

## Immunonutrition effects in the treatment of cancer patients and its complications - a review

### Efeitos da imunonutrição no tratamento de pacientes com câncer e suas complicações – uma revisão

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#### Abstract

The aim of this study was to review and summarize the data from the literature regarding the effects of pre- and postoperative immunonutrition in the outcome of cancer patients. The review was conducted through literature searches in databases such as Medline/Pubmed, Scielo and Lilacs, from July to September 2014, for articles investigating the effects of immunonutrition related to nutritional recovery and pre- and post-operative procedures in cancer patients. We found 32 articles, 27 of which met the inclusion criteria, including review articles, case-control studies, epidemiological studies and cross-sectional studies. From this literature review it was possible to see the benefits of using preoperative immunomodulating diet in cancer patients undergoing major abdominal surgery, including reduction of septic and inflammatory complications during postoperative period and hence the hospital length of stay. Thus, the use of immunonutrition has been shown to be capable to reverse organic and immunological changes caused by both malnutrition and the tumor itself in cancer patients.

**Key words:** Neoplasia. Immunonutrition. Nutrition therapy. Food immunotherapy.

#### Resumo

O objetivo deste trabalho foi revisar, de forma sucinta e objetiva, as evidências disponíveis nos bancos de dados digitais, sobre os efeitos da imunonutrição para a resposta ao tratamento de pacientes com câncer em pré e pós-operatório. Foi realizada uma revisão de literatura, por meio de buscas bibliográficas nos bancos de dados informatizados Medline/Pubmed, Scielo e Lilacs, no período de julho a setembro de 2014, de artigos que investigaram os efeitos da imunonutrição na recuperação do estado nutricional e

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em procedimentos pré e pós-operatório de pacientes com câncer. Foram encontrados 32 artigos, dos quais 27 atenderam aos critérios de inclusão do estudo, compreendendo artigos de revisão, caso-controle, epidemiológicos e transversais. A partir desta revisão de literatura foi possível verificar o benefício do uso da dieta imunomoduladora em pacientes oncológicos submetidos ao tratamento no pré-operatório de cirurgias de grande porte abdominal, diminuindo complicações sépticas e inflamatórias no período pós-operatório e consequentemente o tempo de internação hospitalar. Dessa forma, o uso da imunonutrição mostra-se com capacidade de reverter alterações orgânicas e imunológicas causadas tanto pela desnutrição como pelo próprio tumor em pacientes com câncer.

**Palavras-Chaves:** Neoplasia. Imunonutrição. Terapia nutricional. Imunoterapia alimentar.

## Introduction

According to global estimates of Globocan project, the International Agency for Research on Cancer and the World Health Organization (WHO), there were 14.1 million new cancer cases and a total of 8.2 million cancer deaths worldwide in 2012 (Ferlay et al., 2012). In Brazil, the estimate for the year 2014, which shall be the same for 2015, points out to the occurrence of about 576,000 new cases of cancer, including nonmelanoma skin cases, reinforcing, therefore, the magnitude of the problem in the country (INCA, 2014).

Cancer may be defined as a chronic, multifactorial disease characterized by uncontrolled cell growth. Prevention has taken a major dimension in science due to impaired life quality of patients. Its development involves cellular DNA changes that accumulate over time. When these damaged cells escape the mechanisms involved in protecting the body against growth and spread of such cells, neoplasia is established (Bozzetti et al., 2009).

Oncological pathology significantly influences the body physiological mechanisms, affecting mainly the patient's life quality. In this sense, the nutritional status of cancer patients has been a frequent topic of debate, as one of the greatest challenges in confronting this disease is malnutrition and cachexia - frequently observed in these patients. Weight loss of nutrients attributed to cancer arises from the consumption of lean and fat mass, distinguishing from starvation due to the fact that replacement of missing nutrients does not restore normal nutritional status (Zhang et al., 2012).

In cancer patients, metabolic disorders are significant, increasing malnutrition. The tumor can prevent the normal metabolic control mechanisms, making it possible to develop regardless of the host's nutritional status, while maintaining a high metabolic activity with consumption of the available reserves (NITENBERG; Raynard, 2000; TRANCAS et al., 2010).

