Review paper

Immunomodulation in nutritional treatment – effects on the immune system and future directions

ROBERT SŁOTWIŃSKI[1,2], SYLWIA MAŁGORZATA SŁOTWIŃSKA[3]

[1]Department of Immunology and Nutrition, Medical University of Warsaw, Warsaw, Poland
[2]Department of Surgical Research and Transplantology, Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland
[3]Department of Conservative Dentistry, Medical University of Warsaw, Warsaw, Poland

Abstract

Results of studies presented in this article reveled that modulation of the immune cells activities by specific nutrients (glutamine, arginine, fatty acids) administered in amounts above those normally encountered in the diet may exert harmful effects on the immune system of the severely ill patients. The studies showed that one of the preconditions necessary to provide progress in treating those patients is to find out more about the impact of nutritional status, severe infections and immunonutrition on the expression of genes regulating innate antibacterial response.

Key words: *nutritional treatment, immunomodulation, fatty acids.*

(Centr Eur J Immunol 2012; 37 (1): 75-80)

Introduction

In patients after an extensive surgery, in patients with infections and in oncological patients requiring radio- or chemotherapy, some hopes for improvement in their immunity and treatment results are connected with parenteral or enteral administration of immunologically-active substances. Immunologically active components of nutritional formulations used in the immunity-supporting nutritional treatment (immunonutrition, immunomodulating nutrition) have a significant role in control of functioning of cells participating in the innate and the adaptive immune response to the surgical injury and infection. The general mechanism of immunonutrition is based on modulating the immune system functioning or the consequences of its activation with specific nutrients (e.g. amino acids, fatty acids) administered in amounts above those normally encountered in the diet [1, 2]. Immunomodulation with immunonutrition interferes with mechanisms of the immunological response, including injury, infection and malnutrition, through increasing its activity – stimulation, or inhibiting it – suppression. A current concept of the *immunonutrition* in severely ill and surgical patients aims at achieving better treatment results through improvement in functioning of the intestinal barrier, as well as through decreasing immunosuppression, limiting an excessive inflammatory response (systemic inflammatory response syndrome – SIRS) and improving healing of the wound [3]. It is known that correct healing of a postoperative wound requires an increased supply of nutrients, to maintain activity of the immune cells, including neutrophils, macrophages and lymphocytes, and to contain the infection [4]. A particularly important part of the nutritional treatment in surgical patients is supplying nutrients to cells of the gut associated lymphoid tissue (GALT) to ensure their correct functioning [5-7]. The main objective of the immunomodulating nutritional treatment is to limit the local and systemic inflammatory response (SIRS), following an extensive surgical treatment, injury or severe infection. Mediators in that immune response are cytokines, and in particular tumour necrosis factor (TNF) and interleukin 1 (IL-1), chemokines, components of the complementary system, eicosanoids, nitrogen oxide, free radicals and adhesion molecules. Factors participating in it

Correspondence: Robert Słotwiński, Department of Immunology and Nutrition, Medical University of Warsaw, Pawińskiego 3, 02-106 Warsaw, Poland, phone +48 22 572 02 47; fax +48 22 572 02 46, e-mail: robert_slotwinski@yahoo.com

include components of the innate inflammatory response, i.e. neutrophils, macrophages, Toll-like receptors (TLR) and the nuclear factor κB (NF-κB) [3, 8-13].

In the surgical patients a significant role in regulation of the local and systemic response to injury and infection is played mainly by TLR receptors present on cells of intestinal mucosa and cells participating in the innate immune response to a massive infection. A prolonged and excessive SIRS reaction leads to quick depletion of nutrients [14, 15]. It is accompanied by the compensatory anti-inflammatory response (CARS) reaction which, similarly to SIRS, may lead to the multiple organ failure (MOF). In that period of the immune response (CARS), disturbances of the adaptive immunity occur, in particular, disturbances in cooperation of macrophages, dendritic cells and lymphocytes, as well as disturbances in antigen presentation, apoptosis of lymphocytes, increased IL-4 and IL-10 production and increased immunosuppression [3]. Main nutrients in the immunonutrition are: arginine, glutamine, omega-3 fatty acids, lipid emulsions, nucleotides and antioxidants (β-carotene, vitamins C and E, selenium, zinc, copper). The immunologically active components of nutritional formulations may increase activity of the immune system cells (arginine, glutamine) and contain the inflammatory process (fatty acids). The immunomodulating effect of unsaturated fatty acids may results in a reduced activity of neutrophils, monocytes and lymphocytes, and production of cytokines [16-18]. The immunostimulating effect of amino acids increases phagocytic activity of leukocytes, increases resistance to infections and accelerates the wound healing process [7, 19-23].

