

## Revisión

# Revising concepts of artificial nutrition in contemporary surgery: from energy and nitrogen to immuno-metabolic support

L. Gianotti<sup>1</sup> and M. Braga<sup>2</sup>

<sup>1</sup>Department of Surgery. Milano-Bicocca University. S. Gerardo Hospital. Monza. Italy. <sup>2</sup>Department of Surgery. S. Raffaele University. Milan. Italy.

### Abstract

Profound changes in perioperative management, namely “fast track surgery” have been recently proposed. This is a bundle of various techniques used for subjects undergoing elective operations that allows an improved well-being, faster recovery, shorter hospitalization and better outcome. From a nutritional point of view this new approach translates into a more rapid return of bowel function and thus to safely tolerate oral re-feeding within 1-3 days even after major operations. Nevertheless, the classic indications for perioperative artificial nutritional support remain valid but they should now apply only to a minority of patients.

Extensive research in the last 20 years has clearly shown that modifying the composition of standard nutritional feeds by adding supernormal doses of specific substrates that have immuno-modulatory, anti-inflammatory, anabolic, and tissue protective ability often translates into improved surgical outcome. The most convincing and reproducible results were obtained on the reduction of infectious complication by the perioperative use of enteral formulas enriched with arginine and omega-3 fatty acids.

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Key words: Surgery. Fast track. Artificial nutrition. Immunonutrition. Glutamine. Probiotics. Glucose metabolism. Outcome. Complications.

### Introduction

In the last years, profound changes in the perioperative management have been proposed and proven, in several randomized clinical trials, to be effective in

**Correspondence:** Luca Gianotti.  
Department of Surgery (4.º piano B).  
Ospedale San Gerardo.  
Via Pergolesi, 33.  
20052 Monza, Italy.  
E-mail: luca.gianotti@unimib.it

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### REVISANDO LOS CONCEPTOS EN NUTRICIÓN ARTIFICIAL EN LA CIRUGÍA CONTEMPORÁNEA

### Resumen

Recientemente, se han propuesto cambios notables en el manejo perioperatorio, denominado «cirugía de curso rápido». Esto es un conjunto de técnicas diversas empleadas en individuos sometidos a cirugías programadas que permiten una mejora del bienestar, una recuperación más rápida, una hospitalización más corta y mejores resultados. Desde un punto de vista nutricional, este nuevo abordaje se traduce en una recuperación más rápida de la función intestinal y, por lo tanto, tolerar de forma segura la realimentación en 1-3 días, incluso después de intervenciones mayores. Sin embargo, las indicaciones clásicas del soporte nutricional artificial perioperatorio siguen siendo válidas pero serían aplicables hoy en día a una minoría de pacientes.

La extensa investigación de los últimos 20 años ha demostrado claramente que la modificación de la alimentación nutricional estándar añadiendo dosis supranormales de sustratos específicos que poseen propiedades inmunomoduladoras, antiinflamatorias, anabólicas y protectoras de los tejidos a menudo se traduce en una mejora del resultado quirúrgico. Los resultados más convincentes y reproducibles se obtuvieron con la reducción de las complicaciones infecciosas mediante el uso perioperatorio de fórmulas enterales enriquecidas con arginina y ácidos grasos omega-3.

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Palabras clave: Cirugía. Curso rápido. Nutrición artificial. Immunonutrición. Glutamina. Probióticos. Metabolismo de la glucosa. Resultado. Complicaciones.

enhancing patient recovery and improving outcome after surgery.<sup>1-6</sup> Most of these new protocols were originally proposed and implemented by Kehlet and colleagues.<sup>7-9</sup> This innovative approach to patient care, namely “fast track surgery” is a bundle of various techniques used for subjects undergoing elective operations with the aim of controlling surgery-related stress response and organ dysfunction. The method includes several interventions. Among the most important are: use of epidural anaesthesia, minimally invasive surgical techniques, prevention of hypothermia and perioperative fasting, optimal pain control, intravenous fluid restriction, minimum use or early removal of drains,

naso-gastric tube, and catheters, early mobilization and ambulation.<sup>7-11</sup> From a nutritional point of view this approach allows a faster recovery of bowel function and thus the possibility to tolerate normal food by mouth within 1-2 days after colorectal surgery<sup>1-11</sup> and even 2-3 days after upper GI major operations.<sup>12-14</sup> Consequently, the classic indications for perioperative artificial nutritional support, that howbeit remain valid, should now apply only to a minority of patients. These are predominantly subjects who are at high risk of developing complications after surgery, such as patients who have suffered substantial preoperative weight loss, have very low body mass index (BMI) or exhibit an hyper-inflammatory state. Once patients have developed complications impairing the resumption of oral feeding or affecting the metabolic homeostasis, artificial nutritional support is generally required.

