Perioperative immunonutrition and gut function

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Purpose of review
In the last year, several meta-analyses focused on the potential clinical benefits of perioperative immunonutrition in surgical patients. Purpose of this review is to summarize their results and to draw recommendations about the current indication of immunonutrition in surgery.

Recent findings
Standard enteral preparations have been modified by adding specific nutrients, such as arginine, omega-3 fatty acids and others, which have been shown to upregulate immune response, to control inflammatory response, and to improve gut function after surgery. The majority of the randomized trials found that perioperative immunonutrition improved short-term outcome in patients, who underwent elective major gastrointestinal (GI) surgery. Four meta-analyses including a large number of randomized clinical trials reported that perioperative immunonutrition is associated with a substantial reduction in both infection rate and length of hospital stay. These results have been found in both upper and lower GI patients, regardless of their baseline nutritional status. Promising results have been found also in head and neck surgery.

Summary
In the light of these findings the use of perioperative immunonutrition should be implemented in patients undergoing elective major GI surgery. This should result in a considerable reduction in both postoperative morbidity and costs for healthcare systems. Larger trials are required before recommending immunonutrition as a routine practice in head and neck surgery.

Keywords
arginine, gastrointestinal surgery, immunonutrition, omega-3 fatty acids, postoperative infections

INTRODUCTION
The causes of postoperative infectious complications are multifactorial and dependant to an extent on the primary surgical disease, and the type and magnitude of operation. Nevertheless, there is growing evidence that traumatic and surgical insult is associated with a period of relative immune suppression, which may expose patients to subsequent risk of infection. Despite significant changes in elective surgical care and newer antimicrobial agents, postoperative infectious complications remain common, adding to length of hospital stay, healthcare costs and potential excess mortality. Furthermore, rates of nosocomial infections are rising in surgical and ICUs and the apparent increase in both gram-positive and gram-negative resistant bacteria is of particular concern, making the prevention of infection a major surgical issue.

Artificial nutrition still has an important role among the current strategy to reduce postoperative morbidity and its related costs, particularly in patients undergoing elective major gastrointestinal (GI) surgery [1]. In the last years, several randomized clinical trials focused on the potential clinical benefits of perioperative immunonutrition in surgical patients [2]. The purpose of this review is to summarize their results and to draw recommendations about the current indication of immunonutrition in surgery.

NUTRITION THERAPY
Recently, the main focus of clinical nutrition has moved from the issue to simply cover energy and nitrogen requirements (nutritional support) to the new concept of supplementing selected nutritional substrates because of their specific pharmacological effects (nutritional therapy). Immunonutrition is probably one of the best examples of the application of nutritional therapy in the clinical scenario. The main purpose is to modulate postoperative
KEY POINTS

- Immunonutrition upregulates host immune response, modulates inflammatory response, and improves gut oxygenation after surgery.
- Perioperative immunonutrition reduced both postoperative infection rate and length of hospital stay in patients, who underwent elective major GI surgery.
- Perioperative immunonutrition has been cost-effective as compared to the standard treatment.
- Patients undergoing elective major GI surgery should receive perioperative immunonutrition, regardless of their baseline nutritional status.

Nutrition and the gastrointestinal tract

RESULTS OF CLINICAL TRIALS

Immunonutrition has been associated with modulation of inflammatory response, enhancement of cell-mediated immune response, and up-regulation of gut function parameters early after surgery. In particular, perioperative arginine supplementation was associated with better operative small bowel and colon microperfusion as measured by laser Doppler flowmetry system. Moreover, in the first post-operative days higher circulating levels of nitric oxide, better intestinal mucosa oxygen metabolism measured by intestinal tonometry, and lower plasma levels of intestinal isoenzyme of alkaline phosphatase, which is released in the peritoneal fluid and plasma after intestinal hypoxic insult, were found in patients, who were given perioperative immunonutrition. These findings support the concept that the better gut microperfusion in patients receiving immunonutrition translated in a better gut oxygen tension, delivery, and utilization. It should also be stressed that an intra-operative deficient blood flow and oxygenation of the gut could impair the healing of anastomoses and could promote translocation of endotoxins and bacteria from the gut to systemic blood.