Cachexia linked to cancer is very common in patients with advanced stage of the disease and appears to result not only of increased metabolic demands by the tumor, but also by the inflammatory response associated with it. The growing tumor mass, especially when associated with metastases, is characterized by increased catabolism of endogenous reserves, resulting in increased weight loss and organ dysfunction. Malnutrition enhances greater reduction of endogenous reserves, decreasing the ability of the patient to compensate for the increased energy needs and putting the patient at a greater risk of cachexia (OLIVEIRA; BONETI; PIZZATO, 2011).

When nutritional depletion occurs, decreased immune function also takes place, observed by the immune function test changes. However, other non-nutritional factors like the tumor itself may also be implied, causing immunosuppression (Di Leo et al., 2014). These changes generate immunological complications for the patient, who with impaired immune system, will not have the same response to drug treatment and to surgical procedures, hindering, in this way, a successful treatment. So the immunonutritional control could contribute to

decreased rate of infections and hospital stay in the treatment of cancer patients (reference).

Given the above, due to the effects that cancer may cause in patients, the need for adequate nutrition to decrease the adverse effects and the emergence of new cancer treatments, the present study has been proposed in order to objectively review the available evidences in digital databases about the effects of immunonutrition to the response to treatment of patients with pre and postoperative cancer.

## Methodology

A literature review was carried out through bibliographical research in computerized databases - Medline / Pubmed, Scielo and Lilacs - from July to September 2014, searching and using articles that investigated the effects of immunonutrition recovery of nutritional status and pre- and post-operative procedures in cancer patients. Articles of cross-sectional epidemiological studies, review and case-control were included in the review. Articles that were not completely available in full were excluded, since this fact made it difficult and / or impossible to extract relevant information to the investigation of factors and outcomes studied. The searches were conducted through advanced form using the following key words in Portuguese and their corresponding in English: neoplasms, immunonutrition, treatment, nutritional supplementation, malnutrition, pre and postoperative complications. All keywords are listed in health sciences descriptors.

Data were analyzed according to Gil (2002) through four readings: exploratory, selective, analytical and interpretive. Through exploratory reading, the results obtained by scanning the database were assessed according to the research objectives. When performing selective reading, we selected only those that were actually meaningful to the research. Based on the articles selected, the analytical reading was held in order to organize and

summarize the information in the sources to make possible to obtain answers to research questions. The interpretative reading was the last step of the Reading process, relating what the author's statements with the issues proposed in this study.

## Development

32 articles were found, of which 27 fulfilled the study inclusion criteria, including review articles, epidemiological and transversal case-control. 04 articles were excluded through selective and analytical readings for not suiting the research question of this study, once they involved other diseases or experimental studies.

The articles were divided into two groups. The first group contained articles concerning the nutritional characteristics and metabolic changes in cancer patients. The second group consisted of articles related to the benefits of immunonutrition for immunosuppressed patients or pre-treatment or post-operative patients. Thereafter the results were organized into two themes: 1. Immunonutrition in câncer treatment: concepts, characteristics and components; 2. Impacts of the administration of immunomodulatory diets in câncer patients.

## Immunonutrition in treating cancer: concepts, features and components.

### *Concepts and features*

Immunonutrition is defined as a form of artificial dieting that aims at immune response cell renewal. This involves specific amino acids such as glutamine, arginine, and fibers (Siqueira-Batista et al., 2012). The organic responses to trauma and to some kinds of cancers are mediated by pro-inflammatory cytokines (TNF-alpha, IL-1, IL-6, for instance), counterregulatory hormones (glucagon, catecholamines and cortisol, for example) and other mediators (prostaglandins, thromboxanes

and leukotrienes) which produce various metabolic abnormalities such as increased positive acute phase proteins (C-reactive protein, for example), decrease of negative acute phase proteins (albumin, pre-albumin, transferrin), edema, proteolysis, lipolysis and peripheral insulin resistance (CLOS DU et al., 2000; HALLAY et al, 2002;. Menezes et al, 2011;. streat et al., 2000).

Thus, immunonutrition therapy is a mechanism adopted to balance and improve the organic response to changes caused by the tumor, the drug therapy or surgical procedures to which the patient is subjected (ZHENG et al, 2007;.. Zhang et al, 2012 ). Of those surveyed studies, it was possible to observe that supplementation with immunonutrients is much more common in patients with esophageal, pancreatic and stomach cancer, on the grounds that they are predisposed to septic complications in the postoperative period. Furthermore, the deleterious effect of the surgical process in immunity is combined with the protein-calorie malnutrition and anorexiaque present with distinctive intensity according to the extent and location of the tumor in these patients (HALLAY et al, 2002;. NOVAES; Pantaleão 2012 ).

