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Evidence-based immune-modulating nutritional therapy in critically ill and injured patients

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Evidenz-basierte Immunmodulations-Ernährung beim kritisch Kranken und Schwerverletzten

Zusammenfassung. *Grundlagen:* Immunernährung, sowohl als immun-steigernde (IE) als auch immun-modulierende (IM), besitzt einen wichtigen Stellenwert in der Therapie von kritisch kranken und schwerverletzten PatientenInnen.

Methodik: Übersicht zur Evidenz bezüglich immunmodulierender Ernährung bei kritisch Kranken und Schwerverletzten.

Ergebnisse: Die positive therapeutische Wirkung der immunmodulierenden Ernährung wird heute besser verstanden, vor allem bei akutem Lungenversagen (ARDS), Sepsis und Schock, wie sie beim schwerkranken Menschen vorkommen. Die Wirksamkeit der Ernährung bei diesen PatientenInnen wurde in Level-I-Evidenz nachgewiesen (U.S. Preventive Services Task Force).

Schlussfolgerungen: Die Behandlung Schwerkranker und Verletzter hat sich dahingehend signifikant verändert, dass die Bedeutung der immunmodulierenden Therapie erkannt und umgesetzt werden konnte. Durch eine Biologie-basierte Ernährung unter Berücksichtigung prognostischer Marker (Zytokine etc.) wurden die Ergebnisse bei schweren Erkrankungen deutlich gebessert.

Schlüsselwörter: Akutes Lungenversagen, Immunmodulation, Immunstimulation, Glutamin, Arginin, Sepsis.

Summary. *Background:* Immunonutrition, both immune-enhancing (IE) and immune-modulating (IM), has become an important therapeutic option in the care of critically ill and injured patients.

Methods: Review of current literature and evidence on the use of immunonutrition, in particular use of immune enhancing and immune modulating nutrition support in critically ill and injured patients.

Results: We have gained much knowledge on the changes and on the mechanism of action of key nutrients and their substrates during critical illness and severe injuries, especially in acute respiratory distress syndrome (ARDS), sepsis, and septic shock; accordingly, the use of such nutrients and substrates has increased dramatically and has become Level I evidence (per the U.S. Preventive Services Task Force).

Conclusions: There has been a significant paradigm shift with regard to selecting the appropriate nutritional strategy for critically ill and injured patients. Doing so for a particular patient and particular disease is no longer regarded as a supportive measure. Rather, it is regarded as direct nutritional therapy, based on molecular changes and on the biology of key nutrients induced by the disease process.

Keywords: Immunonutrition, immune-enhancing nutrition, immune-modulating nutrition, glutamine, arginine, nucleotides, antioxidants, selenium, omega-3 fatty acids, γ-linolenic acid (GLA), eicosapentaenoic acid (EPA), branched-chain amino acids (BCAAs), acute respiratory distress syndrome (ARDS).

Introduction

Immunonutrition has gained wider use in the care of critically ill and injured patients. This trend follows an increasing body of literature supporting the idea that different substrates will enhance a depressed immune system or modulate an over-reactive one. For this review article, we identified the nutritional substrates believed to have either an immune-enhancing (IE) or an immune-modulating (IM) property, pointed out their basic mechanisms of action, highlighted the current evidence on their efficacy, and examined the current expert consensus recommendations on their use. In the second half of the

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article, given the strong evidence on the efficacy of IM diets, we focused on their use, particularly in patients with acute respiratory distress syndrome (ARDS).

IE enteral nutrition

Although the biologic properties of IE nutritional substrates have been well studied, their role in routine clinical care is still controversial. Multiple meta-analyses have shown that IM formulations are associated with a reduction in ventilator days, in infectious morbidity, and in hospital length of stay, as compared with standard nutritional regimens [1–5]. However, studies have yet to show a survival benefit with their use.

Moreover, most of those studies assessed a combination of IE substrates, commonly in the form of a commercially available formulation. Therefore, the evidence addressing the efficacy and effect of each of the individual components is much more limited. In the following 6 subsections, we will discuss each of the substrates separately.

