Substrates for Enteral and Parenteral Nutrition  

Module 7.3

Immunonutrition Substrates for Enteral and Parenteral Nutrition

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Learning objectives:

- To understand the definition of immunonutrition;
- To know about each immunonutrient and understand its mechanisms of action;
- To know which substrates may be used in clinical practice;
- To know the options for medical interventions with particular immunonutrients;
- To know the guidelines for immunonutrition in ICU, surgery and gastroenterology.

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Key messages:

- Immunonutrition is a special type of nutritional therapy, in which provision of nutrients covers not only basic needs, but exerts a required clinical effect – it modifies immune system function;
- Glutamine can be beneficial in trauma and burn patients, and may also improve the outcome of surgery;
- Arginine cannot be used in severe sepsis, but is of high value in high-risk elective surgery patients;
- Omega-3-polyunsaturated fatty acids can reverse PN-associated cholestasis in children, reduce postoperative complications after GI surgery, improve the outcome in critically ill ARDS and trauma patients, and influence the progression of pancreatic cancer;
- As some of vitamins and trace elements can act as immunomodulators, their dosage should be significantly increased during catabolic stress;
- During enteral and parenteral nutrition micronutrients should be supplemented on a daily basis, but their dosage must be significantly increased during catabolic stress;
- Malnourished patients undergoing extensive surgery form a particular group who benefit from immunonutrition;
- The use of immunonutrition should be approached cautiously in patients with sepsis; in particular, regimens containing increased amount of arginine are not recommended;
- Further studies are needed to fully understand the mechanisms and clinical value of immunonutrients.
1. Definition of Immunonutrition

It is generally accepted that malnutrition alters immunocompetence and increases the risk of infection. Malnutrition affects both innate and adaptive immune responses. The consequence of protein energy malnutrition is atrophy of the lymphatic tissue in the thymus, lymph nodes and spleen. As a result we can find T lymphocyte deficiency in malnourished patients. The activation of lymphocytes by cytokines and antibodies production is also affected. Phagocytosis and complement cascade activation are decreased.

Nutrients, acting not only as a source of protein, energy or micronutrients, but also capable of modifying the immune system’s response, were called immunonutrients. Nutritional intervention based on those substrates was initially called immunostimulating or immunoenhancing nutrition, and then immunomodulating or simply immunonutrition (1,2). Immunonutrition represents a type of pharmaconutrition. Not every macro- or micronutrient may influence the immune system, but the immunosubstrates include arginine, glutamine, omega-3-fatty acids, selenium, zinc, vitamins C, E, and nucleotides. They can be administered in the form of enteral nutrition or as intravenous interventions, depending on the nutrient.

The results of clinical studies of immunonutrients have often been confusing for two major reasons:
1) authors have usually tried to analyze the impact of immunodiets by using combinations of substrates: for example, arginine, glutamine and omega-3 fatty acids, as well as vitamins C, E and nucleotides were given altogether. It made the assessment of each component impossible, and studies performed with only one of those nutrients are scarce.
2) groups of patients used for those analyses were not homogeneous, even in case of studies carried out in ICU settings or in surgical patients (in respect of the proportion of well-nourished and malnourished patients or the type of intervention which differed amongst studies).

More ambiguities are presented at the end of section 7, but despite these uncertainties, all immunonutrients are presented here and their clinical value is discussed.

2. Amino Acids

2.1. Glutamine

Glutamine (GLN) is the most abundant amino acid in humans, contributing to more than 50% of the body’s free amino acid pool (3). It is non-essential and may be synthesised in vivo, but during catabolic states caused by major surgery, burns, severe trauma or sepsis, GLN consumption may exceed its endogenous production. For that reason it has been called a “conditionally essential” amino acid (4). In situations like those, the skeletal muscle glutamine depletes rapidly and irrevocably.

GLN plays an important role in nitrogen transport, in the maintenance of the cellular redox state, and the mediation of metabolic processes (5). It acts as a precursor for glutathione synthesis, and provides substrate for hepatic gluconeogenesis and nucleotide synthesis in enterocytes, lymphocytes and neutrophils (6-10). It is also the preferred fuel for macrophages and other cells involved in wound repair – it stimulates proliferation of these cells via polyamine synthesis and via glutamate conversion to proline (9,10). Additional functions include participation in acid-base homeostasis, enhancement of the expression of heat shock proteins and the promotion of lymphocyte proliferation (8,9,10,11).

As glutamine is relatively unstable in solution unless it is bound to protein, supplemental glutamine is available in powdered form or in high glutamine hydrolysate formulas.
Parenteral GLN is generally provided as dipeptides such as glycyl-glutamine (GLY-GLN) or alanyl-glutamine (ALA-GLN) (11).

**Experimental data**
Glutamine administration reduces GI bacterial translocation and increases synthesis of nucleic acids; it enhances activation and proliferation of lymphocytes and macrophages, and the expression of interleukins 1 and 2 (IL-1 and 2) (12). In animals GLN supplementation protects the GI mucosa in various models of injury via preservation of intracellular glutathione levels and stimulation of enterocyte proliferation (12). In the cancer setting, it limits protein breakdown and increases protein synthesis (12). In short bowel models the administration of GLN reduces the incidence and severity of diarrhoea and stimulates mucosal growth; it also helps to reduce mucosal permeability in mucosal atrophy related to total parenteral nutrition and during sepsis (11, 12). A lot of mechanisms have been identified through which intraluminal glutamine may affect the gut during and after shock-induced ischaemia/reperfusion (IR) insult. Glutamine is a preferred fuel source and key player in the intermediary metabolism of the gut mucosa. In a rodent gut IR model Kles and Tappenden demonstrated that glutamine absorption is preferred over glucose absorption (13). During ischaemia, glucose transport was severely impaired and not improved by intraluminal glucose infusion, and in contrast to that, glutamine transport was maintained and further enhanced by intraluminal glutamine infusion. It was also proved that intraluminal infusion reverses the shock-induced splanchnic vasoconstriction that persists after effective systemic shock resuscitation, and that this mesenteric vasodilation occurs under IR conditions because of glutamine activation of adenosine A2b receptors, which release nitric oxide into the enteroportal circulation (14). It is also well known that intraluminal glutamine induces a variety of protective mechanisms against IR insults, such as antioxidant enzymes (glutathione and haem-oxygenase-1) or the anti-inflammatory transcription factor, peroxisome proliferator activator receptor gamma (PPAR) (15,16,17). Moreover, glutamine may play a crucial regulatory role in epithelial growth factor activation of extracellularly-regulated kinases, which are necessary in enterocyte proliferation (18).