The injury caused by surgical procedure in patients affected with cancer causes depletion in the body fat storage and lean mass. The higher the surgery and the type of trauma, the more severe are the alterations of the defense mechanisms making the patients highly susceptible to sepsis, and inflammatory complications (BRENER et al, 2007;. Di Leo et al, 2014.).

Besides sepsis, cachexia is one of the most common etiologies of death in cancer patients, accounting for about 5-25% of global mortality. Recently, the impact of anorexia-cachexia syndrome in the quality of life of cancer patients has been evaluated, demonstrating that food intake and weight loss are the primary determinants, contributing approximately 20% to 30% of cancer cases (OLIVEIRA; BONETI; PIZZATO, 2011).

Bispo (2009) confirmed in his study that malnutrition has a negative impact on post surgical evolution, and suggested that nutritional supplementation in the preoperative period may be beneficial, so long as adequate in quality, quantity and duration, as already evidenced by earlier clinical trials.

### **Immunonutrition Components**

The term "Immunonutrition" has been popularized to describe enteral feeding formulas which were supplemented with a combination of arginine and / or glutamine, predominating omega 3 Oils (usually of marine origin), "antioxidante" nucleic and additional acid, such as vitamins and minerals. Animal models and human studies have suggested that the individual components have the beneficial effects (or potentially beneficial) on immune function (CLOS DU et al., 2000; Krenitsky, 2006; streat et al., 2000)

Under this perspective, there is a lack of conclusive studies in humans to evaluate the modulated individually addition of each immunonutrient, in this way it would be possible to determine which nutrients are required and the optimum amounts, prior to the introduction of these into commercial formulas. Considering the exceptional cost and time required for such analysis, the approach to the development of immunonutritional products has been more pragmatic. Manufacturers have used data from studies on animals and human trials to combine the various nutrients in different amounts and formulas (Krenitsky, 2006).

In recent years, arginine formulas,  $\omega$ -3 fatty acids and nucleotides have received special attention by combining components with beneficial actions recognized in wound healing, immune response and inflammatory reactions. The increase in the synthesis of collagen, especially hydroxyproline molecule, appears to be a major contributor to better healing (Caro et al., 2007).

Studies have shown that supplemental arginine may improve nitrogen balance, increase rates of immune function of T cells and increase collagen deposition in large wounds. Cancer patients who received post-operative supplemental arginine (25g / day) showed significant improvement in T lymphocyte response and T cells percentage (CD4 phenotype) compared to randomized patients who received placebo. One of the most frequent complications in malnourished cancer patients is the delay in wound healing, and it has been verified that early immunonutrition, particularly arginine, appears to be responsible for a more effective tissue regeneration (Daly et al., 1988; Braga et al, 2002; PEREIRA FILHO, 2012).

In a systematic review on the use of immunonutrition in critically ill patients, considering septic and non-septic patients, the use of immunonutrition with formulas containing arginine via enteral reduced the incidence of infections, but not mortality (Heyland et al., 2001). Studies that evaluated only the population of septic patients identified damage (increased mortality) using this type of formulation. Such effect may be related to the arginine metabolism alterations in sepsis, connected to the demodulation of secondary microcirculation to increased production of nitric oxide, or maximization of systemic inflammatory response (BERTOLINI et al., 2003).

Normal diet should provide 1-2 nucleotide grams a day of animal proteins, peas, beans, and milk. However, most enteral nutrition formulas are devoid of any preformed nucleotides. Though in humans there are few studies of the effect of supplementation of nucleotides, animals kept under a nucleotide-free diet showed a reduced immune response and decreased survival in response to an infectious challenge when compared to animals that received exogenous nucleotide sources in their diets (BUREN et al, 1985; KULKARNI et al., 1986).

Vitamins and minerals are essential immunomodulatory components, among them we

highlight vitamin E, vitamin C, selenium and zinc. There is data showing that antioxidant vitamins and minerals may positively influence in the prognosis of critically ill patients. According to Crimi, et al. (2004) in critically ill surgical patients reported that those who were given vitamin C and E supplements had reduced pulmonary morbidity as well as a significantly reduced incidence of multiple organ failure.

