of antioxidant micronutrients.

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Key Messages

- Fatty acids are essential to the critically ill patient;
- Intravenous lipids are an integral component of parenteral nutrition (PN); a balanced combination of fatty acids is require, along with a provision of n-3 PUFA;
- Parenteral glutamine should be supplied in nutritional doses to all ICU patients on PN;

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- Enteral glutamine should be supplemented in burn and trauma patients who are critically ill;
- Antioxidant supplementation has a good scientific rationale, but more clinical evidence is needed to indicate with which substrates and in which doses this should be done.

1. Lipids and Specific Fatty Acids
1.1 Introduction to Fatty Acids

Among lipids fatty acids are classified according to structural characteristics including chain length, the presence of double bonds in the chain, the position of double bonds, and their configuration (i.e. cis vs. trans)(1). 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 sub-classified as monounsaturated (one double bond in the chain: MUFA) or polyunsaturated (two or more double bonds in the chain: PUFA). According the chain length, fatty acids are termed short chain (< 8 carbons), medium chain (8 to 14 carbons: MCT) or long chain (16 or more carbons: LCT); 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 (also 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 must 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.

The two 18-carbon polyunsaturated fatty acids (PUFAs), linoleic (n-6) and alpha-linolenic (n-3) acid, are therefore essential dietary constituents. These two PUFAs as well as a rarer dietary n-6 fatty acid, gamma-linolenic acid (GLA) undergo elongation and desaturation in the formation of the 20-carbon PUFAs: eicosapentaenoic (EPA; C20:5[n-3]), arachidonic (AA; C20:4[n-6]) and dihomo-gamma-linolenic acid (DGLA; C20:3[n−6]). 20-Carbon PUFAs are incorporated into membrane phospholipids such as phosphatidyl-choline at the sn-2 position and serve as precursors of the ubiquitous eicosanoids, oxygenated lipid mediators that modulate tissue function, vascular tone and inflammation. Docosahexaenoic acid (DHA, C22:6[n-3]) can be formed from EPA and is a precursor for the 22-carbon docosanoids (2).

EPA and DHA are also obtained from marine food and their dietary supplementation was shown to have anti-inflammatory effects in humans over 20 years ago (3). Since then, a plethora of laboratory, clinical and epidemiologic studies have demonstrated the benefits of increasing n-3 PUFA intake in diseases with a significant inflammatory component.

In short, the rationale behind n-3 PUFA supplementation is (4): a) A normal diet contains a mixture of fatty acids and the typical modern diet contains a greater n-6/n-3 ratio than in the past, b) alpha-linolenic acid is only partially transformed to EPA, c) EPA and AA compete for enzymatic incorporation into phospholipids and transformation to eicosanoids and d) the prostaglandins, leukotrienes and thromboxanes produced from
EPA are less potent than their AA-derived equivalents. In endotoxin-treated rodents, alveolar macrophage phospholipids are enriched with EPA and GLA after only 3 days of enteral feeding (9), resulting in production of less potent eicosanoids, reduced lung permeability and neutrophil infiltrates (1, 5). The various fatty acids may be used by enteral and parenteral routes, the latter being technically most difficult to prepare, which explains the slow evolution towards emulsions with balanced fatty acid composition (6). Whatever the route, the proportion of the different fatty acids in the feeds will be the determinant of the body’s membrane composition after their integration.

1.2 Specific Fatty Acids

1.2.1 LCT
Soybean oil based lipid emulsions are historically the first safe lipid emulsions and have been used widely all over the world for more than 40 years (6). They are recognized as the reference lipid emulsion and have been studied in most of the conditions of critical illness. They are composed of LCTs containing mainly omega 6 fatty acids, and their infusion is associated with high blood levels of the omega 6 polyunsaturated fatty acids linoleic and its metabolite arachidonic acid. This may produce pro-inflammatory eicosanoids that can upregulate inflammatory mediators like TNF-alpha (7).

1.2.2 LCT/MCT
Most of the MCT studies were done in the 1990s, when they were introduced. When LCT and MCT/LCT administration were compared, TNF-alpha production was lower with the second (8). MCT/LCT has been associated with higher plasma pre-albumin and insulin concentrations (9) and better nitrogen balances (10). It was shown that infusion of MCT resulted in significant ketogenesis (11), reason for their mixing with LCT. The LCT/MCT emulsion demonstrated a lower immunosuppressive effect in laboratory studies (12) and fewer clinical infections. In a group of patients after orthotopic liver transplantation, RES (reticulo-endothelial) function recovery was significantly better in the LCT/MCT group. These beneficial effects were observed while maintaining essential fatty acid status (13).