### **The classic artificial nutritional support: energy and nitrogen substrates**

Surgery, like any injury to the body, elicits a series of reactions including release of stress hormones and inflammatory mediators. This release of mediators to the circulation has a major impact on body metabolism. They cause catabolism of glycogen, fat and protein with release of glucose, free fatty acids and amino acids into the circulation, so that substrates are in part diverted from the purposes they serve in the non-stressed state (i.e. physical activity) to the task of raising an adequate organ function and healing response. For optimal organ function, rehabilitation and wound healing, the body needs to be nourished adequately to mobilise enough substrates, largely derived from muscle and adipose tissue, with nutritional support to allow synthesis of acute phase proteins, white cells, fibroblasts, collagen and other tissue components of the wounded area. Thus, in surgical patients the main goals of nutritional support are to reduce consumption of self energy stores and minimize negative protein balance, with the purpose of maintaining tissue and organ functions.

### *The preoperative nutritional support*

It is now well established and documented that severe undernutrition is an independent factor for the occurrence of postoperative complications, as well as increased mortality, length of hospital stay, and sanitary costs.<sup>15-20</sup> Moreover, undernutrition is often associated with other diseases such as cancer, chronic inflammation or organ dysfunction which further expose patients to increased surgical risk.

A period of preoperative nutritional support of at least 7-10 days before surgery is recommended<sup>21-23</sup> if a patient exhibits one or more of the following conditions: weight loss > 15% within 3-6 months, BMI < 18 kg/m<sup>2</sup>, albumin < 30 g/L (with no evidence of hepatic

or renal dysfunction), or grade C at the subject global assessment.<sup>24</sup>

### *The postoperative nutritional support*

Inadequate oral intake for more than two weeks after major operations is associated with a significant increase of morbidity and mortality.<sup>25</sup> Even shorter periods of starvation or insufficient caloric and protein intake are strongly correlated with worse surgical outcome.<sup>26</sup>

Therefore, several guidelines<sup>21-23</sup> recommend to administer artificial nutrition immediately after surgery when patients are expected not to meet their caloric requirement within 7-10 days in the postoperative course independently from their preoperative nutritional status. Artificial nutrition is also recommended as soon as possible when a patient has developed complications impairing the resumption of oral feeding or affecting the metabolic homeostasis such as sepsis.

Striking scientific evidences offered by fast track surgery implementation have shown that oral re-feeding very shortly after major surgery is safe and feasible in most of the patients undergoing colorectal, gynaecologic, urologic and pelvic operations<sup>1-11</sup> as well in upper gastrointestinal procedures such as laryngectomy with primary pharyngeal closure, gastric, pancreatic, and hepato-biliary resection.<sup>12-14</sup> Thus, the number of patients routinely requiring postoperative nutritional support is progressively declining.

Oral intake can be carried out with normal food or liquid oral nutritional supplements (ONS) according to individual tolerance and gastrointestinal function.<sup>26-31</sup> ONS may have the advantages of having more calories and proteins than normal food for matching volume.

Nevertheless, there are clinical situations where early postoperative oral intake can be still contraindicated or difficult to achieve such as major trauma, unconsciousness states, swelling impairment, partial intestinal obstruction or prolonged ileus, or delayed gastric emptying. In these patients surgeons should consider the placement of a feeding jejunostomy or naso-jejunal tube at the time of surgery or in the postoperative course.

### *The route of feeding*

When AN is indicated, the enteral route should be preferred to the parenteral one. This recommendation is now undersigned by all international guidelines<sup>21-23</sup> because enteral feeding is considered more physiological, cheaper, and associated with better outcome particularly in undernourished, critically ill and trauma patients.<sup>32-38</sup> The use of total parenteral nutrition (TPN) should be restricted to the following circumstances: in undernourished patients in whom enteral nutrition is

not feasible or not tolerated; in patients with postoperative complications impairing gastrointestinal function who are unable to receive and absorb adequate amounts of enteral feeding for at least 7-10 days; in patients with suspected intestinal ischemia or hypoperfusion; in patients with high output (> 600 mL) intestinal fistulae.