Clinical aspects of immunonutrition

In the randomised trials it was shown that immunonutrition improved a clinical course of an illness, reduced frequency of severe infections, shortened patient's stay at a hospital, reduced of treatment costs and significantly reduced the death rate in severely ill patients with MOF [24-31]. Those advantages were most convincing in the surgical patients. In patients with severe injuries and infections receiving *immunonutrition*, a significant reduction in duration of the SIRS and significant reduction in incidence of MOF was observed. In clinical studies the immunomodulating nutrition (containing arginine, nucleotides and n-3 fatty acids) reduced incidence of infectious complications in severely ill patients with injuries and after oncological surgeries. Results of a meta-analysis of randomised trials showed that in a group of the most severely ill patients (with SIRS/sepsis/ARDS), the immunomodulating treatment with glutamine and fatty acids improved treatment results; which was not confirmed for enteral administration of arginine [32]. Another meta-analysis concerning results of perioperative application of immunonutrition in patients operated for neoplasms of the gastrointestinal tract, showed reduction in incidence of postoperative complications, shorter stay in a hospital and improvement in selected immunity parameters (increase in the total number of lymphocytes, subpopulation of CD4 cells and IgG levels, and reduction in IL-6 levels) [33]. Multicentre studies showed that use of immunonutrition (glutamine with antioxidants) in severely ill patients treated at intensive care units significantly reduced morbidity and the death rate [34]. Within last 10 years no harmful effect of glutamine (daily doses of 10-30 g) was demonstrated even in critically ill patients. In patients treated at an intensive care unit a risk of death was significantly reduced after using parenteral nutrition containing glutamine (at a dose of 0.2-0.57 g glutamine/kg b.w./day) [7, 35]. The studies were conducted in various populations of patients, in whom various nutrition regimes were used, and this is a significant obstacle in comparing the results. In most of those studies changes in the nutritional status and immunity during immunomodulating nutrition were not monitored simultaneously. Although the beneficial effect of immunonutrition was found, in particular, for a treatment of the surgical patients, yet the mechanism of the nutrition influence on the immune system is still unclear. Lack of that knowledge is one of the fundamental reasons for clinical failure of an immunonutrition treatment in various groups of patients, confirmed by results of the recent studies.

In the recently published large meta-analysis (2730 patients) it was demonstrated that after extensive gastroenterological surgeries, perioperative enteral immunonutrition reduced incidence of complications and duration of hospitalisation, but did not influence the death rate [36]. Immunonutrition applied regularly in the perioperative period was of no effect on improvement of treatment results in patients after elective gastrointestinal surgery [37]. In patients with acute pancreatitis, enteral immunonutrition (with glutamine, arginine and/or omega-3 acids) did not improve treatment results; incidence of complications, duration of hospitalisation and the death rate were assessed [38]. In a group of 3013 patients treated with immunonutrition, mainly at intensive care units, where a diet enriched in arginine without glutamine and fish oil was used, no improvement of treatment results was found versus standard nutrition [39].

With the increasing number of meta-analyses covering large groups of patients, it was demonstrated that immunonutrition could have adverse effects. In patients with severe infections treated with enteral nutrition containing arginine the death rate was higher [40, 41]. In the latest studies the increased death rate was also recorded for patients treated with fatty acids at intensive care units [42, 43]. In other studies, use of lipid emulsions in patients after surgical treatment and in critically ill ones increased incidence of complications [44]. No improvement after treatment with lipid emulsions was also observed in large review studies. Results of studies evaluating various immunological para-

meters varied, and that additionally hampered determining indications for use of lipid emulsions.