Glutamine

Glutamine is an amino acid that serves as the primary fuel for small bowel enterocytes and other rapidly proliferating cells, such as cells in wounds [6]. It is classified as a nonessential amino acid because the human body can synthesize it in sufficient quantities [7], yet during periods of stress, the body's requirements may exceed its capacity to synthesize glutamine [8, 9]. Glutamine is involved in many immune functions, including the production of heat shock proteins [10].

Studies have shown that supplementation with glutamine may lead to a decrease in nosocomial infections in patients with systemic inflammatory response [11], a decrease in blood infections in burn patients [12], and a decrease in pneumonia, sepsis, and bacteremia in trauma patients [13]; other studies, however, have refuted any effect of glutamine on reducing mortality [14]. Parenterally administered glutamine has been associated with a decrease in gram-negative bacteremia [15]. Thus, the addition of glutamine to enteral nutrition has been recommended for burn, trauma, and other intensive care unit (ICU) patients in the 2009 Society of Critical Care Medicine (SCCM)/American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) nutritional guidelines [16].

Arginine

Similarly, arginine is considered a nonessential amino acid in healthy individuals [17], but its role is much more important in critically ill patients because requirements for it increase during periods of stress [18]. Arginine seems to be necessary for normal T-lymphocyte function; levels of arginine are closely regulated by some specialized immune cells called myeloid suppressor cells [16]. It may also stimulate the release of hormones such as growth hormone, prolactin, and insulin [19]. Moreover, arginine appears to have trophic effects on the immune system in humans, resulting in weight gain, increased nitrogen retention, and improved wound healing [20, 21]. A systematic review of 22 randomized clinical trials (RCTs) showed that in a priori subgroup analysis, patients fed commercial formulations with high arginine experienced a significant reduction in infectious complications. Surgical patients appeared to have the greatest benefit, as compared with their nonsurgical counterparts [22].

The use of arginine supplementation, however, has been linked to a potentially increased mortality rate in hemodynamically unstable septic patients, as compared with standard enteral and parenteral nutrition [23, 24]. The proposed mechanism is that arginine is a biosynthetic substrate for nitric oxide production and that increased levels of nitric oxide then lead to increased vasodilation and hemodynamic instability [22, 25]. But other studies have disputed those findings and, instead, showed a reduced mortality rate in moderately septic patients [26].

The current recommendations are that IM formulations containing arginine are safe to use in patients with mild to moderate sepsis, but that caution should be employed in patients with more severe sepsis [16]. The idea that nutritional support with formulas containing arginine increases mortality is simply not practical: most hemodynamically unstable patients do not receive large enough amounts of enteral nutrition during the acute deterioration phase to cause any significant drop in their hemodynamic status.

Nucleotides

Nucleotides are perhaps best known for their role in the synthesis of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), hence, for their role in genetic coding. However, nucleotides also play a role in adenosine triphosphate (ATP) metabolism; they are a part of many coenzymes involved in carbohydrate, protein, and lipid synthesis. Nucleotides may be synthesized by some cells. But it is believed that rapidly dividing cells, such as epithelial cells and T-lymphocytes, are unable to produce nucleotides and that, during periods of stress, a relative deficit of nucleotides develops [27].

Nucleotides have been implicated in the modulation of immune function. Exogenous nucleotides have been found to be needed for the helper/inducer T-cell response [28]. In the clinical setting, IM nutritional formulas containing nucleotides have been shown to significantly reduce infections, ventilator days, and length of hospital stay, for both critically ill and postsurgical patients [2, 29]. However, those studies have not addressed the isolated effects of nucleotides as a substrate, so further studies addressing them are needed [30].

Antioxidant vitamins and trace minerals

Oxidative stress has been increasingly recognized as a central component underlying the pathophysiology of

critical illness. Vitamins with antioxidant properties include vitamins E and C (ascorbic acid); trace minerals include selenium, zinc, and copper.

A meta-analysis of 11 clinical trials showed that overall use of antioxidants was associated with a significant reduction in mortality (relative risk [RR], 0.65; 95% confidence interval [CI], 0.44 to 0.97, $P = 0.03$), but had no effect on infectious complications [31]. Among the antioxidants, selenium may be the most effective [32, 33]. A systematic analysis suggested that selenium supplementation, with or without other antioxidants, was associated with a reduction in mortality (RR, 0.59; 95% CI, 0.32 to 1.08, $P = 0.09$) [31].