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are fats belonging to the polyunsaturated fatty acids, of the omega-3 family, found in greater quantities of fish. Both EPA and DHA are often present in immunonutritional formulas. These fatty acids compete with arachidonic acid (omega-6) and thus influence the production of prostaglandins, leukotrienes, thromboxanes and prostacyclins (Borges et al., 2014).

Addition of EPA and DHA enteral nutritional products results in a reduction of proinflammatory mediators in stressed patients. Early research in animal models for burns suggested that adding fish oils rich in omega-3 could reduce infectious complications. Moreover, the increased omega-3 fats beyond a certain extent, appeared to increase mortality in an animal model of peritonitis. Marine fat sources may increase the production of free radicals and, thus, increases the need of antioxidants (Krenitsky et al., 2006).

### **Impacts on the administration of immunomodulatory diets in cancer patients**

Malnutrition in hospitalized patients is a major problem associated with increased morbidity and postoperative mortality. In the context of gastrointestinal surgery, although elective, it takes on more significant contours, influencing the healing process and compromising the surgery outcome. Preoperative supplementation can restore biochemical and immunological normality levels not only in malnourished patients, but also in patients without disturbance of the nutritional status



(Zhang et al., 2012).

Several studies show that malnourished patients have further risk of postoperative complications and mortality. Among them, the Waitzberg et al. study (2001) found that almost 50% of patients in the public health system (*SUS*) are moderately or severely malnourished. According to Bozzetti et al. (2007) and Nascimento et al. (2014) malnourished patients undergoing tumor resection operations have a higher incidence of complications, as well as increased mortality, increased interaction time and hospital costs.

The ability of nutritional supplementation improve nutritional status and reduce morbidity and mortality after surgery, yet unable to reverse the catabolic response to aggression, suggests that its effect is optimized if initiated in preoperative period (Zhang et al. 2012). In this context, several studies have shown that in severe or moderate malnutrition, preoperative nutritional therapy carried out between 07 to 14 days is associated with reduced postoperative infections and length of hospital stay (WU, 2006).

Nutritional management in the preoperative period affects postoperative complications. Recently, there have been reports that infectious, inflammatory and immunosuppressive postoperative complications were reduced by the intake of oral preparations containing nutrients that enhance immune function, such as omega-3, arginine and nucleic acids. Inflammatory mediators derived from  $\omega$ -3, such as the E3 prostaglandin, thromboxane, LT5 leukotriene have light physiological activities and anti-inflammatory effects. Arginine and nucleic acid also have immunopotentiating activity in proliferating cells and their effects are expected to promote wound healing and help stabilize the intestinal mucosa (MIKAGI et al., 2011).

A clinical trial involving preoperative nutritional supplementation in patients with digestive cancer has found that the level of malnutrition is extremely variable, attesting in some studies that it is possible

to reduce postoperative complications in the group with supplement, relatively to the control group, without significant associated iatrogenic nutrition (Bozzetti et al., 2001).

Zheng et al. (2007) concluded that immunonutrition is effective and safe to decrease postoperative infection and reduce hospital stay, by increasing the humoral and cellular immunity of patients in the postoperative period compared to the control group. For some healthcare professionals nutritional supplementation is conceivable only in combination with potentially effective anti-cancer therapies.

Nutritional supplements should start at diagnosis and kept until there is no risk of malnutrition. It is believed that the initiation of preoperative supplementation would enhance the benefits already demonstrated with the sole administration in the postoperative period, possibly achieving a reduction in hospital stay and length of antibiotic therapy and post-operative complications with consequent lower costs. These benefits have even been demonstrated in patients with good nutritional status undergoing elective colorectal resection for cancer, showing that further than a mere nutritional support, supplementation must be seen as a metabolic support for cancer patients (Bozzetti et al., 2009).

Controversies exist regarding the use of immunonutrients in critically ill patients. Many meta-analysis have suggested that there are potential risks when immunomodulatory formulas are used inappropriately (MIZOCK, 2010). Severe disease is accompanied by various combinations of systemic inflammation and generalized immunosuppression, which may be improved or exacerbated with immunonutrients therapy. In septic patients, especially, arginine supplementation may have detrimental effects (CHIARLA et al., 2006). Plasma levels of nitric oxide from arginine gradually increases as it increases the severity of sepsis, especially in the presence of multiple organ

dysfunction. The ESPEN (European Society for Metabolism and Nutrition) recommends the use of arginine only for patients without major severity criteria, known with APACHE II score less than 15 (SINGER, et al., 2009). Yet, ASPEN (American Society for Parenteral and Enteral Nutrition) discourages the use of arginine in septic patients at all (MARTINDALE, et al., 2009).