The combination of enteral and parenteral nutrition should be considered in patients in whom at least 60% of energy needs cannot be met via the enteral route.

In completely obstructing lesions, surgery should not be postponed because of the risk of aspiration or severe bowel distension leading to bacterial translocation and peritonitis.

In patients with shock of any cause, AN (both enteral and parenteral) is not indicated until complete correction of the vital functions has been obtained.

### *Energy and nitrogen requirement*

In acute and chronic disease the resting metabolic rate is elevated above the values calculated by the Harris-Benedict equations. The degree of hypermetabolism is on average not more than 110-120% of predicted.<sup>39-42</sup> Only during selected situations such as major burn injury, severe sepsis, and major trauma this value may be increased substantially to 160-180%.<sup>41,43-45</sup>

Therefore, 25 kcal/kg of ideal body weight furnish an approximate estimate of daily energy expenditure and requirements, and under conditions of severe stress requirements may approach 30 kcal/kg of ideal body weight.

The main consideration when giving energy, particularly during parenteral nutrition is to avoid overfeeding.<sup>42,46,47</sup> This is mostly true in severely undernourished subjects. To avoid this problem, calorie and nitrogen requirement should be calculated with indirect calorimetry or based on usual body weight. Moreover, in such cachectic patients care should be taken to increase the amount of calories and protein slowly to prevent the refeeding syndrome. Hyperalimantation is known to increase energy expenditure, oxygen consumption and carbon dioxide production<sup>48,49</sup> and especially in patients with low cardiac and respiratory reserve these effects may be deleterious.<sup>50</sup> In addition, hyperalimantation may induce fatty liver and lead to hypertriglyceridemia with harmful effects on immune function. Thus, at present, it is recommended to maintain the glucose:fat calorie ratio at 60:40 or even 70:30 of the non-protein calories. When fluid restriction is indicated a 50:50 ratio is accepted.

It is well established that muscle protein degradation during stress conditions is regulated by pro-inflammatory modulators like tumour necrosis factor-alpha, interleukin 1, 6 and others, and therefore cannot be or only partially reversed by nutrition.<sup>51-54</sup> The value of nutritional support comes instead from its support of

protein synthesis in the muscle limiting net whole body protein loss, in the liver yielding acute phase proteins, and in the immune system yielding white cells crucial in the response to trauma or disease. As for energy need, protein/nitrogen requirement should be calculated on the basis of ideal body weight. Proteins and amino acids given enterally and parenterally are used by the host in part for anabolic pathways and to some extent to produce energy. Therefore, the caloric rate of nitrogen should be included in the calculation of the total calorie required.

In illness/stressed conditions a daily nitrogen delivery equivalent to a protein intake of 1.5 g/kg ideal body weight (or approximately 20% of total energy requirements) is generally effective to limit nitrogen losses.

### **The metabolic and immune support: the new targets of nutritional therapy**

Although the above concepts and indications of classic AN remain valid, extensive clinical research in the last 20 years has clearly shown that perioperative administration of supernormal doses of specific nutritional substrates may have immuno-modulatory, anti-inflammatory, anabolic, and tissue protective ability and this often translate into improved surgical outcome when compared with standard nutritional formulas or traditional treatment protocols. For this reason this new area of nutritional therapy has been generically named immunonutrition or pharmaconutrition.

### *The use of preoperative carbohydrate load and glucose metabolism*

Recent strong evidences show that fasting patient overnight before elective surgery is useless. In fact, free intake of clear fluids until 2 hours before anaesthesia is safe and beneficial in most of the subjects<sup>55-57</sup> and does not increase the risk of aspiration except for those patients with impaired gastric outlet or proven gastroesophageal reflux. Allowing patients to drink relieves the feeling of thirst that many patients experience before surgery. Even more important are the metabolic effects of undergoing surgery in a non-fasted state.<sup>58</sup>

A fed state may be induced prior to elective surgery by providing a carbohydrate load. The induced changes in metabolism upon entering surgery has been shown to have several effects on the response to the operation. In particular, studies have reported positive effects in the postoperative recovery period such as improved protein balance,<sup>59</sup> improved preservation of lean body mass<sup>60</sup> and muscle strength<sup>61</sup> and reduced length of hospital stay after operation.<sup>62,63</sup> Moreover, for those patients without contraindication to free intake of fluids, carbohydrate drinks has been also shown to minimise insulin resistance, postoperative hyperglycaemia, heighten insulin sensitivity, reduce stress

response, anxiety and postoperative nausea and vomiting in general and orthopaedic surgery, and to be cardioprotective in cardiac surgery.<sup>64-66</sup> A recent large randomized trial by Mathur et al., did not confirm a beneficial role of preoperative carbohydrate loading on fatigue and discomfort, glucose metabolism, insulin resistance, muscle strength, protein synthesis and postoperative morbidity and length of hospitalization in abdominal surgery.<sup>67</sup>

The overwhelming majority of the data available in this field is based on studies in non-diabetic patients.