As results of many meta-analyses showed, immunonutrition should be applied with great caution and only in selected groups of patients. High levels of immunologically active nutrients may be harmful [45]. Use of glutamine in patients for planned surgeries, with severe infections and respiratory failure is not justified (guidelines of the European Society for Clinical Nutrition and Metabolism – ESPEN). On the other hand, its enteral administration (20-30 g daily) improves treatment results in patients with injuries and with burns. Arginine should not be used in patients with severe infections (sepsis). Administration of arginine (at a dose of 12 g/day) to patients for planned surgeries, with injuries and burns, is advantageous (guidelines of the American Society for Parenteral and Enteral Nutrition – ASPEN). Omega-3 fatty acids are recommended mainly for patients with acute respiratory failure during severe infection (e.g. enterally within 24-48 hours of admission, at a dose of 7-10 g EPA/DHA per day, ESPEN and ASPEN guidelines).

The review of the latest clinical results indicates that immunonutrition in a group of the most severely ill patients should not be used without monitoring of selected immunological parameters. This requires appropriate laboratory facilities available in specialist centres, allowing evaluation of adverse changes in immunity during the nutritional treatment (e.g. increase in SIRS or CARS response). It is known that increasing malnutrition related to an underlying disease (e.g. neoplasm), injury and infection significantly affects immunity. The effect of malnutrition on the immune system cells is related, amongst the others, to increased immunosuppression (lack of energy substrates for cells, reduction in number and activity of Th1 lymphocytes, dominating activity of Th2 lymphocytes), disturbed regulation of the inflammatory response (change in production of cytokines, chemokines), increased cell apoptosis (apoptosis of lymphocytes and intestinal endothelial cells with inflammatory lesions) and to disturbances in a signal transmission to a cell (disturbances in tyrosine kinase phosphorylation and activation of transcription factors). The nutrients should be selected depending on a treated group of patients and a current immunity status. Administering nutrition increasing the initial inflammatory response (e.g. arginine or soya bean oil based lipid emulsions with high levels of omega-6 fatty acids) during overwhelming SIRS reaction will intensify SIRS and increase a risk of a severe infection and MOF. Increase in immunosuppression during intensive CARS reaction (e.g. by administering a lipid emulsion with increased content of omega-3 fatty acids) may cause an irreversible immunological paralysis and MOF. It is known that omega-3 fatty acids increase apoptosis of Th1 lymphocytes, reduce proliferation of lymphocytes and monocytes, chemotaxis and adherence of leucocytes, and have a strong anti-inflammatory and immunosuppressive effect. The answer to the question, whether increased effectiveness of immunonutrition should be connected to regulation of mechanism of the inflammatory response to massive infection by supplying appropriate "fuel" to the immune system cells, requires further studies. It is still unknown whether for improvement in immunity it is sufficient to supplement nutritional deficiencies (hoping for autoregulation of immunity disorders), or, at this stage of studies, it is better to limit nutritional intervention in poorly known immunological mechanisms.

Immunomodulation with fatty acids

An interesting example for regulation with immunomodulating nutrition of immunological disorders accompanying malnutrition is advancement in a treatment of severely ill patients with lipid emulsions. It is known they have both pro- and anti-inflammatory effect. The clinical tests show a significant improvement in treatment results after modifications in composition of standard lipid emulsions by reducing content of linoleic acid (omega-6 fatty acids) in favour of oleinic (omega-9 MUFA), linolenic, and EPA and DHA (omega-3 acids) acids, being precursors of series-3 prostaglandins and tromboxanes, series-5 leucotrienes, resolvins and D1 protectins with anti-inflammatory effect.

A limiting pro-inflammatory effect of soya bean oil based lipid emulsions by decreasing synthesis of pro-inflammatory leucotriens and prostaglandins (reduction of SIRS) was connected to a reduced incidence of complications in a group of parenterally fed patients [46]. A concept of replacing n-6 PUFA acids with medium-chain triglycerides (MCT), not being precursors of pro-inflammatory eicosanoids, was a next step in modification of the lipid emulsion composition. It was demonstrated they were resistant to peroxidation, reducing oxidative stress, as well as being more "immuno-neutral" [47, 48]. It was found, however, they could increase lipid membrane liquidity in granulocytes, decrease leukocytes migration, increase production of pro-inflammatory mediators and cause cardiovascular disorders. In enteral feeding in patients with acute respiratory failure (ARDS) treated at an intensive care unit, pro-inflammatory γ-linolenic acid (18:3 n-6) was combined with anti-inflammatory n-3 acids (EPA), with a significant improvement in treatment results [49-51]. Administering in parenteral feeding n-3 PUFAs to patients after extensive surgical treatment (study covered 661 patients) shortened stay at ICU and in a hospital [52, 53]. In the randomise studies it was demonstrated that a treatment with lipid emulsions containing MCT/LCT triglycerides, fish oil, olive oil, did not have a significant effect on the death rate and incidence of infections in patients treated at ICU [54, 55]. Use of olive oil (n-9 MUFA) in parenteral nutrition, on the other hand, significantly shortened time of mechanical ventilation and duration of those patients' stay at an intensive