**Clinical data**
Clinical studies showed a protective effect of GLN on intestinal mucosa trophism and T-lymphocyte responses (12,19). A meta-analysis has shown that intravenous administration of 20–40 g/24 h of Gin-dipeptide improves short-term outcome in abdominal surgery patients (20). Studies of Houdijk et al, and Jones et al. performed in ICU and in multiple trauma patients showed positive outcomes after the use of glutamine-supplemented enteral formulas at a level of 10 g to 14 g glutamine per litre (21,22). Studies in severely burned patients showed that the addition of glutamine to a standard enteral feeding formula had a favorable effect on the preservation of intestinal structure (23). A meta-analysis of 14 clinical trials examined the effects of glutamine supplementation in mixed populations of critically ill and surgical patients (24). Authors observed that its supplementation with higher doses (>0.2 g/kg/d) was associated with decreased rates of mortality, infectious complications, and hospital length of stay (24). Another meta-analysis recommended using enteral glutamine in burned or trauma patients based on the impact on mortality and a trend toward reduced infectious comorbidity (25, 26). The study of McQuiggan et al confirmed that enteral glutamine during active shock resuscitation is not only safe but also enhances enteral tolerance (21).

In various clinical studies in the ICU setting, intravenous administration of GLN (0.2–0.4 g/kg/day) in the form of dipeptide (0.3–0.6 g/kg/day) contributed to improved glycaemic control and morbidity, and to reduce the prevalence of infections and mortality (28). In their vast meta-analysis Marik and Zaloga noted that enteral nutrition with supplemented glutamine appeared to be beneficial (decreased infections and LOS) in burns patients, probably because burns are associated with severe gastrointestinal mucosal injury, leading to increased bacterial translocation, resulting in secondary multi-
system organ dysfunction syndrome (MODS) (29). In experimental and clinical studies, both enteral and parenteral glutamine have been demonstrated to restore the integrity of the GI mucosa and decrease bacterial translocation (22). The potentially protective role of GLN against radiotoxicity and chemotoxicity is less obvious and needs further well-conducted placebo-controlled studies.

The meta-analysis of clinical trials in surgical patients performed by Wang et al. showed that parenteral administration of glutamine was related to positive clinical outcomes. The perioperative administration of glutamine dipeptide was beneficial and resulted in the reduction of the length of hospital stay (LOS) and had a tendency to reduce infectious complications (11). Also, randomized controlled studies showed that administration of enteral immunodiet containing glutamine were beneficial in surgical patients when administered pre- or postoperatively (1,19). Malnourished surgical patients are the most likely to benefit from immunodiet (30,31,32,33). Haematopoietic stem cell transplantation patients may also benefit from intravenous glutamine. Further studies are needed, however, to determine the underlying mechanism for the observed positive effect after GLN dipeptide supplementation via the total parenteral route, and its optimal timing and dose response.

2.2. Arginine

Arginine (ARG) is a non-essential amino acid, which may become essential in stress conditions, like glutamine. Its effects on the immune system are also similar to those of GLN, because of analogous pathways (12). ARG is synthesized in the kidneys from citrulline, which stems from glutamine digested in the intestine. Arginine plays an important part in the transport, storage, and excretion of nitrogen via the urea cycle. Its conversion to citrulline by nitric oxide synthase (NOS) leads to nitric oxide (NO) formation, which is a potent mediator of the inflammatory response. NO induces the recruitment and migration of leucocytes, and influences the infiltration of the gastrointestinal mucosa by granulocytes. NO in small amounts positively affects innate immunity, but the disproportionate production of NO due to NOS induction by inflammatory cytokines or bacterial endotoxins has pro-inflammatory effects (12).

Arginine promotes the proliferation of rapidly dividing cells such as lymphocytes, enterocytes and fibroblasts by stimulating the release of growth hormone and polyamine synthesis from ornithine (12).

**Experimental data**

Animal models have shown the following effects of arginine supplementation: stimulation of thymic growth, the mononuclear response to mitogens, proliferation of lymphokine-activated natural killer (NK) cells, the release of growth hormone, prolactin, insulin, glucagon, and polyamines (12). Those models also demonstrated that suppression of NO production resulted in the increase of gastrointestinal (GI) permeability and splenic atrophy and decreased haematopoiesis along with the reactivity of mast cells and worsened overall survival (12). On the other hand, arginine supplementation in severe sepsis may be deleterious because elevated levels of NO may result in increased GI vascular permeability (12). In radiation enteritis arginine administration increased mucosal thickness and villous height, improved barrier function, and diminished bacterial translocation in short bowel patients. It also helped in wound healing (12). In experimental studies, L-arginine improved wound healing, restored postoperative depressed macrophage function and lymphocyte responsiveness, and augmented resistance to infection (34,35).

**Clinical data**

Nutrition enriched with arginine proved to be beneficial in high-risk elective surgery patients, while it failed to improve outcomes in trauma patients and patients with sepsis (36). The explanation for that observation is unclear; it seems, however, that in the latter groups conversion of arginine to nitric oxide is increased, moreover, arginine may augment inflammatory responses in these patients (36). In contrast to ICU, in surgical
patients, arginine levels are decreased and arginine degradation (via arginase) is increased in patients with surgical trauma. Therefore, in those patients ARG may restore depressed humoral and cell-mediated immunity and promote wound healing (36). In the study of Ferreras et al. patients fed with the arginine and ω-3–supplemented formula had higher local hydroxyproline levels in their surgical wounds and developed fewer surgical wound complications (38).

2.3. Taurine, Leucine, Cysteine

Leucine represents the group of branched amino acids and it is the most abundant essential amino acid. Taurine is the most abundant amino acid in leucocytes (up to 60% of total amino acids) (39). Cysteine is a precursor for glutathione synthesis. In in vitro studies leucine was shown to regulate the protein turnover in skeletal muscle and adipose tissue. Cysteine was able to modulate glutathione metabolism and influence the interaction between monocytes and lymphocytes. Taurine improved cell membrane stability and acted as an antioxidative factor. No confirmed data exist, however, on the clinical value of these potent amino acids. Further human studies are required.

3. Nucleotides

Nucleotides are biologically active substances, which participate in the important processes of DNA and RNA synthesis, production of adenosine triphosphate (ATP), cyclic adenosine monophosphate (cAMP), some coenzymes (e.g. nicotinamide adenine dinucleotide (NAD+), flavin adenine dinucleotide (FAD), coenzyme A (CoA)) and biosynthesis intermediates (e.g. uridine diphosphate glucose (UDP-glucose)) (12).

Nucleotides are usually synthesized from endogenous substrates, such as glutamine, glycine, aspartate, carbon dioxide and tetrahydrofolate, but, like arginine and glutamine, their synthesis during catabolic stress may be insufficient. The gut and gut-associated lymphoid tissue are affected the most in such states, and the “salvage pathway” is used for those tissues. In that mechanism dietary nucleotides are utilized directly (12).