When given orally, the drink is a mixture of complex carbohydrates, i.e. maltodextrins, in a concentration of about 12% in a volume of 400-800 mL and dispensed between the evening before operation and 2 hrs before anaesthesia induction.<sup>68,69</sup>

For those who cannot eat or are not allowed to drink preoperatively for whatever reason, a glucose infusion at a rate of 5 mg/kg/min will have very similar effects on postoperative insulin resistance. When given intravenously, carbohydrate loading is achieved using a glucose solution with a higher concentration, usually 20%, to administer a sufficient quantity in a low volume to ensure a sufficient insulin response.<sup>70</sup> Studies where i.v. glucose loading or oral carbohydrate intake alone or in combination with other nutrients or insulin have been reviewed in more detail in recent years.<sup>58,62,71-78</sup>

In patients with normal glucose tolerance, preoperative glucose administration will also ensure glycemic control when greater quantities of glucose are infused (i.e. earlier postoperative AN) without the development of hyperglycaemia.<sup>79</sup>

Since hyperglycaemia is one of the most important independent factor for the development of postoperative complications (in particular infectious one),<sup>80-82</sup> it will be challenging to see, in future large randomized trial, if preoperative carbohydrate loading and subsequent better control of glucose metabolism will be associated with a significant decrease of septic morbidity after major elective surgery.

#### *The use of nutritional substrates with immune modulating activity*

Extensive laboratory and clinical research in the last 30 years has shown that there are nutritional substrates affecting the host response to injury. Among the most studied are: glutamine, arginine, and omega-3 fatty acids. Their mechanisms of action have been reviewed by several Authors.<sup>83-85</sup>

Formulas containing multiple substrates may have conceptual limitations. In fact, it is impossible to fully understand the potential mechanism of protection of these multiple component diets and to attribute a specific biologic effect to each single substrate. Moreover, it may be that a fix formulation is not the optimal one in all type of patients and in the various phases of the post-operative or post-injury course. Nevertheless,

pragmatically speaking it was important to test if the clinical use of these diets could offer some true outcome advantages over standard formulas.

The use of formulas enriched with different mixtures of such nutrients in the clinical arena is still under investigation, but there are now sufficient data to strongly suggest the routine use in some cohort of surgical patients.<sup>21,22,86-88</sup>

Several Authors have consistently highlighted that some these new diets may improve host defense mechanisms and effectively modulate the inflammatory response.<sup>89-92</sup> In particular, patients receiving supplemented formulas had a significant higher lymphocyte T and B count and improved function, increased levels of immunoglobulins, CD4+ cells, IL-2 and its receptors, phagocytosis ability of macrophages, delayed-type hypersensitivity response to skin tests. Decreased plasma levels of proinflammatory cytokines (IL-6, TNF-alpha) and eicosanoids, and nitrogen loss have been reported.

The first clinical experiences with immunonutrition were focused, for technical reasons, on postoperative infusion. A series of trials showed that this approach was moderately effective in reducing complications. Daly and colleagues, in two subsequent studies,<sup>90,93</sup> were the first to report that the postoperative administration of an immune-enhancing formula, containing arginine, omega-3 fatty acids and RNA, significantly reduced the infection rate of more than 50% compared to standard enteral diets. However, in one of those studies,<sup>90</sup> the control diet was not isonitrogenous compared to the experimental formula. In three large subsequent trials<sup>94-96</sup> these advantages on morbidity by postoperative immunonutrition were not fully confirmed. In particular, an Italian trial<sup>94</sup> showed 15% infectious complications in the group receiving immunonutrition and 23% in the group receiving the standard diet (p NS). Instead, the severity of the septic episodes (as measured by sepsis score) was significantly lower in the immunonutrition group than in the control group. Length of postoperative stay (LOS) was 16 days versus 19 days respectively (p = 0.01). More pronounced effects of postoperative immunonutrition were found in subgroups of high risk surgical patients such as malnourished or receiving homologous blood transfusion.<sup>97</sup> These results were confirmed in head and neck cancer patients.<sup>98</sup>