Prospective, randomized, double-blind clinical trials demonstrated that patients fed before and after elective major GI surgery with a diet supplemented with arginine, omega-3 fatty acids, and nucleotides had a significant reduction of both postoperative infections and length of hospital stay when compared with patients fed with a standard enteral formula. It could be suggested that the reduction of postoperative infections found in the supplemented group is the translation of the immunologic and metabolic advantages previously reported in patients receiving perioperative immunonutrition. These results supported the concept that a key point in elective surgical GI patients is to anticipate the provision of immunonutrients before operation.

According to previous studies, European Guidelines reported that perioperative immunonutrition is effective regardless of the baseline nutritional status of the patients. In fact, preoperative administration of immunoenhancing diets reduced postoperative infection rate not only in malnourished patients, but also in a series of well nourished patients with GI cancer, who received immunonutrition only before surgery. In these patients, prolonging the administration of immunonutrients postoperatively did not further improve clinical outcome.

The vast majority of randomized clinical trials carried out so far confirmed the clinical benefits of immunonutrition in elective surgical patients. Nevertheless, several trials differed for patient groups, nutritional formulas and protocols for immunonutrition administration as well as control groups that received various treatments such as...
standard enteral formula, parenteral nutrition or no nutritional support. Therefore, systematic reviews and meta-analyses have been carried out to further clarify the clinical relevance of perioperative immunonutrition.

Earlier meta-analysis found that perioperative immunonutrition was associated with no change in postoperative mortality, however a significant decrease in both infection rate and length of hospital stay, have been reported [2]. However, selection of trials included in the analyses was suboptimal resulting in data heterogeneity and non-homogeneous control groups. In fact, some of the included studies compared enteral immunonutrition with total parenteral nutrition, which is known to be less effective in elective surgical patients with a working gut. In these cases the better outcome found in the immunonutrition group could be explained not only by the properties of specific substrates given, but also by the different route of nutrients administration.

**RECENT META-ANALYSES**

Recently, four meta-analyses have been published [4,5,6,7]. Cerantola et al. [4] included 21 randomized clinical trials with an overall 2730 patients, who underwent elective major surgery for either upper GI or lower GI diseases. More than 70% of recruited patients were well nourished (median malnutrition rate in the overall series was 26%). In all the included randomized clinical trials, control groups received an isoenergetic, isonitrogenous standard enteral formula. Postoperative mortality was similar in the immunonutrition and control groups. The most important finding was that immunonutrition significantly reduced overall morbidity rate, particularly postoperative infectious complications. Moreover, immunonutrition shortened length of hospital stay probably as a direct consequence of lower postoperative complication rate.

Marik and Zaloga [5] included 21 randomized clinical trials partially overlapping with Cerantola meta-analysis, with an overall 1908 patients. According to Cerantola meta-analysis, immunonutrition significantly reduced both infectious complications and length of hospital stay. Interestingly, studies were grouped according to the type of immunonutrition as follows: arginine supplementation alone, omega-3 fatty acids supplementation alone or together. The best results have been obtained when arginine and omega-3 fatty acids were given together. It could be speculated that they may act synergistically to modulate both immune and inflammatory postoperative response and consequently to improve short-term postoperative outcome. Moreover, beneficial effects on clinical outcome have been found in both malnourished and well nourished patients, in accordance with European Guidelines [1].

Drover et al. [6] included 35 randomized clinical trials with more than 3000 patients, who underwent major elective GI or non-GI surgery. According to meta-analyses by both Cerantola et al. [4] and Marik and Zaloga [5], immunonutrition has been associated with a reduction in both postoperative infectious complications and length of hospital stay, whereas, no effect on postoperative mortality was found. In addition to the whole series analysis, the authors carried out four subgroups analyses focused on the following topics: first, type of surgery: 25 GI studies vs. 10 non-GI studies (seven head and neck surgery, two cardiac surgery, one gynecology surgery), second, site of GI disease (upper GI vs. lower GI surgery), third, type of immune-enhancing formula used: arginine–omega-3 fatty acids–nucleotides (Impact Nestle Inc.) vs. other arginine-supplemented diets, and lastly timing of immunonutrition supplementation. (only before surgery, only after surgery, or both). Significant outcome benefits from immunonutrition were found in both GI and non-GI surgery, in both upper GI and lower GI surgery, only when the diet containing arginine–omega-3 fatty acids–nucleotides was used, and particularly when immunonutrition treatment was started before surgery. Possible explanation for the better effect of the diet containing arginine–omega-3 fatty acids–nucleotides vs. other formulas is the higher arginine concentration and the specific combination of nutrients that can interact to produce benefit.