Experimental data
In animal models nucleotides activated macrophages, increased the number of T-helper cells and the expression of cytokines in the spleen (IL-2). The administration of nucleotides increased villus height and crypt depth during long-term parenteral nutrition (PN), reduced diarrhoea in lactose intolerance, helped tissue recovery from ischaemia–reperfusion injury and GI mucosal trophism in PN-fed rats, increased recovery rates in cardiac ischaemia and radiation, as well as decreasing bacterial translocation in severe starvation (12).

Clinical data
Studies in a paediatric population demonstrated that nucleotide supplementation in infant formula milk positively affects lipid metabolism, resistance to infection, growth and development (39). The incidence and duration of acute diarrhoea was lowered in infants fed with a nucleotide-supplemented formula (40). Nucleotide-enriched diets decreased the prevalence of infectious complications and length of hospital stay in patients with GI cancer undergoing major elective surgery, but in those studies nucleotides were used in an admixture together with other immunonutrients. Dietary nucleotides were recently shown to modestly reduce the feeling of incomplete evacuation and abdominal pain in irritable bowel syndrome (41).

4. Omega-3-polyunsaturated Fatty Acids

Omega-3 fatty acids are polyunsaturated fatty acids (PUFA) with a terminal double bond on carbon number 3 (42). The simplest omega-3 fatty acid is alpha-linolenic acid. Fish oil contains other n-3–PUFAs: eicosapentaenoic acid (EPA, C20:5, n-3) and docosahexaenoic acid (DHA, C22:6, n-3). Contrary to saturated fatty acids, which exert proinflammatory
effects, EPA and DHA have been considered to be of benefit in patients at risk of inflammation due to their favourable immunomodulatory and anti-inflammatory properties (43,44,45). They act directly (by replacing arachidonic acid as an eicosanoid substrate and by producing anti-inflammatory lipid mediators, including resolvins, protectins and lipoxins) and indirectly (by altering the expression of inflammatory genes by influencing the activation of transcription factor). Therefore it has been postulated that the administration of n-3 LC-PUFA from fish oil (EPA and DHA) leads to a more balanced immune response which may result in a faster resolution of inflammation and recovery (44,45).

Mechanisms of action of omega-3-FA include:
- alterations in the physical properties of the cell membrane;
- effects on cell signaling pathways (transcription factors reported to be modified by the presence of long-chain omega-3 FA include nuclear factor kappa B (NFkB) and peroxisome proliferator activated receptor (PPAR)-alpha and gamma;
- alterations in the pattern of lipid mediators produced.

Mean intakes of long-chain omega-3 fatty acids among adults in the United Kingdom, in other Northern European, North American and Australasian countries reach 0.15–0.25 g/d (12). The oil obtained from the flesh of oily fish or the livers of lean fish is named ‘fish oil’ and it has the distinctive characteristic of being rich in long-chain omega-3 fatty acids (12). It is important to realize that when we discuss effects of the administration of emulsions containing omega-3-fatty acids or composed of fish oil, we are de facto discussing the impact of eicosapentaenoic acid (EPA, 20 carbons and 5 double bonds) and docosahexaenoic acid (DHA, DHA, 22 carbons and 6 double bonds) and in some cases alpha linolenic acid (ALA, 18 carbons and 3 double bonds). Hence it would be appropriate to concentrate on EPA and DHA content, and not the amount of fish without describing the percentage of EPA and DHA in the solution.

Various oily fish contain different amounts of omega-3 fatty acids, and so do fish oils. EPA and DHA comprise about 30% of the fatty acids in a typical preparation of fish oil. That is, a 1g capsule of fish oil can provide approx. 0.3 g of EPA plus DHA. Also the relative proportions of the individual long-chain omega-3 fatty acids vary among fish. For example, cod liver oil is richer in EPA than DHA, whereas tuna oil is richer in DHA than EPA. These observations apply also to the content of EPA and DHA in enteral and parenteral substances, further complicated by the fact that they were constructed using two different monographs on omega-3 published in European pharmacopoeiae.

Three lipid emulsions that include fish oil as a component are available for use in parenteral nutrition: Omegaven, Lipoplus, and SMOFLipid. Omegaven is a pure fish-oil emulsion (100 g lipid/l) that contains approximately 3 g EPA w 100 ml, Lipoplus (known also as Lipidem) represents a mix of 50% medium-chain triglycerides, 40% soybean oil and 10% fish oil. Each 100 ml of Lipoplus will typically contain about 0.8-1.7 g of EPA + DHA in 100 ml. SMOFLipid is a mix of 30% medium-chain triglycerides, 30% soybean oil, 25% olive oil and 15% fish oil. Each 100 ml of SMOFLipid will typically contain about 3 grams of EPA and 0.36 g of DHA.

**Experimental data**

Animal model studies demonstrated that a diet containing omega-3-PUFAs inhibits the hepatic synthesis of triglycerides and partially replaces arachidonic acid (AA) with EPA and DHA in the phospholipid pool of the membrane (12). Their presence improves the structure of the membrane, ligand/receptor binding, enzyme secretion, antigen presentation and activates intracellular signaling pathways (12). When released from the membrane, EPA and DHA depress AA-derived eicosanoid synthesis by cyclooxygenase and lipoxygenase in platelets, monocytes and macrophages, thereby delaying platelet aggregation and progression of atherogenesis. In experimental models, omega-3 PUFAs also show protective effects against the development of tumours, metastases and cachexia (45).

EPA and DHA were able to influence the resolution of the inflammatory state by induction of recently discovered resolving factors, such as resolvins, protectins and lipoxins.
In vitro and in vivo studies have shown that omega-3-PUFA may decrease “sprouting angiogenesis”, suppress endothelial cell proliferation, decrease tumour microvessel density and even decrease tumour growth (46,47,48).

**Clinical data**

In heart disease patients the administration of omega-3 PUFAs results in a lower prevalence of coronary artery disease, which is confirmed by the observation of fish-based food-consuming populations (e.g. Inuits). A diet rich in omega-3 PUFAs decreases the incidence of renal and cardiovascular disease (e.g. hypertension, arrhythmia), probably by inhibiting thrombogenesis and cytokine-dependent inflammation. In patients with pancreatic cancer, fish-oil supplementation helps to reduce inflammation and to stabilize energy expenditure. Fish oils improved the quality of life in pancreatic cancer patients by reducing cachexia, increasing appetite and increasing performance status (50).

Parenteral infusion of n-3 LC-PUFA from fish oil has repeatedly been shown to be effective in reversing PN-associated cholestasis in children, when administered alone or in combination with a soybean oil based lipid emulsion (51, 52). The long-term use of omega-3 enriched parenteral nutrition in home settings also showed a trend for the preservation of liver function.

Meta-analyses of clinical trials confirm the reduction of postoperative complications and the shortening of LOS in surgical patients (53). For those reasons the European Society of Clinical Nutrition and Metabolisms (ESPEN) has already acknowledged that the optimal PN regimen for surgical patients should include supplemental n-3 fatty acids (Grade C (19). Also critically ill patients may benefit from the administration of omega-3 diets. This kind of therapy should be used in ARDS patients, mild sepsis (Grade B) and trauma patients (Grade A) (28).