A multicenter German trial<sup>95</sup> reported similar results, in a similar population, with an overall complication rate of 22% in the patients treated with postoperative enteral immunonutrition versus 31% in the control group (p NS). However, the Authors found, in the treated group, a significant reduction of infections occurring after postoperative 5. The mean LOS was shorter in the immunonutrition group than in the controls (27 versus 30.6 days).

An American trial by Heslin et al.<sup>96</sup> did not find any difference in postoperative complications by comparing groups of GI cancer patients postoperatively

treated with either immune-enhancing diet or simple crystalloid and fluid replacement. The treated patients had 44% complication rate *versus* 33% in the control group. Also the median LOS was similar in the two groups (11 *versus* 10 days respectively). It was noteworthy that in the treated group the average intake of immune-nutrients was very limited, approximately 30% of the nutritional goal.

More recent publications confirmed previous results showing that the benefits of postoperative administration of immune-enhancing diets compared to standard enteral feeds were sparse.<sup>99,100</sup> Noteworthy, in a randomized study by Farreras et al.,<sup>101</sup> patients with gastric cancer receiving postoperative enteral immunonutrition, exhibited an higher wound deposition of hydroxyproline (59.7 nmol *vs.* 28.0 nmol  $P = 0.0018$ ) and a significant lower rate of surgical wound healing complications (0% *vs.* 26.7%;  $P = 0.005$ ) when compared to patients fed with the control formula. These findings might also account for the lower rate of anastomotic leak found in patients treated with immunonutrition.<sup>88</sup>

All the above trials underlined somehow the intrinsic limitation of the postoperative approach to the issue of enteral immunonutrition. If it is believed that these nutrients have pharmacological effects, it should be also clear that to obtain positive results, adequate plasma and tissue levels need to be accomplished at the time of operation and in the early postoperative course. Enteral nutrition requires a progressive increase of the infusion rate during the first 3-4 days after injury to be tolerated and reach the full strength. Thus, however enteral feeding is begun early postoperatively, the amount of immune-enhancing substrates given in the first days might be insufficient to elicit a prompt modulation of the host response. Yet, the first days after surgery represent the critical "window" for the development of infectious complications because during this period the injury-induced immunosuppression is maximal.

Conceptually a more rational approach is to anticipate the administration of immuno-enhancing diets before an operation to obtain efficacious concentrations of immunonutrients both at the time of surgical injury and in the early postoperative phase. This approach was technically possible when oral formulation of these feeds became available on the market.

In phase II RCTs<sup>102-104</sup> patients receiving immunonutrition before and after surgery (perioperative approach) exhibited a more controlled postoperative depression of both polymorphonuclear cells and lymphocyte function, an attenuation of the post-operative exuberant inflammatory response and an improved intraoperative gut microperfusion and intramucosal jejunal pH. In patients perioperatively fed with a supplemented or a standard diet, our group also evaluated the *in vivo* intestinal tissue oxygen pressure that was measured during the entire surgical procedure and afterward. The results showed that immunonutrition was capable of markedly improving the splanchnic oxygen supply during surgery and throughout the 7 post-operative days.

These findings were probably due to adequate plasma and tissue concentrations of the immunonutrients already being available at the time of surgical stress and thus stimulated further trials to evaluate the possible benefit of perioperative immunonutrition on outcome.

A study by McCarter et al.<sup>105</sup> evaluated the effect of a seven-day preoperative oral supplementation with diets enriched either in arginine, arginine plus omega-3 PUFAs or placebo in patients scheduled to undergo surgery for GI cancer. They did not find any difference for T cell function, eicosanoid production, proinflammatory cytokine levels and postoperative infection rate among groups. The Authors themselves suggested that the small sample size (approximately 12 patients per group), the lack of demonstrability of correct oral intake and absorption of substrates, did not allow any firm conclusion. Different results were obtained in two large randomized controlled double-blind phase 3 trials, carried out in patients with gastrointestinal malignancy. The first study<sup>106</sup> enrolled 206 patients who were randomized to drink 1 liter/day of either a control diets or the same formula enriched with arginine, omega-3 fatty acids and RNA for 7 days before operation. Jejunal infusion with the same diets was started 6 hours after surgery and continued until postoperative day 7. Intent-to-treat analysis showed a 14% infectious complication rate in the supplemented group versus 30% in the control group ( $p = 0.009$ ). LOS was 11 versus 13 days respectively. The second trial<sup>107</sup> was performed in 154 patients who were treated with a very similar perioperative nutritional protocol as above. Also in this study, significantly fewer infectious complications occurred in the immunonutrition group compared to the control group (14 *versus* 27;  $p = 0.05$ ).