The current recommendation is to provide a combination of antioxidant vitamins and trace minerals, especially including selenium, to all critically ill patients receiving specialized nutrition therapy [16].

Omega-3 fatty acids

Omega-3 fatty acids from an individual's diet are rapidly incorporated into the cell membranes, influencing membrane stability, membrane fluidity, cell mobility, and cell-signaling pathways. Moreover, they are able to mitigate the potency of the inflammatory response and have thus been implicated in a reduction in cardiovascular diseases. In an animal model, they protected against bacterial translocation and gut-derived sepsis, even when the diet was also supplemented with arginine or glutamine [34]. Their role in modulating the immune system in conditions such as ARDS is well described.

Branched-chain amino acids (BCAAs)

After injury and sepsis, an energy deficit that may develop in skeletal muscle is met by increased oxidation of branched-chain amino acids (BCAAs). Evidence indicates that skeletal muscle is the major site of BCAA degradation [35–38].

A recent study demonstrated that critically ill patients who were unable to be fed enterally but who were given total parenteral nutrition (TPN) fortified with BCAAs at high concentration (at either 23% or 45%) had significantly lower morbidity and mortality, as compared with patients on standard TPN (1.5 g/kg/day of protein) [38]. The decrease in mortality correlated with higher doses of BCAAs (at 0.5 g/kg/day or higher).

Furthermore, BCAA-rich parenteral nutrition formulas have been shown to correct the plasma amino acid imbalance that consistently exists in critically ill patients. Such formulas also improve plasma concentrations of prealbumin and retinol-binding protein in septic patients.

In a series of trauma patients, BCAA supplementation improved nitrogen retention, transferrin levels, and lymphocyte counts. Since the concentration of BCAAs is low in septic patients, probably as a result of overuse of BCAAs, supplementation with BCAAs may be beneficial. BCAAs are believed to be needed for lymphocytes to synthesize protein, RNA, and DNA as well as to divide in response to stimulation [39].

Immune modulating nutrition in ARDS

Acute Respiratory Distress Syndrome (ARDS) is one entity in which inflammatory processes are believed to significantly contribute to its pathophysiology. Recent studies have shown that certain lipid-containing enteral feeding solutions may have an IM role in ARDS patients; hence, new nutritional formulas have been incorporated into their care. In recent years, nutritional support with IM formulas has become the standard of care in ARDS patients. The use of IM formulas has also been expanded to other clinical conditions, but in this section, we will focus on ARDS.

ARDS is a constellation of clinical, radiologic, and physiologic abnormalities that are present in a variety of medical and surgical patients. It is an entity that occurs in a subset of patients with severe acute lung injury (ALI); it may coexist with left arterial or pulmonary capillary hypertension. ARDS is defined by its acute onset, bilateral infiltrates on a chest radiogram, a pulmonary-artery wedge pressure <18 mm Hg, and a P/F ratio of less than 200 [40].

Many clinical conditions and factors – direct or indirect – are associated with the development of ARDS. Direct causes of pulmonary injury include traumatic contusions, aspiration, pneumonia, and inhalation injuries from caustic substances or chemicals. Indirect causes include sepsis, polytrauma, shock, massive blood transfusion, and pancreatitis. The common pathway is the underlying inflammatory response in the lung itself, regardless of whether or not the primary insult occurred in the lung.

The mainstay of ARDS management has been an array of supportive measures, including, most recently, low tidal volume mechanical ventilation. Other measures include aggressive pulmonary toilet, pressure control ventilation with or without inverse ratio ventilation, and proning (prone positioning). Failure of those measures has prompted the use of others, such as tracheal gas insufflations, inhaled nitric oxide (NO), extracorporeal membrane oxygenation (ECMO), high-frequency oscillatory ventilation (HFOV), and partial liquid ventilation. Most such measures, however, are merely supportive, because they do not address the main issue in ARDS: the immunologic derangement at the molecular level.