care unit, versus emulsions containing MCT/LCT. In the n-9 MUFA effect on the immune system, most often dominated the inhibiting influence on release of chemokines and adhesion molecules, low susceptibility to peroxidation and limited influence on production of eicosanoids (they are "immuno-neutral"), and significant reduction in the inflammatory response (reduction in TNF, IL-6, IL-8), versus MCT/LCT emulsions.

It should be emphasised that while waiting for further randomised clinical trials, parenteral nutritional treatment with lipid emulsions demonstrating the highest immunological activity (with high content of omega-6 and omega-3 acids) should be used with great caution in severely ill patients, particularly when changes in immunity are not monitored. Treating that group of patients with PUFAs (without immunological monitoring) may contribute to more pronounced oxidative stress, intensified immunosuppression and deteriorated treatment results. To improve the treatment results for patients in a severe condition, at this stage of knowledge development immunonutrition should be treated as auxiliary for the main therapy (supplementing protein and energy deficiencies, as well as other nutrients, with n-6 PUFA content limited in favour of n-9 MUFA and MCT/LCT). Poorly known mechanisms regulating immunity disorders in severely ill patients justify a treatment with emulsions having a reduced influence on the immune system (Fig. 1).

To improve treatment results in the group of severely ill patients after extensive surgery more attention should be paid to explaining molecular mechanisms regulating innate antibacterial response. A prerequisite for advancement in treatment of those patients is more detailed knowledge about influence of the nutrition status and severe infections, and of nutritional treatment on expression of genes of selected proteins in the signal pathways of the innate antibacterial response cells. It is known that immunonutrition with fatty acids may have an selective inhibitory effect on a signal cascade related to the innate antibacterial response (mainly leukocytes and macrophages), independently at each stage of: a) interaction of endotoxin with the TLR-4 receptor, b) activation of kinases phosphorylating the inhibitor of transcription factor NF-κB (IκB) and c) translocation to the nucleus and binding of NF-κB to an appropriate DNA sequence (inhibition of transcription of genes mediating the inflammatory reaction) [11, 44, 56-58]. That indicates the crucial role of the TLR-4 receptor in regulation of response to the increased fatty acids levels circulating in peripheral blood in sepsis. Interaction of those fatty acids with the TLR-4 receptor intensifies inflammatory reaction and increases resistance to insulin and damage to tissues. That can be prevented by using appropriate nutritional formulations. Attempts at modulating the immune response to the operative injury and infection with immunonutrition indicate that in the future such treatment can be a valuable supplement of the therapy using blocking of selected signal pathways to reduce hazardous consequences of a massive infection, including mainly the increased inflammatory response.