Some trials also addressed the cost-effectiveness analysis of immunonutrition because the high cost on these new enriched formulas represents a major concern and it may be considered a major drawback for their wide and routine use. In our study<sup>108</sup> the cost of perioperative immunonutrition was substantially higher than standard enteral diet (347 euros and 104 respectively). However, this additional cost of immuno-enhancing diet was largely overcompensated by the substantial reduction (about 2,400 euros per complication-free patient) of health care resources consumed to treat postoperative infections. Moreover, the total costs to manage postoperative complications represents a 7.5% consumption of the Disease-related-group reimbursement rate in the immunonutrition group versus 23.1% in the control group. These economic findings were consistent with the data reported in other studies.<sup>107,109</sup> Yet none of the mentioned trials<sup>106,107</sup> was designed to randomize separately malnourished and well-nourished patients. Thus, we run a subsequent post-hoc analysis showing that immunonutrition was effective in reducing post-operative complications regardless the baseline nutritional status. Moreover, we observed in an additional post-hoc analysis that the patients receiving only pre-operative

immunonutrition, because non-compliance to post-operative enteral infusion had a significant reduction of morbidity, suggesting that the simple pre-operative approach might be sufficient to improve outcome when compared to standard diet. To better understand the impact of perioperative immunonutrition on outcome, in both malnourished patients (weight loss > 10%) and well-nourished (weight loss < 10%) patients, we designed two new prospective studies. In the first trial<sup>110</sup> well-nourished patients (n = 305) were randomized to receive: no peri-operative nutritional support (group A), only pre-operative oral immunonutrition (group B), or peri-operative enteral immunonutrition (group C). The overall postoperative morbidity was 31% in group A, 14% in group B, and 16% in group C (p = 0.03), and LOS was 14.0 days, 11.6, and 11.2 respectively (p = 0.01). The protective effect of preoperative immunonutrition was shown also in a subgroup of obese patients which should be considered at high surgical risk despite they do not experience weight loss. This is probably due to the ability of immunonutrients to control the metabolic syndrome and the hyperinflammatory state that characterize obese subjects.

In the second trial,<sup>111</sup> malnourished patients (n = 150) were randomized to receive three different nutritional regimens: only post-operative standard enteral nutrition (group A), pre-operative oral immunonutrition plus post-operative standard enteral nutrition (group B), or peri-operative enteral immunonutrition (group C). The results showed that the rate of complication was 42% in group A, 28% in group B, and 18% in group C (p = 0.02) and LOS was 15.3 days, 13.2, and 12.0 respectively (p = 0.01). These data suggest that the simple preoperative oral supplementation with immunonutrition is the optimal approach in well-nourished patients, while the perioperative treatment should be preferred in malnourished subjects.

A further cost-effectiveness analysis confirmed that preoperative immunonutrition in well-nourished patients

allowed a substantial and significant saving of health care resources when compared to standard treatment.<sup>112</sup>

In 2006 Waitzberg et al. performed a systematic review of published and unpublished clinical trials concerning the issue of immunonutrition.<sup>88</sup> The results are summarized in table I.

The advantages of pre- or perioperative immune-enhancing diets on surgical outcomes have been subsequently confirmed in several subsequent trials<sup>113-119</sup> but not in others.<sup>120</sup>

Also supernormal doses of glutamine, as a single key nutrient, has been studied extensively.