Pathophysiology

In order to propose an IM effect of nutritional formulas on ARDS, we first must delineate its pathophysiology. The human body responds to infection and injury by releasing a complex variety of inflammatory mediators and oxidating molecules, which, depending on the context in which they are produced, may be beneficial or detrimental. Among the many cytokines involved in the inflammatory process, the key mediators are interleukin-1 (IL-1), IL-6, and tumor necrosis factor alpha (TNF-α).

Furthermore, evidence indicates that a neutrophil-predominant pulmonary edema fluid from pulmonary lavage is partly responsible for the development of ARDS [41]. Activation of neutrophils and proinflammatory cytokines initiates or exacerbates the inflammatory response in ARDS and ALI – increasing capillary permeability, resulting in severe acute hypoxemia due to pulmonary edema, and ultimately leading to fibrosing alveolitis or fibrotic lung injury, all of which causes a higher mortality rate.

Dietary fish oil and borage oil have been implicated in the suppression of the intrapulmonary inflammatory response by modulating the eicosanoid pathway, leading to overall decreased levels of neutrophils in broncho alveolar lavage [42]. Moreover, fish oil and borage oil alter the fatty acid composition of lung phospholipids by decreasing the arachidonic acid level and increasing the eicosapentaenoic acid (EPA) level [42]. When fish oil and borage oil are used in combination, the dihomo-γ-linolenic acid level increases as well. It has been suggested that the incorporation of EPA into phospholipids modulates the eicosanoid metabolism, causing it to produce less biologically active 3-series prostaglandins and 5-series leukotrienes (LTs) [43, 44]. In animal models, the inhibition of LTB_4 has been shown to reduce vascular permeability in the lungs and to decrease the response of neutrophils to endotoxins.

Experiments have also shown that supplementation of parenteral nutrition with γ-linolenic acid (GLA) increased prostaglandin E_1 and the plasma arachidonic ratio. In an animal model, such supplementation also reduced the ratio of thromboxane B_2 (TXB_2) and 6-keto-prostaglandin F 1-α. Those effects were via the increase in dihomo-γ-linolenic acid (a precursor to the anti-inflammatory eiosanoids) and via the increase in prostaglandin E_1 (PGE_1) (which modulates the arachidonic acid pathway).

Dietary considerations

Patients with severe pulmonary disease or those requiring mechanical ventilation may theoretically not tolerate an excess-carbohydrate nutritional formula because of its higher respiratory quotient. The effect of the additional CO_2 produced translates to increased respiratory work required to eliminate CO_2. The practical effect may or may not be as significant, but lipid-enriched formulas have been proposed to facilitate the weaning from ventilatory support; thus, as much as 30% of the no protein caloric requirements could now be provided by lipids. Of concern, the provision of lipids, traditionally as long-chain triglycerides (LCTs), has been associated with immunologic abnormalities such as dysfunction in phagocytosis, reticuloendothelial system dysfunction, depression of cardiac function, and increased survival of gram-positive bacteria.

Studies have shown that nutritional formulas containing medium-chain triglycerides (MCTs) – when given in a 1:1 LCT: MCT ratio – may be beneficial to septic patients with ARDS, as evidenced by changes in the venous admixture (Qva/Qt), in the mean pulmonary artery pressure (MPAP), and in the P/F ratio. Not only does a high-fat, low-carbohydrate nutritional regimen appear to be beneficial for patients in acute respiratory failure requiring ventilatory support, but the type of fatty acids provided may also have an effect on recovery.

Key studies

A prospective, multicenter, double-blinded, randomized, controlled trial involving 146 patients with ARDS first showed a benefit of the EPA + GLA + antioxidants diet on pulmonary neutrophil recruitment, gas exchange, mechanical ventilation requirements, length of ICU stay, and new organ failures. In that trial, patients in the 2 randomization arms received, for at least 4 to 7 days, either (1) an enteral compound with EPA + GLA or (2) an isonitrogenous isocaloric standard diet [45]. Subsequent studies by the same authors also showed a decrease in inflammatory mediators from bronchoalveolar lavage fluids (BALFs), namely, a decrease in IL-8 and in LTB_4, as well as an associated