**5. Vitamins**

Vitamins may improve immune system function by enhancing innate defence mechanisms as well as via cell-mediated immunity, and the production of antibodies (54).

In stress conditions vitamin E acts as a free radical scavenger, while vitamin C acts as an enzyme co-factor and scavenger of lipid peroxidation products. Vitamins A, B6, B12, C, D and E support the Th1 cytokine-mediated immune response and the production of cytokines and prostaglandins. Vitamins A and D affect the cell-mediated and humoral antibody response and support the Th2-mediated anti-inflammatory cytokine response (12).

In commercially available PN solutions vitamins should ideally be added just before administration for stability reasons (12). The recommended doses for adult patients are usually 10 IU/day (9.1 mg/day) of vitamin E, 200 mg/day of vitamin C. In all lipid emulsions, the concentration of vitamin E should be >0.4 mg/g of PUFAs to avoid lipid peroxidation (55). It is emphasized that the determination of nutritional requirements should be based on the monitoring of plasma concentrations together with the measurement of SIRS.

**6. Trace elements**

Like the vitamins, trace elements also contribute to the immune defense at various levels (54). They too form part of the antioxidant defence system. Some of them act as enzyme cofactors (e.g. selenium for glutathione peroxidase) to eliminate species involved in the initiation of free-radical chain reactions (12).

Iron, zinc, copper and selenium work synergistically with vitamins to support the Th1 cytokine-mediated immune response and the production of cytokines and prostaglandins, at least in part through regulation of redox-sensitive transcription factors. Selenium, copper and zinc improve the function of the skin/mucosa barrier by counteracting cellular damage caused by reactive oxygen species (54,56). In animal models plasma levels of
selenium and zinc decrease significantly 6 hours after burn injury; this selenium depletion led to a decrease in the activity of superoxide dismutase and an increase in oxidative stress and lipid peroxidation (12,57). In parallel clinical situations trace element supplementation may counteract oxidative damage. In animals it was observed that the optimal plasma selenium and reactivation of glutathione peroxidase were achieved 24 h after the injection of sodium selenite (57). Micronutrient supplementation in artificial nutrition is recommended for all types of patients with a level of evidence graded C, but level A evidence exists for burns patients, in whom trace elements should be supplemented at higher than standard doses (30). Berger et al. confirmed that the prevalence of bronchopneumonia and extended LOS were reduced by supplementation of trace elements with a daily dose of 40 umol copper, 2.9 umol selenium and 406 umol zinc for 30 days after burn injury (58). The recommended dose of selenium for adult patients is 60–400 ug/day, it is always, however, significantly increased during catabolic stress. During parenteral nutrition both groups of micronutrients should be supplemented on a daily basis.

7. Summary of Clinical Indications for Immunonutrition

7.1. The Immune Response to Surgical Trauma

A surgical procedure is a specific type of partially controlled trauma that, in addition to the intended therapeutic effect, causes extensive changes in the functioning of multiple systems in the patient’s body. Its response to a surgeon’s actions is complex and integrated, and has as its goal the restoration of overall homeostasis as soon as possible. Homeostasis is dependent on many factors; those pivotal include the patient’s nutritional status, the underlying disease and, consequently, the type of surgical intervention and the immune response to that trauma. These factors affect each other, thereby determining the final effect of the therapeutic intervention.

In the maintenance of an organism’s homeostasis the immune system plays a crucial role. Through a number of modulating signals (such as the release of cytokines) it either directly or indirectly influences whole body metabolism, thus influencing the effect of surgery. It has long been known that, among other things, chronic inflammation leads to cachexia and that compromised immunity increases the incidence of postoperative complications. However, it was not until a few years ago that the mechanisms of the body’s direct immune response to injury, including surgery, started to be tested. Until then it had been considered a two-step mechanism: initially with the systemic inflammatory response syndrome, to be followed by the compensatory anti-inflammatory response syndrome. In the light of current research it becomes clearly evident that the injury itself causes a specific immune deficiency by disrupting the immune balance, and changes, inter alia, the ratio of Th1/Th2 lymphocytes (59).

Following the rupture of natural protective barriers in the form of skin, mucous membranes, or opening of the gastrointestinal tract, tissues are directly exposed to pathogens. According to the mechanisms of the innate and adaptive response, at the site of injury and then within the entire body, a series of characteristic changes occurs that aims at reducing damage and producing a quick response preventing the spread of infection. Initially, it is the site of injury that plays an important role in stimulating the response through the activity of neutrophils and macrophages present at the site. They produce cytokines and other mediators – such as platelet activating factor, oxygen free radicals, nitric oxide (arginine) and arachidonic acid metabolites (lipids) – that act both locally and systemically. They affect the cells directly, but also indirectly, through the changes in blood flow and activation of the complement system.

The next step involves the antigen-presenting cells (monocytes, macrophages and dendritic cells) which migrate to lymphatic glands and initiate the response which is mediated by lymphocytes. Helper T lymphocytes play a major role in that process: they are divided into two groups: Th1 (play an important role in killing intracellular pathogens), and Th2 (important for antibody production and a defence against
extracellular parasites). Each of these groups mediates the inflammatory response through specific cytokines: Th1 cells primarily secrete Interferon alpha, IL-2, and TNF-alpha, which promote cellular immunity, whereas Th2 cells secrete a different set of cytokines (anti-inflammatory), primarily IL-4, IL-10, and IL-13, which promote humoral immunity and depress cell-mediated immunity.

As a result of an injury the hypothalamic-pituitary-adrenal axis and the sympathoadrenal system are activated, and are presumed to be secondarily (the release of cortisol, catecholamines together with the release of PGE2) responsible for the TH1/TH2 imbalance and the impaired cellular immunity that occurs following tissue damage and trauma. It is interesting to note that cytokines secreted by Th2 lymphocytes enhance arginine consumption, (i.a. in bone marrow suppressor cells (myeloid-derived suppressor cells)), causing an arginine deficient state which further impairs lymphocyte function (1). That partially justifies the indications for arginine supplementation in patients who have undergone surgery. Unfortunately, some surgical patients experience complications in the form of anastomotic leaks, abscess formation or even of sepsis and multiple organ failure. They constitute a separate group of patients who require special attention (60). Routine supplementation with arginine is not currently recommended.