1.2.3 Olive Oil
Olive oil has built a reputation of safety and neutrality on immune response (14). A small randomized trial in burn patients investigated the metabolic effects of PN containing LCT/MCT to an olive oil-based emulsion (15). No difference was found in the levels of acute-phase proteins but a reduction in the inflammatory cytokine TNF-alpha was observed. Another retrospective study (16) did not find any difference in infection rate, acute-phase proteins, or major health outcomes in critically ill patients. The peak leukocyte count and the fibrinogen level at the end of the study were higher in the olive oil group. Compared to LCT these solutions cause less liver alterations (17). A review of available literature confirmed the safety of these solutions across a wide range of diagnostic categories (14).

1.2.4 Omega 3 Fatty Acids and Fish Oil
Omega-3 fatty acids decrease the production of inflammatory cytokines and eicosanoids. They act both directly (by replacing arachidonic acid (AA) as an eicosanoid substrate and by inhibiting AA metabolism) and indirectly (by altering the expression of inflammatory genes through effects on transcription factor activation). Thus, long-chain n-3 fatty acids may benefit patients at risk of hyperinflammation and sepsis (18).

Intravenous fish oil, providing EPA and DHA, perfused to septic shock patients modifies the plasma free fatty acid composition to predominance of the omega-3 acids EPA and DHA over AA (19). Mechanisms of action have been summarized elsewhere (20).
1.2.5 Mixtures of Fatty Acids

Technical developments have enabled the development of mixture of lipids composed of LCTs, MCTs, fish oil and olive oil have been shown to provide better anti-oxidant status in stressed patients in the ICU. The latest randomised trials and meta-analysis show that these emulsions are safe, and cause less liver alterations than LCT emulsions (21, 22). A meta-analysis of randomised controlled trials shows that these 4 fatty acids emulsions are safe, and generally associated with less liver function alterations and attenuation of the inflammatory response (22).

1.3 Enteral Feeding Studies with Fatty Acid Modulation

Two prospective, controlled studies published in 2006 (23, 24) comparing two high fat enteral formulas previously used in Gadek’s ARDS study (25) on critically ill patients showed promising results in conditions such as ARDS and severe sepsis. In Pontes-Arruda et al’s randomized trial (23), including 165 patients with severe sepsis or septic shock and a PaO2/FiO2 ratio of < 200 mm Hg omega-3 feeding improved clinical outcome and mortality rate, which was 32.7% versus 52.1% in the control group. New organ dysfunction was also reduced in the intervention group. Improvement in oxygenation and independence from mechanical ventilation were more readily achieved in patients receiving omega-3 containing feeds. Singer et al’s trial included 100 critically ill patients with ARDS or ALI (24), ventilated with a lung protective strategy. Compared to their baseline PaO2/FiO2, the omega-3 group demonstrated significantly better increases in oxygenation on days 4 (48%) and 7 (25%) as well as faster recovery of lung compliance. Length (duration) of ventilation (LOV) was also shorter in the treatment group, but there were no significant differences in the other secondary outcomes, length of ICU/ hospital stay and mortality between the two groups. The problem with the studies was the high proportion of fat (52% of total energy) delivered to the patients which was not “standard”, and explains that later randomised studies using lower amounts of fat did not show similar respiratory, infectious or length of stay benefits (26, 27).

One of these trials which delivered omega-3 twice-daily enteral supplementation was stopped for futility reasons (28). The interpretation of this later study was complicated by the fact that the intervention group received 5 times less proteins, both groups being underfed.

1.4 Parenteral Lipid Studies

The historical development and the time of the appearance of the fatty acid emulsions on the market explains the sequence of the published studies (6).

Intravenous lipid emulsions are first an energy source, that provides 9 to 10 kcal/g of lipid. Further, they provide essential fatty acids (linoleic acid and alpha linolenic acid). They can be administered safely at the rate of 0.7 to 1.5 g/kg/day (26), if triglyceride levels are monitored. They are found in esterified form in the bloodstream, are linked to glycerol and form triglycerides and phospholipids (18).

Lipid formulations used in PN are composed of triglycerides with phospholipids as emulsifiers. There are a number of different formulations (29):

- Soybean oil-based; generally referred to as long chain triglycerides (LCT).
- Mixtures (usually 50:50) of LCT and medium chain triglycerides (MCT).
- Mixture (20:80) of LCT and olive oil.
- Structured lipids (these are triglyceride mixtures with predetermined-structured chain length formed by enzymatic manipulation of LCT and MCT) – structured lipids will soon to disappear from the market as they are very expensive to produce.
- Omega-3 from Fish oil for use as a supplement to be combined with soybean oil.
• Mixtures of lipids including fish oil in variable amounts (e.g. 30:30:25:15 mixture of LCT, MCT, olive oil and fish oil; 40:50:10 mixture of LCT, MCT and fish oil).