Tab. 1: Anti-inflammatory immune-modulating (IM) enteral nutrition (Oxepa®, Abbott Nutrition, Columbus, OH) *vs.* standard enteral nutrition (Stand EN) in patients with acute respiratory distress syndrome (ARDS), acute lung injury (ALI), and sepsis [16])

Study	Population	Study groups	Mortality	LOS days, mean ± SD	Vent days, mean ± SD	New organ dysfunction
Gadek et al. [45]	ARDS ICU ($n = 146$)	Oxepa	11/70 (16%) ICU	11.0 ± 0.9 ICU[a]	9.6 ± 0.9[a]	7/70 (10%)[a]
		Stand EN	19/76 (25%) ICU	14.8 ± 1.3 ICU	13.2 ± 1.4	19/76 (25%)
		Oxepa		27.9 ± 2.1 Hosp		
		Stand EN		31.1 ± 2.4 Hosp		
Singer et al. [47]	ARDS and ALI ($n = 100$)	Oxepa	14/46 (30%) at 28 d[a]	13.5 ± 11.8 ICU	12.1 ± 11.3	NR
		Stand EN	26/49 (53%) at 28 d	15.6 ± 11.8 ICU	14.7 ± 12.0	
Pontes-Arruda et al. [48]	Severe sepsis ICU ($n = 165$)	Oxepa	26/83 (31%) at 28 d[a]	17.2 ± 4.9 ICU[a]	14.6 ± 4.3[a]	32/83 (39%)[a]
		Stand EN	38/82 (46%) at 28 d	23.4 ± 3.5 ICU	22.2 ± 5.1	66/82 (80%)

SD = standard deviation; NR = not reported; ICU = intensive care unit; LOS = length of stay; d = day(s); $P \leq 0.05$.

decrease in BALF neutrophils and protein permeability, suggesting a possible mechanism of the observed benefit [46]. A subsequent single-center, prospective, randomized, controlled, unlabeled study expanded the criteria to include patients with ALI in addition to ARDS; oxygenation and lung compliance improved [47].

Subsequently, another prospective, multicenter, double-blinded, randomized, controlled trial involving 165 patients showed a significant decrease in the 28-day mortality rate (absolute mortality reduction, 19.4%, $P = 0.037$) in patients with sepsis or septic shock requiring mechanical ventilation who received the EPA + GLA + antioxidant diet, as compared with the control group. Moreover, in patients on that diet *vs.* the control group, the number of ventilator-free days (13.4 ± 1.2 *vs.* 5.8 ± 1.0 days) and ICU-free days (10.8 ± 1.1 *vs.* 4.6 ± 0.9 days) also increased, and new organ dysfunction significantly decreased [48].

A recent meta-analysis of 24 RCTs assessed the outcome of critically ill patients randomized to an IM diet, which included supplementation with arginine, glutamine, fish oil, and combinations of those components. The IM diet, as compared with the control diet, had no effect on the mortality rate or the length of hospital stay. However, a subgroup analysis showed that patients with systemic inflammatory response syndrome (SIRS), sepsis, or ARDS who received fish oil alone had a significantly improved outcome in terms of the mortality rate, the rate of secondary infections, and the length of hospital stay [5].

The 3 RCTs mentioned in the meta-analysis that addressed fish oil alone are summarized in Table 1. Note that the SCCM/A.S.P.E.N. guidelines include a Grade a recommendation, for patients with ARDS and ALI, for an enteral formula with an anti-inflammatory lipid profile (EPA + GLA) and with antioxidants, given the consistent evidence provided by those 3 large RCTs [16]. Grade A designates the strongest recommendation, supported by at least 2 large RCTs with clear-cut results and a low risk of false-positives (alpha error) or false-negatives (beta error).

Conclusions

Selecting the appropriate nutritional strategy for critically ill and injured patients has undergone a paradigm shift. Previously, the decision was regarded as supportive, simply a measure to provide for the individual patient's energy and nutritional requirements. But now, the decision is increasingly complex: the type of formula is expected to alter the body's metabolic response to injury, to balance oxidative processes, and to help regulate the immune system, which may be deranged because of the underlying disease.

Conflict of interest

The authors declare that there is no conflict of interest.

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