7.2. Immunomodulating Nutrition in the Perioperative Period

Nutritional status is a key parameter influencing the potential outcome of surgical treatment (61,62). Undoubtedly, malnutrition and then trauma in the form of surgery significantly weaken the organism’s immune response, which results in an increased number of infectious complications, and impaired wound and anastomotic healing, or in prolonged hospitalization (63). Therefore, the majority of research carried out so far and investigating the effects of immunonutrition on the human body pertains to groups of surgical patients (64-75). In large part, the research deals with the role of glutamine, arginine, fatty acids (omega-3-PUFA) and diets high in nucleotides. Of central importance seem to be questions about the indications for immunonutrition (only malnourished patients or patients with good nutritional status as well), timing of nutritional intervention (pre-, post-, peri-operatively), and about the route of administration of nutrient mixtures (enterally, intravenously, or in a mixed way). The answers vary depending on the composition of the nutrient mixture. Considerations regarding these aspects of immunonutrition were discussed in the previous chapter. It is important to realize that, as mentioned above, many authors have now tried to analyze the clinical impact of the various forms of pharmaconutrition. The most important studies are presented in Table 1.

**Table 1. Studies on immunonutrition in surgical patients**

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>Number of patients (n)</th>
<th>Study groups</th>
<th>Type of diet</th>
<th>Patient characteristics</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Senkal 1997</td>
<td>154</td>
<td>IMEN vs isocaloric</td>
<td>Impact</td>
<td>Operated on for upper GI cancer</td>
<td>17/77 vs 24/77 (p&lt;0.05), shortening of hospital stay</td>
</tr>
<tr>
<td>Daly 1992</td>
<td>85</td>
<td>IMEN vs isocaloric</td>
<td>Impact</td>
<td>Operated on for upper GI cancer</td>
<td>11 vs 33%, shortening of hospital stay by 5 days</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Study Design</td>
<td>Intervention</td>
<td>Patients</td>
<td>Impact</td>
</tr>
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<td>--------</td>
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<tr>
<td>Heslin 1997</td>
<td>1997</td>
<td>IS vs isocaloric</td>
<td>Impact</td>
<td>Operated on for upper GI cancer</td>
<td>No differences</td>
</tr>
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<td>Daly 1995</td>
<td>1995</td>
<td>Postoperative IMEN, outpatient MEN, standard postoperative and outpatients</td>
<td>Impact</td>
<td>Operated on for upper GI cancer</td>
<td>Reduction of complication rate (10 vs 43%), shortening of hospital stay by 6 days</td>
</tr>
<tr>
<td>Braga 2002</td>
<td>2002</td>
<td>Pre- and postoperative IMEN &amp; standard EN</td>
<td>Impact</td>
<td>Operated on for upper GI cancer</td>
<td>Reduction of complication rate</td>
</tr>
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<td>Braga 1996</td>
<td>1996</td>
<td>Standard EN, IMEN, TPN</td>
<td>Impact</td>
<td>Operated on for upper GI cancer</td>
<td>No reduction of complications</td>
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<tr>
<td>Braga 1999</td>
<td>1999</td>
<td>IMEN vs standard EN</td>
<td>Impact</td>
<td>Operated on for upper GI cancer</td>
<td>Complications in 14 vs 30% (p=0.009)</td>
</tr>
<tr>
<td>Gianotti 2002</td>
<td>2002</td>
<td>Preop- and postop IMEN</td>
<td>Impact</td>
<td>Operated on for upper GI cancer</td>
<td>Reduction in infectious complications if preop IMEN was used</td>
</tr>
<tr>
<td>Lobo 2006</td>
<td>2006</td>
<td>IMEN vs EN (Nutrison High Protein)</td>
<td>Stresson</td>
<td>Operated on for upper GI cancer</td>
<td>No effect</td>
</tr>
<tr>
<td>Chen 2005</td>
<td>2005</td>
<td>IMEN vs standard EN</td>
<td>Stresson</td>
<td>Operated on for upper GI cancer</td>
<td>Increased serum Ig, IL-2, CD4 and CD4/CD8 ratio, decrease of IL-6 and TNF-alpha</td>
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<td>Heys 1999</td>
<td>Metaanalysis 111 RTC, 1009 pts.</td>
<td>IMEN vs standard EN</td>
<td>Impact</td>
<td>Operated on for upper GI cancer</td>
<td>Decrease of complications and hospital stay, no differences in mortality</td>
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<tr>
<td>Heyland 2001</td>
<td>Metaanalysis 22 RTC 2419 pts.</td>
<td>IMEN vs standard EN</td>
<td>Impact</td>
<td>Various, mostly ICU</td>
<td>Decrease of complications, no differences in mortality</td>
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<td>Waitzberg 2006</td>
<td>Metaanalysis</td>
<td>IMEN vs standard EN</td>
<td>Impact</td>
<td>Decrease of complications</td>
<td></td>
</tr>
<tr>
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<td>--------------------------</td>
<td></td>
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<tr>
<td>17 RTC</td>
<td></td>
<td></td>
<td>Various, mostly operated on for upper GI cancer</td>
<td></td>
<td></td>
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<tr>
<td>2083 pts.</td>
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<th>Marik 2010</th>
<th>Metaanalysis</th>
<th>IMEN: vs standard EN as postoperative feeding</th>
<th>Impact</th>
<th>Various, mostly operated on for upper GI cancer</th>
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<tr>
<td>21 RTC, 1918 pts</td>
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<table>
<thead>
<tr>
<th>Centarola 2011</th>
<th>Metaanalysis:</th>
<th>IMEN vs standard EN postoperative</th>
<th>Impact</th>
<th>Various, mostly operated on for upper GI cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 RTC, 27 pts.</td>
<td></td>
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</tbody>
</table>

Particular benefit from immunonutrition supplemented with glutamine is seen in malnourished surgical patients (18-20). The administration of glutamine, both before and after surgery, improves the treatment outcome by reducing the number of complications (limiting the incidence of infections and shortening hospital length of stay). On the basis of randomized controlled studies and meta-analyses, it is believed that intravenous and enteral administrations are equally beneficial (21,22).

ESPEN guidelines (30):

- Enteral administration of glutamine is indicated in trauma and burn patients.
- If parenteral nutrition is indicated in critically-ill patients (ICU patients with complications), the glutamine administration should be 0.2 to 0.4 g/kg bw/day (0.3 to 0.6 g/kg bw/day L-alanyl-L-glutamine). In such doses glutamine supplementation has proven effective in reducing mortality, the number of infectious complications, and length of hospital stay.

In contrast to glutamine, a proven effect of arginine-enriched nutrition is limited in practice to high-risk patients undergoing elective surgery. Due to a potential mechanism responsible for enhanced inflammatory response (overproduction of nitric oxide), that sort of nutrition is not recommended in sepsis (23). In patients with uncomplicated surgical infection, however, the level of arginine is usually lowered, therefore such patients can benefit from its supplementation (it accelerates wound healing and the immune response). Although the intravenous route of administration is preferred, some reports about the effectiveness of oral supplementation are also to be found (76).

Nucleotide enriched diets have similar indications, especially for patients with GI cancer undergoing major elective surgery. Very often nucleotides are one of the immunomodulating components found in immunonutrition mixtures, but there is a lack of studies investigating their selective influence on the postoperative course.