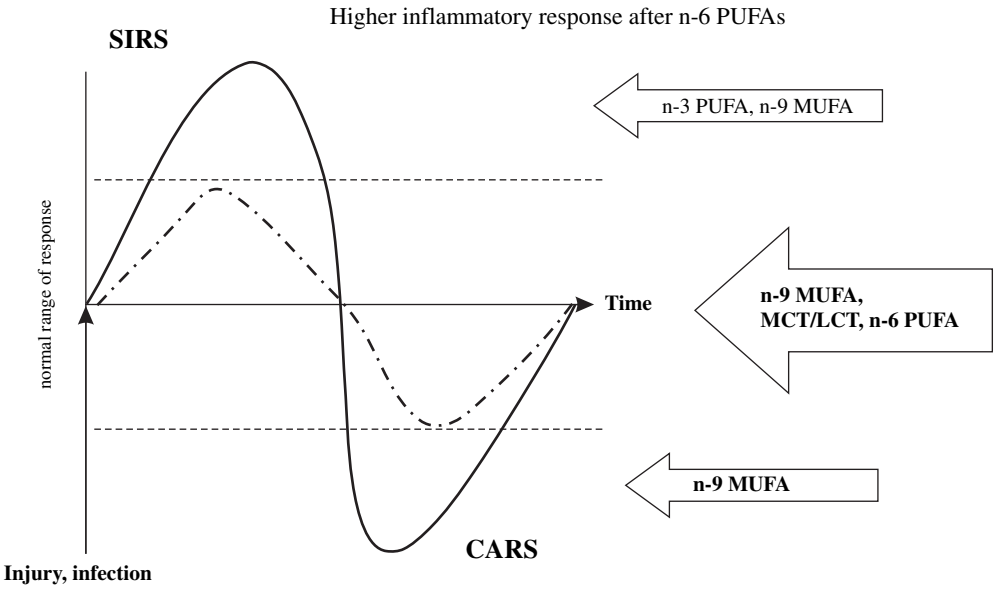

Fig. 1. The concept of lipids emulsion therapy in the context of exaggerated pro-inflammatory (SIRS) and anti-inflammatory (CARS) response to injury and infection

Acknowledgment

This work was supported by Project No. 2 3068B P01 funded by the Ministry of Science and Higher Education in Poland.