## Conclusion

There is no doubt regarding the benefit of using immunomodulating diet in patients undergoing treatment in the preoperative of major abdominal surgeries, reducing septic and inflammatory complications in the postoperative period and consequently reducing hospital stay as well. It is clear that the use of immunonutrition has the ability to reverse organic and immunological changes caused either by malnutrition or the tumor itself in cancer patients. It is essential, however, that the findings available regarding the effectiveness of this nutritional intervention go beyond the sphere of scientific theory and start to be regularly used in clinical practice to improve the quality and increase the patients' response to treatment.

## References

BRAGA, M.; GIANOTTI, L.; VIGNALI, A.; & DI CARLO, V. Preoperative oral arginine and n-3 fatty acid supplementation improves the immunometabolic host response and outcome after colorectal resection for cancer. *Surgery*, v. 132, n. 5, p. 805-814, 2002.

BERTOLINI, G.; IAPICHINO, G.; RADRIZZANI, D.; FACCHINI, R.; SIMINI, B. Early enteral immunonutrition in patients with severe sepsis: results of an interim analysis of a randomized multicentre clinical trial. *Intensive Care Medicine*, New York, v. 29, p. 834-840, 2003.

BISPO, S.I.B. *Efeito da nutrição pré-operatória em doentes desnutridos com patologia oncológica digestiva*. 164f. Dissertação (Mestrado em Nutrição Clínica) – Universidade de Coimbra, Portugal. 2009.

BORGES, M. C.; SANTOS, F. D. M. M.; TELLES, R. W.; CORREIA, M. I. T. D.; LANNA, C. C. D. Ácidos graxos poliinsaturados ômega-3 e lúpus eritematoso sistêmico: o que sabemos? *Revista Brasileira de Reumatologia*, São Paulo, v. 54, n. 6, p. 459-466, 2014.

BOZZETTI, F.; GIANOTTI, L.; BRAGA, M.; DI CARLO, V.; MARIANI, L. Postoperative complications in gastrointestinal cancer patients: the joint role of the nutritional status and the nutritional support. *Clinical Nutrition*, Edinburgh, v. 26, n. 6, p. 698-709, 2007.

BOZZETTI, F.; BRAGA, M.; GIANOTTI, L.; GAVAZZI, C.; MARIANI, L. Postoperative enteral versus parenteral nutrition in malnourished patients with gastrointestinal cancer: a randomized multicentre trial. *The Lancet*, London, v. 358, n. 9292, p. 1487-1492, 2001.

BOZZETTI, F.; ARENDS, J.; LUNDHOLM, K.; MICKLEWRIGHT, A.; ZURCHER, G.; MUSCARITOLI, M. ESPEN Guidelines on Parenteral Nutrition: non-surgical oncology. *Clinical Nutrition*, Edinburgh, v. 28, n. 4, p. 445-454, 2009.

BRENER, S.; JEUNON, F. A.; BARBOSA, A. A.; GRANDINETTI, H. D. A. M. Carcinoma de células escamosas bucal: uma revisão de literatura entre o perfil do paciente, estadiamento clínico e tratamento proposto. *Revista Brasileira de Cancerologia*, Rio de Janeiro, v. 53, n. 1, p. 63-69, 2007.

BUREN, C. T. V.; KULKARNI, A. D.; FANSLAW, W. C.; RUDOLPH, F. B. Dietary nucleotides: a requirement for helper/inducer T-lymphocytes. *Transplantation*, Baltimore, v. 40, p. 694-697, 1985.

CARO, M. M. M. A.; LAVIANO, A.; PICHARD, C. Nutritional intervention and quality of life in adult oncology patients. *Clinical Nutrition*, Edinburgh, v. 26, n. 3, p. 289-301, 2007.

CHIARLA, C.; GIOVANNINI, I.; SIEGEL, J. H. Plasma arginine correlations intrauma and sepsis. *Amino Acids*, New York, v. 30, n. 1, p. 81-86, 2006.