The ESPEN guidelines advise as follows (20,21):

- Use preoperative enteral nutrition, preferably with immune modulating substrates (i.a. arginine, nucleotides) for 5–7 d in all patients undergoing major abdominal surgery independent of their nutritional status.
- Use EN, preferably with immuno-modulating substrates (arginine, n-3 fatty acids and nucleotides) perioperatively independent of the nutritional risk for patients:
  - undergoing major neck surgery for cancer (laryngectomy, pharyngectomy)
  - undergoing major abdominal cancer surgery (oesophagectomy, gastrectomy, and pancreatoduodenectomy)
  - after severe trauma.
- The supply of diets enriched in nucleotides and arginine is indicated in trauma patients.
• Immunomodulating diets (including those enriched with arginine and nucleotides) may be harmful in severe sepsis, therefore are not recommended. Apart from that, ESPEN found the use of fatty acids (omega-3-PUFA) optimal for surgical patients requiring parenteral nutrition. Intravenous infusion of PUFA emulsions is reasonable to achieve the anti-inflammatory effect much faster than in the case of enteral diets (19).

On the basis of research conducted so far, it has been expressly demonstrated that the use of immunomodulating nutrition significantly reduces the risk of acquired infections, wound complications, and length of hospital stay in the postoperative course. In malnourished patients enteral immunonutrition shows greater efficacy than using a standard nutritional formula. Immunonutrition should be used in patients undergoing major surgical procedures within the abdominal cavity, operated on due to head and neck cancer, and in severe trauma patients. Immunonutrition should not constitute a routine treatment in the postoperative period of all patients undergoing surgery. In patients who show either mild or no signs of malnutrition, using that sort of nutritional treatment will not bring the hoped-for clinical benefits, but will instead increase treatment costs. Patients with severe sepsis should be treated with special care; in accordance with the guidelines of ESPEN, immunonutrition (especially rich in arginine) should be avoided in that context.

8. Immunonutrition in Gastroenterology

8.1. Crohn’s Disease and Ulcerative Colitis

Despite differences in the clinical picture, the underlying cause of both diseases is chronic inflammation within the wall of gastrointestinal tract, being the result of immune system disorders. Therefore, it is natural to direct treatment at fighting inflammation and altering the immune system response. Pharmacotherapy involves symptomatic treatment (anti-inflammatory drugs, corticosteroids), but also attempts more targeted therapies (monoclonal antibodies). It is known, however, that nutrition, enteral in particular, plays an important role in attempts to attain remission (especially in Crohn’s disease in children). Furthermore dietary treatment is used not only to maintain proper nutritional status, but also to treat complications of both diseases (fistulas, short bowel syndrome, etc).

Taking into consideration the aforementioned aspects, it would seem that immunonutrition should be an additional way of obtaining a therapeutic effect. Unfortunately, contrary to the expectations, so far there is no satisfactory clinical trial that expressly confirms the clinical value of immunonutrition. The available research most often refers solely to experimental attempts.

According to ESPEN guidelines on enteral and parenteral nutrition, in both Crohn’s disease and ulcerative colitis there is no clear benefit of using an immunomodulating formula (omega-3-PUFA, glutamine, and/or TGF-beta enriched) (77,78). Although there are encouraging experimental data, the present clinical studies are insufficient to permit the recommendation of glutamine, n-3 fatty acids or other pharmaconutrients in CD (79-81).

8.2. Experimental Colitis

Experimental research with omega-3-PUFA conducted on animal model (rats with induced colitis) has given emphasis to the benefits of immunonutrition used in parenteral nutrition (82). It was shown that the association of an MCT/LCT-containing lipid emulsion with fish oil with a high n-3/n-6 ratio impelled great beneficial impact, attenuating morphological and inflammatory consequences and decreasing colonic concentrations of proinflammatory mediators.

The current knowledge based on clinical trials does not however allow a clear formulation of recommendations for the use of immunonutrition in patients with inflammatory bowel disease. Nevertheless, taking into account their underlying immune system disorders,
demonstrating a beneficial effects of immunonutrition, with special reference to fatty acids, seems to be a matter of time.

8.3. Acute Pancreatitis

The mainstay of treatment of acute pancreatitis is appropriate nutritional intervention. If going back to oral feeding is not possible within 5 days after the onset of the disease, standard treatment now involves enteral feeding via a nasogastric tube. Apart from supplying energy and protein, enteral feeding is supposed to minimize the risk of bacterial translocation and secondary infection of pancreatic necrosis, maintaining intestinal transit, and providing essential nutrients for the intestinal villi. Nevertheless, severe acute pancreatitis may require parenteral or mixed nutrition (enteral and parenteral). In the case of acute pancreatitis, as in inflammatory bowel diseases, there are few data to support an advantage of immunonutrition (83-92). In accordance with the guidelines of ESPEN, whenever there is a necessity to use parenteral nutrition, parenteral glutamine supplementation should also be considered (>0.30 g/kg Ala–Gln dipeptide) (93). It eventuates from the lack of clear clinical evidence of such enteral immunonutrition advantage when compared to standard mixtures (both polymeric and semi-elemental).

Only animal studies suggested that enteric diet enriched with glutamine, arginine, and probiotics has a positive effect on gut barrier function and immune function (pigs with severe acute pancreatitis) (94,95). EN maintained gut barrier function and immune function. It should be taken into consideration, however, that there are conflicting data regarding probiotics and their potentially harmful effects in impairment of visceral perfusion.

9. Metabolic Abnormalities in ICU Patients and Possibilities of Nutritional Intervention

When discussing nutritional issues in the Intensive Care Unit (ICU), it is of utmost importance to define the ICU patient to get a picture of the scale of metabolic abnormalities which must be treated. The ESPEN definition is as follows: the ICU patient is a patient developing an intensive inflammatory response with failure of at least one organ (SOFA >4) (1). In other words, patients admitted only for monitoring (typical ICU stay below 3 days) are not representative ICU patients. The latter are those with an acute illness necessitating support of organ function during an ICU episode expected to be longer than 3 days (28).

The response to critical illness is a complex one. It involves an increase in glycolysis and gluconeogenesis and protein turnover with significant protein loss (mostly from muscle, skin and the gastrointestinal tract) and increased resistance to insulin in liver, muscle and adipose tissue. Only a small part of available glucose is fully oxidized in stressed insulin dependent organs even in aerobic conditions, and substantial amounts are necessary for glycolysis. The latter is essential in erythrocytes which lack a full Krebs cycle and rely on glycolysis (12). The amino acids derived from protein degradation are to some degree re-utilized for protein synthesis, but in critically ill individuals a substantial proportion is irreversibly degraded and the nitrogen component metabolized to urea (12). All these changes also affect the immune system, its actions dependent on many factors, such as the severity of disease, the phase of response and concomitant disease.