References

1. Grimble RF (2001): Nutritional modulation of immune function. Proc Nutr Soc 60: 389-397.
2. Xu J, Yunshi Z, Li R (2009): Immunonutrition in surgical patients. Curr Drug Targets 10: 771-777.
3. Calder PC (2007): Immunonutrition in surgical and critically ill patients. Br J Nutr 98 Suppl. 1: S133-S139.
4. Haydock DA, Hill GL (1986): Impaired wound healing in surgical patients with varying degrees of malnutrition. JPEN J Parenter Enteral Nutr 10: 550-554.
5. Detsky AS, Baker JP, O'Rourke K, et al. (1987): Predicting nutrition-associated complications for patients undergoing gastrointestinal surgery. JPEN J Parenter Enteral Nutr 11: 440-446.
6. Reynolds JV, O'Farrelly C, Feighery C, et al. (1996): Impaired gut barrier function in malnourished patients. Br J Surg 83: 1288-1291.
7. Kelly D, Wischmeyer PE (2003): Role of L-glutamine in critical illness: new insights. Curr Opin Clin Nutr Metab Care 6: 217-222.
8. Riedemann NC, Guo RF, Ward PA (2003): Novel strategies for the treatment of sepsis. Nat Med 9: 517-524.
9. Cohen J (2002): The immunopathogenesis of sepsis. Nature 420: 885-891.
10. Hotchkiss RS, Karl IE (2003): The pathophysiology and treatment of sepsis. N Engl J Med 348: 138-150.
11. Singer P, Shapiro H, Theilla M, et al. (2008): Anti-inflammatory properties of omega-3 fatty acids in critical illness: novel mechanisms and integrative perspective. Intensive Care Med 34: 1580-1592.
12. Kessel A, Toubi E, Pavlotzky E, et al. (2008): Treatment with glutamine is associated with down-regulation of Toll-like receptor-4 and myeloid differentiation factor 88 expression and decrease in intestinal mucosal injury caused by lipopolysaccharide endotoxaemia in a rat. Clin Exp Immunol 151: 341-347.
13. Zhao Y, Joshi-Barve S, Barve S, Chen LH (2004): Eicosapentaenoic acid prevents LPS-induced TNF-alpha expression by preventing NF-kappa B activation. J Am Coll Nutr 23: 71-78.
14. Lorne E, Dupont H, Abraham E (2010): Toll-like receptors 2 and 4: initiators of non-septic inflammation in critical care medicine? Intensive Care Med 36: 1826-1835.
15. Słotwiński R, Słotwińska S, Kędziora S, Bałan BJ (2011): Innate immunity signaling pathways: links between immunonutrition and responses to sepsis. Arch Immunol Ther Exp 59: 139-150.
16. Caughey GE, Mantzioris E, Gibson RA, et al. (1996): The effect on human tumor necrosis factor α and interleukin 1β production of diets enriched in n-3 fatty acids from vegetable oil of fish oil. Am J Clin Nutr 63: 116-122.
17. Wallace FA, Miles EA, Evans C, et al. (2001): Dietary fatty acids influence the production of Th1- but not Th2-type cytokines. J Leukoc Biol 69: 449-457.
18. Calder PC, Yaqoob P, Thies F, et al. (2002): Fatty acids and lymphocyte functions. Br J Nutr 87: S31-S48.
19. Manhart N, Vierlinger K, Akomeah R, et al. (2000): Influence of enteral diets supplemented with key nutrients on lymphocyte subpopulations in Peyer's paches of endotoxin-boostered mice. Clin Nutr 19: 265-269.
20. Kudsk KA, Wu Y, Fukatsu K, et al. (2000): Glutamine-enriched total parenteral nutrition maintains intestinal interleukin-4 and mucosal immunoglobulin A levels. JPEN J Parenter Enteral Nutr 24: 270-274.
21. Kirk SJ, Hurson M, Regan MC, et al. (1993): Arginine stimulates wound healing and immune function in elderly humans beings. Surgery 114: 155-159.
22. Moffat FL Jr, Han T, Li ZM, et al. (1996): Supplemental L-arginine HCL augments bacterial phagocytosis in human polymorphonuclear leukocytes. J Cell Physiol 168: 26-33.
23. O'Riordain MG, De Beaux A, Fearon KC (1996): Effect of glutamine on immune function in the surgical patient. Nutrition 12 (11?12 Suppl): S82-84.
24. Atkinson S, Sieffert E, Bihari D (1998): A prospective, randomized, double-blind, controlled clinical trial of enteral immunonutrition in the critically ill. Guy's Hospital Intensive Care Group. Crit Care Med 26: 1164-1172.
25. Griffiths RD, Jones C, Palmer TE (1997): Six-month outcome of critically ill patients given glutamine-supplemented parenteral nutrition. Nutrition 13: 295-302.
26. Kudsk KA, Minard G, Croce MA, et al. (1996): A randomized trial of isonitrogenous enteral diets after severe trauma. An immune-enhancing diet reduces septic complications. Ann Surg 224: 531-543.
27. Weimann A, Bastian L, Bischoff WE, et al. (1998): Influence of arginine, omega-3 fatty acids and nucleotide-supplemented enteral support on systemic inflammatory response syndrome and multiple organ failure in patients after severe trauma. Nutrition 14: 165-172.
28. Galbán C, Montejo JC, Mesejo A, et al. (2000): An immune-enhancing enteral diet reduces mortality and episodes of bacteremia in septic intensive care unit patients. Crit Care Med 28: 643-648.
29. Jolliet P (1999): Immunonutrition in critically ill. Intensive Care Med 25: 631-638.
30. Senkal M, Zumtobel V, Bauer KH, et al. (1999): Outcome and cost-effectiveness of perioperative enteral immunonutrition in patients undergoing upper gastrointestinal surgery. Arch Surg 134: 1309-1316.
31. Bower RH, Cerra FB, Bershadsky B, et al. (1995): Early enteral administration of a formula (Impact) supplemented with arginine, nucleotides, and fish oil in intensive care unit patients: results of a multicenter, prospective, randomized, clinical trial. Crit Care Med 23: 436-439.
32. Marik PE, Zaloga GP (2008): Immunonutrition in critically ill patients: a systemic review and analysis of the literature. Intensive Care Med 34: 1980-1990.
33. Zheng Y, Li F, Qi B, et al. (2007): Application of perioperative immunonutrition for gastrointestinal surgery: a meta-analysis of randomized controlled trials. Asia Pac J Clin Nutr 16 Suppl 1: 253-257.
34. Heyland DK, Dhaliwal R, Day AG, et al. (2006): REducing Deaths due to OXidative Stress (The REDOXS Study): Rationale and study design for a randomized trial of glutamine and antioxidant supplementation in critically-ill patients. Proc Nutr Soc 65: 250-263.
35. Novak F, Heyland DK, Avenell A, et al (2002): Glutamine supplementation in serious illness: a systematic review of the evidence. Crit Care Med 30: 2022-2029.