Marimuthu et al. [7] reported that perioperative immunonutrition significantly reduced both postoperative infectious complications and length of hospital stay not only after major abdominal surgery, but only in a subgroup of patients, who underwent head and neck surgery.

Arginine deficiency after surgical stress was reported more than 30 years ago, although the mechanisms behind this have remained unknown for years. An early postoperative increase of myeloid derived cells expressing arginase 1, which deplete arginine has been recently reported [6]. Coupled with a poor arginine intake this can lead to an arginine-deficiency state and consequently to a suppression of T-lymphocyte function. We can speculate that arginine supplementation can overcome this deficiency and omega-3 fatty acids can blunt upregulation of myeloid derived cells and decrease arginase 1 expression. Further studies are required to better elucidate other possible
interactions between arginine, omega-3 fatty acids, and nucleotides. Moreover, dose-response studies should better clarify which is the optimal dose of each substrate to maximize benefits in surgical patients.

COST–BENEFIT ANALYSIS

Despite good results from both randomized clinical trials and meta-analyses, the high cost of these new nutritional products could be considered a major drawback for their routine use. In view of the worldwide increasing concerns over exploding costs in medical care, the decision process for adopting the use of new products for routine treatment should not only weigh clinical benefits and risks, but also consider whether these benefits are worth the healthcare resources used. This decision-making process should be informed by cost-effectiveness analyses of clinical trials. In such economic studies the following costs should be calculated: the mean in-hospital-related costs of routine surgical care per patient, the costs of treating postoperative infectious and noninfectious complications, the costs of nutrition, and the overall costs for all patients.

Economic analysis carried out by blind economists on data gathered from a prospective randomised clinical trial showed that perioperative immunonutrition led to a substantial saving in healthcare resources consumed [8]. In fact, the saving due to a significant reduction in postoperative infectious complications by perioperative immunonutrition more than offsets the higher cost of the supplemented diet. Some general limitations of such an economic analysis should be noticed on the transferability of the present clinical and economic data, which may also influence their reproducibility. Comparable cost saving by the routine use of perioperative immunonutrition might be achieved in hospitals where the same type of operations are performed on a similar volume and complication rate. Moreover, the economic parameters may differ from country to country based on the type of health-care system and reimbursement rates.

CONCLUSION

Perioperative immunonutrition improved gut oxygenation and metabolic postoperative response, and significantly reduced both postoperative infection rate and length of hospital stay in patients undergoing elective major GI surgery. Promising results have been obtained also in non-GI surgery, especially in head and neck surgery, however larger trials are required before recommending immunonutrition as a routine practice in head and neck surgery.

According to literature data, immunonutrition should be prescribed to all patients undergoing elective major GI surgery with a substantial risk of infectious complications, regardless of their baseline nutritional status.

Future trials should investigate the efficacy of immunonutrition in patients undergoing minimally invasive GI surgery and/or receiving early after surgery recovery programmes, both associated with a reduction of postoperative complications and length of hospital stay. Another interesting field of research could be testing the efficacy of long-term treatment with immune-enhancing diets in cancer patients receiving neoadjuvant therapy.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 518–519).


This is the first meta-analysis showing the clinical benefits of perioperative immunonutrition in either upper or lower GI surgery.


This is the largest meta-analysis published on perioperative immunonutrition so far in either GI or non-GI surgery. A subanalysis found that the best clinical benefits have been obtained when arginine and omega-3 fatty acids have been given together.


This is the first meta-analysis showing significant clinical benefits from perioperative immunonutrition in head and neck surgery.