It is obvious that the increased metabolic needs related to stress are likely to accelerate the development of malnutrition, which is always associated with compromised clinical outcomes. In a randomized study, 300 patients undergoing major surgery received continuous total parenteral nutrition (PN) or exclusively intravenous glucose (250–300 g/d) for 14 days; the PN patients had 10 times less mortality than those on glucose (94). It is important to remember that nutritional support can partially compensate for negative energy and protein balance, but it cannot completely reverse catabolism in peripheral tissues like muscle, skin and bone until the convalescence phase begins (12).
The above observations confirmed the need to feed critically ill patients. Therefore an obvious next step was to create an intervention, which should be able not only to cover basic needs, but also influence the clinical course. Hence the interest in immunonutrition as a potential treatment option for ICU patients.

Up-to-date studies on glutamine, arginine, omega-3-PUFAs and micronutrients have been performed, and their biological activities examined. Although some results were conflicting and sometimes confusing, three of the most important scientific societies dealing with nutrition and metabolism have been able to formulate guidelines and recommendations based on some of those experiments.

9.1. Glutamine

Studies performed in multiple trauma ICU patients showed a beneficial impact of glutamine-supplemented enteral formula with administration of 10 g to 14 g glutamine per litre (21,22). Studies in severely burned patients showed that the addition of glutamine to a standard enteral feeding formula had a favorable effect on the preservation of intestinal structure (36). Another meta-analysis recommended using enteral glutamine in burned or trauma patients based on the impact on mortality and a trend toward reduced infectious comorbidity (25). McQuiggan et al demonstrated that enteral glutamine during resuscitation from acute shock is not only safe but also enhances enteral tolerance (27).

In various clinical studies in the ICU setting, intravenous administration of glutamine (0.2–0.4 g/kg/day) in the form of dipeptide (0.3–0.6 g/kg/day) contributed to improve glycaemic control, and to reduce the prevalence of infections and mortality (28). Marik and Zaloga proved that enteral nutrition with supplemented glutamine appeared to be beneficial in burn patients, probably because burns are associated with a severe gastrointestinal mucosal injury, leading to increased bacterial translocation, resulting in secondary multi-system organ dysfunction syndrome (MODS) (36).

The above led to the construction of guidelines by leading scientific societies, such as the European Society for Clinical Nutrition and Metabolism (ESPEN), the Canadian Critical Care Society together with The Canadian Society for Clinical Nutrition, and the American Society for Parenteral and Enteral Nutrition (ASPEN), which recommend use of glutamine-containing formula in the following ICU patients (28,29,30,31):

a) all burn and/or trauma patients (recommendations of ESPEN and Canadian Societies),

b) all ICU patients in whom parenteral nutrition is needed (ESPEN),

c) in critically ill postoperative or ventilator-dependent patients requiring parenteral nutrition, due to the positive impact of parenteral glutamine administration, a decrease in infectious complications, decrease in hospital length of stay, and possible decrease in mortality (ASPEN),

d) parenteral glutamine may be beneficial in adult burn patients or acute pancreatitis patients who require PN.

ESPEN and the Canadian Society also described situations, in which glutamine is not recommended:

a) in patients with severe sepsis: these patients are not only not likely to benefit from immunomodulating formula, but may also be harmed

b) the routine use of enteral glutamine in all critically ill patients

c) in critically ill patients receiving enteral nutrition - there are insufficient data to generate recommendations for intravenous glutamine.

According to the ASPEN position there are no absolute contraindications to the use of parenteral glutamine, but liver function tests should be monitored in all patients and it should be used with caution in end-stage hepatic failure patients and patients with hepatic insufficiency (31). ASPEN pointed out that further research is needed on glutamine supplemented PN in the following areas: specific adult patient populations; paediatric patients; use of glutamine supplementation in combination with parenteral and enteral nutrition or enteral/oral nutrition alone; dipeptide vs. free L-glutamine; timing and dosing; cost-benefit analysis; and further elucidation of parenteral glutamine’s mechanisms of action (31).
When considering the right dosage: PN glutamine supplementation should probably be given early and in doses > 0.2 g/kg/day to be effective. [95] ESPEN recommended a dosage of 0.2–0.4 g/kg/day of L-glutamine (e.g. 0.3–0.6 g/kg/day alanyl-glutamine dipeptide), but also emphasized the dose-dependency effect of immunodiets; therefore ICU patients with severe illness who do not tolerate more than 700 ml enteral formula per day should not receive an immune-modulating formula enriched with arginine, nucleotides and n-3 fatty acids (28). It is also important to remember that continuous renal-replacement therapy may increase glutamine loss by 4–7 g/day further enhancing the case for glutamine supplementation in this context (95). A new multicentre study of Heyland et al. undermined the position of glutamine in ICU patients. The study showed higher mortality in ICU patients receiving glutamine along with antioxidants or alone (96). It must, however, be remembered that these researchers used the maximum dose of intravenous glutamine and administered oral amino acid as well. That type of administration could have significantly influenced the outcome, hence more studies are needed.

9.2. Arginine

Although arginine along with other nutrients was proven to help to reduce postoperative complications in surgical patients, nutrition enriched with arginine surprisingly failed to improve outcomes in trauma patients and patients with sepsis (34). The main reason for that is the increased concentration of nitric oxide in the bodies of those ICU individuals (in contrast to surgical patients). As Marik and Zaloga summarized, patients with sepsis and surgical trauma regulate arginine metabolism differently (36). Arginine levels are lower and arginase activity is higher in patients following surgical trauma than in sepsis, hence NO is elevated in sepsis and decreased following surgical trauma. It was clearly shown in the study by Bertolini et al., which compared a formula containing extra L-arginine, omega-3 fatty acids, vitamin E, beta-carotene, zinc, and selenium with a standard formula. After recruitment of 237 patients, the study was stopped because an analysis of 39 of patients with severe sepsis revealed that the immunomodulating formula was associated with a significantly higher ICU mortality than in those receiving the standard formula (44.4% versus 14.3%; P=0.039) (97). Although those observations were contraindicated by other studies, the evidence resulted in the construction of very strict guidelines and recommendations for the use of arginine. According to ESPEN, arginine–enriched enteral diets should be used in the case of ARDS and trauma patients as well as in mild sepsis (<15 APACHE II), while they are contraindicated in severe sepsis (28). Canadian recommendations even more sturdily discourage the use of arginine-containing diets in critically ill patients; according to them diets supplemented with arginine should never be used in this context (29).

9.3. Nucleotides

The administration of nucleotides helped tissue recovery from ischaemia–reperfusion injury and increased recovery rates in cardiac ischaemia and radiation injury as well as decreasing bacterial translocation in severe starvation (12). They were clinically effective in major elective surgery patients (12). Data regarding their role in critically ill patients are lacking, and more studies are needed.