36. Cerantola Y, Hübner M, Grass F, et al. (2011): Immunonutrition in gastrointestinal surgery. Br J Surg 98: 37-48.
37. Helminen H, Raitanen M, Kellosalo J (2007): Immunonutrition in selective gastrointestinal surgery patients. Scand J Surg 96: 46-50.
38. Petrov MS, Atduev VA, Zagainov VE (2008): Advanced enteral therapy in acute pancreatitis: is there a room for immunonutrition? A meta-analysis. Int J Surg 6: 119-124.
39. Peterik A, Milbrandt EB, Darby JM (2009): Immunonutrition in critical illness: still fishing for the truth. Crit Care 13: 305.
40. McCowen KC, Bistrian BR (2003): Immunonutrition: problematic or problem solving? Am J Clin Nutr 77: 764-770.
41. Stechmiller JK, Childress B, Porter T (2004): Arginine immunonutrition in critically ill patients: a clinical dilemma. Am J Crit Care 13: 17-23.
42. McClave SA, Hurt RT (2010): Clinical guidelines and nutrition therapy: better understanding and greater application to patient care. Crit Care Clin 26: 451-466.
43. Wohlmuth C, Dünser MW, Wurzinger B, et al. (2010): Early fish oil supplementation and organ failure in patients with septic shock from abdominal infections: a propensity-matched cohort study. JPEN J Parenter Enteral Nutr 34: 431-437.
44. Calder PC (2006): n-3 polyunsaturated fatty acids, inflammation, and inflammatory disease. Am J Clin Nutr 83: 1505S-1519S.
45. Mizock BA (2010): Immunonutrition and critical illness: an update. Nutrition 26: 701-707.
46. Heyland DK, Montalvo M, MacDonald S, et al. (2001): Total parenteral nutrition in the surgical patient: a meta-analysis. Can J Surg 44: 102-111.
47. Wanten G (2006): An update on parenteral lipids and immune function: only smoke, or is there any fire? Curr Opin Clin Nutr Metab Care 9: 79-83.
48. Wanten GJ, Calder PC (2007): Immune modulation by parenteral lipid emulsions. Am J Clin Nutr 85: 1171-1184.
49. Gadek JE, DeMichele SJ, Karlstad MD, et al. (1999): Effect of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in patients with acute respiratory distress syndrome. Enteral Nutrition in ARDS Study Group. Crit Care Med 27: 1409-1420.
50. Singer P, Theilla M, Fisher H, et al. (2006): Benefit of an enteral diet enriched with eicosapentaenoic acid and gamma-linolenic acid in ventilated patients with acute lung injury. Crit Care Med 34: 1033-1038.
51. Pontes-Arruda A, Arag?o AM, Albuquerque JD (2006): Effects of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in mechanically ventiled patients with severe sepsis and septic shock. Crit Care Med 34: 2325-2333.
52. Heller AR, Rössler S, Litz RJ, et al. (2006): Omega-3 fatty acids improve the diagnosis-related clinical outcome. Crit Care Med 34: 972-979.
53. Wichmann MW, Thul P, Czarnetzki HD, et al. (2007): Evaluation of clinical safety and beneficial effects of a fish oil containing lipid emulsion (Lipoplus, MLF541): data from a prospective, randomized, multicenter trial. Crit Care Med 35: 700-706.
54. García-de-Lorenzo A, Denia R, Atlan P, et al. (2005): Parenteral nutrition providing a restricted amount of linoleic acid in severely burned patients: a randomized double-blind study of an olive oil-based lipid emulsion v. medium/long-chain triacylglycerols. Br J Nutr 94: 221-230.
55. Huschak G, Zur Nieden K, Hoell T, et al. (2005): Olive oil based nutrition in multiple trauma patients: a pilot study. Intensive Care Med 31: 1202-1208.
56. Lee JY, Sohn KH, Rhee SH, Hwang D (2001): Saturated fatty acids, but not unsaturated fatty acids, induce the expression of cyclooxygenase-2 mediated through Toll-like receptor 4. J Biol Chem 276: 16683-16689.
57. Weldon SM, Mullen AC, Loscher CE, et al. (2007): Docosahexaenoic acid induces an anti-inflammatory profile in lipopolysaccharide-stimulated human THP-1 macrophages more effectively than eicosapentaenoic acid. J Nutr Biochem 18: 250-258.
58. Novak TE, Babcock TA, Jho DH, et al. (2003): NF-kappa B inhibition by omega-3 fatty acids modulates LPS-stimulated macrophage TNF-alpha transcription. Am J Physiol Lung Cell Mol Physiol 284: L84-L89.