- CRIMI, E.; LIGUORI, A.; CONDORELLI, M.; CIOFFI, M.; ASTUTO, M.; BONTEMPO, P.; NAPOLI, C. The beneficial effects of antioxidant supplementation in enteral feeding in critically ill patients: a prospective, randomized, double blind, placebo-controlled trial. *Anesthesia & Analgesia*, Cleveland, v. 99, p. 857-863, 2004.
- DALY, J. M.; REYNOLDS, J. O. H. N.; THOM, A. R. L. E. N.; KINSLEY, L. I. N. D. A.; DIETRICK-GALLAGHER, M. A. R. I. A. N. N. E.; SHOU, J. I. A. N.; RUGGIERI, B. R. U. C. E. Immune and metabolic effects of arginine in the surgical patient. *Annals of Surgery*, Philadelphia, v. 208, n. 4, p. 512-523, 1988.
- DI LEO, A.; PEDRAZZANI, C.; BENCIVENGA, M.; CONIGLIO, A.; ROSA, F.; MORGANI, P.; RICCI, F. Gastric Stump Cancer after distal gastrectomy for benign disease: clinicopathological features and surgical outcomes. *Annals of Surgical Oncology*, New York, v. 21, n. 8, p. 2594-2600, 2014.
- DU CLOS, T. W. Function of C-reactive protein. *Annals of Medicine*, London, v. 32, n. 4, p. 274-278, 2000.
- FERLAY, J.; SOERJOMATARAM, I.; ERVIK, M.; DIKSHIT, R.; ESER, S.; MATHERS, C.; REBELO, M.; PARKIN, D. M.; FORMAN, D.; BRAY, F. Cancer incidence and mortality worldwide: IARC Cancer Base No. 11. *Globocan*, Lyon, v. 1, 2012.
- GIL, A. C. *Como delinear uma pesquisa bibliográfica*. São Paulo: Atlas, 2002.
- HALLAY, J.; KOVÁCS, G.; KISS, S. Z. S.; FARKAS, M.; LAKOS, G.; SIPKA, S.; BODOLAY, E.; SÁPY, P. Changes in nutritional state and immune-serological parameters of esophagectomized patients fed jejunally with glutamine-poor and glutamine-rich nutrients. *Hepato Gastroenterology*, Stuttgart, v. 49, n. 48, p. 1555-1559, 2002.
- HEYLAND, D. K.; NOVAK, F.; DROVER, J.; JAIN, M.; SU, X.; SUCHNER, U. Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. *JAMA*, Chicago, v. 286, n. 8, p. 944-953, 2001.
- INCA. Instituto Nacional de Câncer José Alencar Gomes da Silva. Estimativa 2014: Incidência de Câncer no Brasil. Disponível em: < [www.inca.gov.br/estimativa/2014/](http://www.inca.gov.br/estimativa/2014/) >. Acesso em: 20 jun. 2014.
- KRENITSKY, J. Immunonutrition-Fact, Fancy or Folly? *Studia Liturgica*, v. 36, n. 1, p. 47, 2006.
- KULKARNI, A. D.; FANSLAW, W. C.; DRATH, D. B.; RUDOLPH, F. B.; VAN BUREN, C. T. Influence of dietary nucleotide restriction on bacterial sepsis and phagocytic cell function in mice. *Archives of Surgery*, Chicago, v. 121, n. 2, p. 169-172, 1986.
- MARTINDALE, R. G.; MCCLAVE, S. A.; VANEK, V. W.; MCCARTHY, M.; ROBERTS, P.; TAYLOR, B.; OCHOA J. B.; NAPOLITANO, L.; CRESCI, G. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: society of critical care medicine and american society for parenteral and enteral nutrition: executive summary. *Crit Care Medicine*, New York, v. 37, n. 5, p. 1757-1761, 2009.
- MIKAGI, K.; KAWAHARA, R.; KINOSHITA, H.; AOYAGI, S. Effect of preoperative immunonutrition in patients undergoing hepatectomy; a randomized controlled trial. *Kurume Medical Journal*, Kurume-Shi, v. 58, n. 1-8, 2011.
- MIZOCK, B. A. Immunonutrition and critical illness: an update. *Nutrition*, New York, v. 26, p. 701-707, 2010.
- MENEZES, R. M.; FERREIRA, K. A. S. L.; SOUZA, L. M.; BARROS, H. L. A.; PESSANHA, M. J. P. Instrumentos utilizados no Brasil para avaliar qualidade de vida em pacientes com câncer de cabeça e pescoço: revisão integrativa. *Revista Saúde-UnG*, Guarulhos, v. 5, n. 1, p. 54-66, 2011.
- NASCIMENTO, J. C.; ESTEVAM, E.; FÉLIX, A. C. F.; PAIVA, D. C. S.; MOREIRA, B. E. Análise do tempo de jejum inadequado em pacientes admitidos na UTI de um hospital oncológico. *Revista Científica da Faminas*, Muriae, v. 10, n. 2, p. 11-20, 2014.
- NITENBERG, G.; RAYNARD, B. Nutritional support of the cancer patient: issues and dilemmas. *Critical Reviews in Oncology/Hematology*, Boca Raton, v. 34, n. 3, p. 137-168, 2000.