9.4. Omega-3-polyunsaturated Fatty Acids

A review of the effect of including fish oils in PN in ICU patients concluded that there was a significant reduction in the length of stay, but no differences in mortality were noted (98). A multi-centre study, which enrolled 661 patients (SAPS II score >32) showed that intravenous fish oil supplementation had favorable effects on survival, infection rate, antibiotic requirements and length of stay when administered in doses between 0.1 and 0.2 g/kg/day (99). The greatest influences were observed in patients with abdominal sepsis. In the study of Wichmann et al., the mixed soybean LCT/MCT/fish oil emulsion
significantly increased EPA, LTB5 production and antioxidant levels, as well as yielding a significantly shorter length of hospital stay (17.2 vs. 21.9 days, p=0.006) (100). For those reasons ESPEN recommends its use in ARDS patients (Grade A), mild sepsis (Grade B) and trauma patients (Grade A) (28). Canadian recommendations endorse the use of an enteral formula with fish oils, borage oils and antioxidants in patients with Acute Lung Injury (ALI) and acute respiratory distress syndrome (ARDS) (28).

9.5. Micronutrients

In animal models, plasma levels of selenium and zinc significantly decreased 6 hours after burn injury, which led to a decrease in the activity of superoxide dismutase and an increase in oxidative stress and lipid peroxidation (2,31,32). In situation like that trace element supplementation may counteract oxidative damages. ESPEN recommends micronutrient supplementation for ICU patients at standard doses in all types of patient receiving artificial nutrition (28).

In burn patients trace elements should be supplemented at higher than regular dosage (16). The reason for this is explained by the example of selenium. Its turnover is always significantly increased during catabolic stress. Generally speaking, antioxidant vitamins (including vitamin E and ascorbic acid) and trace elements (including selenium, zinc, and copper) are believed to improve patient outcome, especially in burns, trauma, and critical illness requiring mechanical ventilation (101, 102).

9.6. Execution of Immunonutrition in ICU

The selection of the right ICU patient for immunonutrition and the proper choice of diet are not the only problems regarding this type of intervention. Another very important issue lies in the dosage of nutrients, so also the question of tolerance and compliance. According to ESPEN guidelines, ICU patients who cannot tolerate at least 700 ml per day of enteral diet should not receive immunomodulating (enriched with arginine, nucleotides and omega-3-PUFAs) formulas, because that type of intervention is of no clinical value (30).

During parenteral intervention, the dosage of immunonutrients also matters. Glutamine should be administered at the dose of 0.2 to 0.4 g/kg bw/day (0.3 to 0.6 g/kg bw/ day L-alanyl-L-glutamine – the intravenous form of glutamine). The administration of fish oil should at least reach the level of 0.1 g/kg bw/day. The recommended dose of selenium for adult patients is 60–400 ug/ day.

The selection of efficient enteral diet may be difficult. Impact® (Nestle), as in the surgical studies, was the diet most often used in the studies which indicated the clinical value of immunonutrition, as presented in Table 1. It does not mean that the other diets do not work or should not be used, it just indicates the need for more clinical studies. Table 2 presents the largest clinical analyses on ICU immunonutrition.
Studies on immunonutrition sometimes give puzzling results, mostly due to discrepancies between in vitro and in vivo research. In many cases preclinical studies prove beneficial impact of immunodiets on the immune system, but the outcome of clinical observations is then different. Some other reasons for these ambiguities are as listed:
- Heterogeneity of study groups in the various studies (the ratio of malnourished patients to well-nourished patients was different in each study, and it is obvious that nutrition helps malnourished patients even without an immunomodulating component)
- Heterogeneity of nutritional interventions (intervention took place pre-, peri- or postoperatively or even in other phases of the clinical course)
- Various formulas were used (Impact, Stresson, Reconvan – their nutrient content varies considerably; for example Impact® does not contain glutamine)
- Various caloric loads were used during nutritional support (authors used hypercaloric, iso- or hypocaloric diets, and the compliance with treatment was also flawed in almost 50% of studies)
- Heterogeneity of definitions (definitions for complications differed or were unknown, various definitions describing nutritional status were used)
- Poor methodology: small number of ITT analyses, lack of well-designed, randomized studies

The above factors are probably the main reasons for the conflicting results from the clinical studies, and which have made the assessment of the real clinical value of immunonutrition difficult even in meta-analyses. In future, study designs should consider these factors more carefully in the planning phase to avoid further disappointment. Those ambiguities, however, indicate the need for careful use of the guidelines, which are based on the real clinical impact of immunonutrition in ICU patients.

### Table 2. Studies on immunonutrition in ICU patients

<table>
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<tr>
<th>AUTHOR(S)</th>
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<th>Type of diet</th>
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<td>Impact</td>
<td>Decreased complication rate in IMEN, but higher mortality</td>
</tr>
<tr>
<td>Atkinson et al. 1998 (104)</td>
<td>398</td>
<td>IMEN vs isocaloric</td>
<td>Impact</td>
<td>Mechanical ventilation and ICU stay reduced</td>
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<tr>
<td>Caparros et al. 2001 (105)</td>
<td>235</td>
<td>Experimental formula vs standard</td>
<td>Experimental formula</td>
<td>Standard formula better results</td>
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<td>Kieft et al, 2005 (106)</td>
<td>597</td>
<td>IMEN vs standard</td>
<td>Stresson</td>
<td>ICU stay similar, shorter ventilator days in Immunogroup</td>
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<tr>
<td>Dent et al, 2003 (107)</td>
<td>170</td>
<td>IMEN vs standard</td>
<td>Optimal vs Osomolite HN</td>
<td>Mechanical ventilation and ICU stay reduced</td>
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<tr>
<td>Heyland et al. 2001 (108)</td>
<td>Meta-analysis  22 RTC 2419 pts.</td>
<td>IMEN vs standard EN</td>
<td>Impact</td>
<td>Decrease of complications, no differences in mortality</td>
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</table>
on EBM, and clearly signpost the requirement for more clinical studies. Nonetheless, immunodiets, when used wisely, can improve the outcomes of therapy.

11. Summary

Immunonutrition represents a form of nutritional support, which covers not only basic nutritional demands, but also modifies functions of the immune system. Immunosubstrates include arginine, glutamine, omega-3-fatty acids, selenium, zinc, vitamins A, C and E, and nucleotides. They can be administered in the form of enteral nutrition or intravenously. Glutamine can be beneficial in trauma and burn patients, and may also improve the outcome of surgery. Arginine cannot be used in severe sepsis patients, but is of value in high-risk elective surgery patients. The latter group may also benefit from nucleotides. Omega-3-unsaturated fatty acids can reverse PN associated cholestasis in children, reduce postoperative complications after GI surgery, improve the outcome in critically ill ARDS and trauma patients, and favourably influence pancreatic cancer growth. During enteral and parenteral nutrition micronutrients should be supplemented on a daily basis, and their dosage must be significantly increased during catabolic stress. Further in vitro and in vivo studies are needed to fully understand the mechanisms and clinical value of immunonutrients.

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