A large unblinded, multicentre study including 661 critically ill patients (SAPS II score 32) showed that the impact of the omega-3 emulsions on infection rate, antibiotic requirements, length of stay and on survival was dose-related, with an optimal impact with doses between 0.1 and 0.2 g/kg/day (30). The strongest effects were observed in abdominal sepsis. Most studies have been using omega 3 PUFA in smaller doses and in surgical patients. Randomized trials consistently show a benefit on length of stay, with no impact on survival (31). This was recently confirmed by a meta-analysis including 23 studies and 1502 patients, the inclusion of omega-3 in the lipids delivered with PN results lower infection rates and shorter length of stay, resulting in potentially important economic savings (32).

Use of alternative IV fat emulsions in PN, particularly olive and fish oil, was associated with improved clinical outcomes (33).

2. Glutamine

Since the 1980s it has repeatedly been shown that a poor glutamine status whether determined in muscle or in blood is present in the sickest critically ill patients, and that a low status is associated with increasing mortality (34). Glutamine is the most abundant amino acid in the human body, its main pool being in the muscle. In critical illness, there is an increased release of glutamine from the muscle into the blood, but also an increased uptake from the blood by the liver and immune cells, while the uptake by the gut mucosa remains unchanged or is relatively decreased. Because the glutamine demand in critical illness is higher than glutamine supply from the reserves, a relative shortage develops, leading to the concept that glutamine is a conditionally essential amino acid in such disease states.

A systematic review of randomized trials was published confirming parenteral glutamine supplementation in severely ill patients may reduce infections, length of stay and mortality (35).

At the other end, clinical studies have shown that extremely high levels of glutamine also carry an increased risk of mortality (36).

2.1 Mechanisms of Action

Glutamine (GLN) is a key metabolic and immune element, acting not only as an energy fuel for most cells (which is extremely important for rapidly replicating ones, like the enterocytes and the immune cells), as an anaplerotic substance (C atom donor in the Krebs cycle, therefore contributing to the synthesis of other amino acids), but also as an important antioxidative substrate (glutathione precursor), a stimulant of cellular mediated immune response, an intracellular signalling molecule, and a regulator of expression of genes related to signal transduction, apoptosis and metabolism (37). At the intracellular level, its actions are mediated through stimulation of heat shock protein expression, especially from the 70 kDa family (38). HSP induction leads to an attenuation of NF-kB activation, which subsequently inhibits the nuclear synthesis of proinflammatory cytokines, like TNF- alpha and IL-6 (39).

An important immune action of glutamine comes from its effect on intestinal permeability (40), maintaining the integrity of the intestinal barrier through its trophic effects on both the enterocytes and GALT (gut-associated lymphoid tissue) and subsequently IgA secretion (41). Maintenance of the intestinal barrier could, in part, explain the reduction in infectious complications observed in the majority of clinical trials.
2.2 Current Guidelines and Recommendations

Considering its key roles as a metabolic and immune substrate as mentioned above, and also the early and sustained drop in plasma levels in critical illness, which correlates with survival (34), GLN supplementation is theoretically indicated in all critically ill patients. Although not yet clearly proven by all clinical trials, its supplementation should be early together with nutrition in a nutritional dose and for a sufficient period of time – as long as the patient remains in a critical condition.

The best route for GLN administration is yet to be demonstrated, although available RCT's show a more positive effect on morbidity and also on mortality by the intravenous route (42). Indeed, parenteral GLN, delivered as a dipeptide (e.g. alanyl-glutamine) for stability and storage reasons in patients receiving TPN, has proved in a number of clinical trials to decrease infections, length of stay and long-term mortality in critically ill patients mainly when used along with PN. Several consistent meta-analysis have been published (35, 42).

Enteral GLN has proven beneficial in terms of decreasing infectious complications and length of stay in several categories of ICU patients, but particularly in burn and trauma patients (29). The weaker evidence for GLN by the enteral route might be related to a reduced availability to its different sites of action compared to its direct intravenously administration.

Based on the benefits demonstrated in the clinical trials, most national and international societies for clinical nutrition make strong recommendations for GLN supplementation in ICU patients. ESPEN guidelines stipulate “when PN is indicated in ICU patients, the aminoacid solution should contain 0.2 – 0.4 g/kg/day of L-glutamine (corresponding to 0.3 – 0.6 g/kg/day alanyl-glutamine dipeptide” (grade A recommendation) (29). Enteral GLN is indicated in burn and trauma patients (also grade A) (43).