- NOVAES, M. R. C. G.; PANTALEÃO, C. M. Arginina: bioquímica, fisiologia e implicações terapêuticas em pacientes com câncer gastrointestinal. *Revista de Ciências Médicas*, Campinas, v. 14, n. 1, p. 65-75, 2012.
- OLIVEIRA, H. S. D.; BONETI, R. S.; PIZZATO, A. C. Imunonutrição eo tratamento do câncer. *Ciência & Saúde*, v. 3, n. 2, p. 59-64, 2011.
- PEREIRA FILHO, J.S.; BICALHO, L.; SILVA, D.A. Uso de própolis associada a outros componentes no tratamento de feridas oncológicas após excisão. *Acta Biomedica Brasiliensia*, v. 3, n. 2, p. 15-25, 2012.
- SINGER, P.; BERGER, M. M.; VAN DEN BERGHE, G.; BIOLO, G.; CALDER, P.; FORBES, A.; GRIFFITHS, R.; KREYMAN, G.; LEVERVE, X.; PICHARD, C. ESPEN Guidelines on Parenteral Nutrition: intensive care. *Clinical Nutrition*, Edinburgh, v. 28, n. 2, p. 387-400, 2009.
- SIQUEIRA-BATISTA, R.; GOMES, A.P.; VELASCO, C.M.M.O.; ARAUJO, J.N.V.; VITORINO, R.R. ROQUE-RINCO, U.G.; FREITAS, B.A.C.; BRESSAN, J. Nutritional support in sepsis. *Revista Brasileira de Clínica Médica*. São Paulo, v. 10, n.5, p. 420-426, 2012.
- STREAT, S. J.; PLANK, L. D.; HILL, G. L. Overview of modern management of patients with critical injury and severe sepsis. *World Journal of Surgery*, New York, v. 24, n. 6, p. 655-663, 2000.
- TRANCAS, B.; CARDOSO, G.; LUENGO, A.; VIEIRA, C.; REIS, D. Depressão no doente oncológico: considerações diagnósticas e terapêuticas. *Acta Médica Portuguesa*, Lisboa, v. 23, n. 6, p. 1101-1112, 2010.
- WAITZBERG, D. L.; CAIAFFA, W. T.; CORREIA, M. I. T. D. Hospital malnutrition: the Brazilian national survey (IBRANUTRI): a study of 4000 patients. *Nutrition*, New York, v. 17, n. 7, p. 573-80, 2001.
- WU, G. H.; LIU, Z. H.; WU Z. H.; WU, Z. G. Perioperative artificial nutrition in malnourished gastrointestinal cancer patients. *World Journal of Gastroenterology*, Beijing, v. 12, n. 15, p. 2441, 2006.
- ZHANG, Y.; GU, Y.; GUO, T.; LI, Y.; CAI, H. Perioperative immunonutrition for gastrointestinal cancer: A systematic review of randomized controlled trials. *Surgical Oncology*, Oxford, v. 21, p. 87-95, 2012.
- ZHENG, Y.; LI, F.; QI, B.; LUO, B.; SUN, H.; LIU, S.; WU, X. Application of perioperative immunonutrition for gastrointestinal surgery: a meta-analysis of randomized controlled trials. *Asia Pacific journal of clinical nutrition*, London, v. 16, n. 1, p. 253-257, 2007.

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