Dose and timing for GLN administration in the critically ill is of utmost importance. Most recommendations indicate a dose of 0.2 – 0.4 g GLN/kg/day (which corresponds to 0.3 – 0.6 g of the dipeptide/kg/day). The duration of administration in the majority of trials was 5 – 7 days, although a duration of > 9 days has been shown to improve 6 month survival significantly when compared to less than 9 days (44). Indeed, considering its important roles in acute illness and the early and sustained increased requirements throughout critical illness, it is reasonable to supplement GLN early and as long as the patient remains critical. Glutamine delivered for less than 48 hours brings no advantage (45). A low dose (0.2 g/kg/day) and for a short duration (5 days) brings no significant benefits (46).

The large randomized controlled trial called REDOXS (47) including 1218 patients has not changed the above recommendations for several reasons. The study tested in a 2*2 factorial design de combined delivery of enteral and intravenous GLN combined or not with antioxidants versus placebo achieving the delivery of the largest ever tested doses (0.78 g/kg/day). The supplementation was started within the first 24 hours of ICU admission, and in the majority of patients without any simultaneous feeding: the majority of patients were underfed during the first week, receiving less than 40% of their energy target. Enrolment criteria were totally different from previous trials: 2 organ failures were required and resulted in 93% of patients being in shock, and 36% suffering renal failure. The latter has often been considered a relative contraindication to the delivery of GLN. A higher mortality was observed in the GLN groups, who due to hazards in randomization ended having significantly more patients with 3 and more organ failures on admission (p<0.01): on its own the later fact explains the modest increase in mortality. Nevertheless this study is important as it showns that isolated GLN without feeding is not beneficial.
3. Antioxidants

In critically ill patients, an increase in free radical production is demonstrated, as a result of the increased inflammatory response – the oxidative stress is proportional to the severity of the condition (48). The consecutive increased reactive oxygen species production may overwhelm the endogenous antioxidant defences: the latter consist of many types of molecules including several micronutrients (49), which require external supply. An uncontrolled oxidative stress further contributes to organ damage, multiorgan failure and to induce a state of “malignant inflammation”. Several studies previously showed a decrease in total antioxidant capacity in ICU patients (50) and this directly correlated with increased mortality. Decreases in plasma alpha-tocopherol, beta-carotene, ascorbate, and selenium have been repeatedly observed in critically ill patients. This is particularly the case for Selenium in Europe, where the generel population has a low selenium status due to the low soil content of this element. It is therefore a natural conclusion to add vitamins and trace elements with antioxidative effects (AOX) to the nutritional support in such patients. Moreover, industrial parenteral formulations do not contain micronutrients, for reasons of stability and avoidance of chemical interaction. These should be added routinely to all TPN solutions/mixtures, just before administration. Two sorts of trials have been conducted with AOX micronutrients: repletion trials (such as in major burns and trauma which are characterised by important losses of micronutrients) and supplementation trials in sepsis and inflammatory conditions. The first type of trials have resulted in clear beneficial effects in terms of reductions of infectious complications, of length of stay, and improved wound healing (51, 52). Several trials have been conducted in critically ill patients with sepsis and septic shock (53, 54), using high doses i.e. 1000 to 2000 mcg/day which is much higher than the recommended parenteral doses of 50 mcg/day. Benefits observed have been modest reductions of mortality, and of infectious complications. The REDOXS trial (47), which included mainly a North American population which is selenium replete, showed no effect with 800 mcg/day. Obviously the pre-illness status and the type of acute disease with presence of not of losses, as well as the dose matters in terms of requirements for AOX. Globally though this type of intervention is positive in a broad category of patients as shown by a meta-analysis (55). Point of care determinations will probably help adjust the interventions.

4. Summary

Fatty acids are special substrates for artificial nutrition. The addition of eicosanoids such as EPA and DHA, as well as GLA in enteral feeding has been associated with clinical improvement of patients suffering from acute respiratory distress syndrome, acute lung injury and severe sepsis. Their administration is recommended in these conditions. When IV lipid emulsions are used, we may choose between various formulas. They may include LCT and MCT, but also omega 3 or omega 9 fatty acid enriched emulsions, as well as a mixture of all the above. Clear clinical advantages of these emulsions have not yet been shown.

Glutamine is an amino acid with important roles in critical illness. When used with PN It has been shown to decrease infections, length of stay and even long term mortality. Glutamine should be supplemented intravenously in nutritional doses to any critically patient on total parenteral nutrition. Enteral GLN is indicated so far in burn and trauma patients.

Antioxidants are important micronutrients for the acute phase reaction. They should be routinely and daily added in patients receiving PN, as these formulations do not pre- contain micronutrients. More trials are needed to indicate which antioxidants, which combinations and also which amounts are optimal for the critically ill.
5. References