Exogenous glutamine supplementation might be important in critical, catabolic and stress conditions because there is a flux of endogenous glutamine from muscles to other tissues/organs with rapid cell turnover and metabolism, such as gut, bone marrow, brain, immune cells, and fibroblasts which use glutamine as their principal metabolic fuel.<sup>121</sup> Patients receiving glutamine supplementation maintain glutamine tissue and plasma pool with improved immune response, increased protein synthesis, less negative nitrogen balance, preserved gut barrier structure and function, improved wound healing, reduced oxidative stress, and better glucose metabolism.<sup>121-125</sup> Clinical benefits of intravenous glutamine supplementation have been reported in elective surgery, however this regimen has been tested in few underpowered trials. From these studies, Novak et al.,<sup>126</sup> generated a meta-analysis with total of 220 elective surgical patients. They could demonstrate that the administration of glutamine dipeptide was associated with a significant reduction of complication rate (RR: 0.36, 95% CI: 0.14-0.92) and length of hospital stay (-3.54 days). A more recent meta-analysis by Zheng et al.,<sup>127</sup> included 5 trials with a total of 215 patients. The combined analysis indicated that the use of glutamine dipeptide significantly reduced postoperative infective events (OR: 0.24, 95% CI: 0.06-0.93, p = 0.04) and duration of hospitalization (-3.55 days). A third meta-analysis

**Table I**  
Cumulative analysis of 14 studies comparing enteral immuno-nutrition (IMPACT®) with standard feeds.  
Modified from Waitzberg DL et al.<sup>88</sup>

	Pre-op		Peri-op		Post-op	
	Relative risk (95% CI)	P value	Relative risk (95% CI)	P value	Relative risk (95% CI)	P value
Abdominal abscess	0.44 (0.16-1.19)	0.11	0.43 (0.21-0.91)	0.03	0.48 (0.24-0.89)	0.04
Wound infection	0.56 (0.29-1.07)	0.08	0.61 (0.38-0.96)	0.03	0.81 (0.42-1.54)	0.52
Pneumonia	0.38 (0.18-0.83)	0.01	0.54 (0.34-0.87)	0.01	0.73 (0.41-1.30)	0.29
UTI	0.64 (0.28-1.47)	0.29	0.53 (0.23-1.19)	0.12	0.38 (0.12-1.06)	0.06
Sepsis	0.29 (0.05-1.71)	0.17	0.53 (0.22-1.27)	0.15	0.73 (0.27-1.94)	0.52
Overall infectious complications	0.42 (0.30-0.59)	<0.001	0.49 (0.39-0.62)	<0.001	0.56 (0.39-0.82)	0.003
Anastomotic dehiscence	0.51 (0.24-1.05)	0.07	0.52 (0.28-0.95)	0.03	0.69 (0.32-1.46)	0.32
Length of hospitalization	-3.4 days (-5.6/-1.2)	0.001	-2.4 days (-3.1/-1.7)	<0.001	-3.5 days (-5.1/-1.9)	0.006

UTI: urinary tract infection.

sis<sup>128</sup> evaluating studies performed in Asia and Europe reached similar conclusions.

More recently, glutamine supplementation was tested by Jo et al.,<sup>129</sup> after pancreatoduodenectomy in 60 patients and showed no clinical advantages in terms of postoperative morbidity. All patients had cancer, the vast majority of them were well-nourished, and the dose of free glutamine was 0.20 g/kg/day. Oguz and colleagues<sup>130</sup> used an association of high dose perioperative glutamine dipeptide (1g/kg/day) and enteral feeding in 109 patients undergoing elective colorectal surgery for cancer. Also in this report most of the patients had a normal nutritional status or mild malnutrition. They could show a significant reduction of wound infection and dehiscence and abdominal abscess formation with an associated reduction of hospitalization in the group receiving glutamine.

A large, Italian multicentre trial including 428 well-nourished patients candidate to elective major gastrointestinal surgery for cancer, did not confirm any clinical benefit of glutamine supplementation. Patients were randomized to receive either intravenous infusion of L-alanine-L-glutamine dipeptide (0.40 g/kg/day; equal to 0.25 g of free glutamine) (Ala-Glu group, n = 212), or no supplementation (control group, n = 216). Glutamine infusion begun the day before operation and continued postoperatively for at least five days. Overall postoperative complication rate was 34.9% in Ala-Glu and 32.9% in control group (p = 0.65). Infectious morbidity was 19.3% in Ala-Glu group and 17.1% in controls (p = 0.55). The rate of major complications was 7.5% in treated patients and 7.9% (17/216) in controls (p = 0.90). Mean length of hospital stay was 10.2 days vs. 9.9 days in treated and control subjects respectively (p = 0.90).<sup>131</sup>

The indication to glutamine supplementation in patients with severe weight loss and high risk of surgical morbidity still remains an open issue. They might represent cohorts with more elevated glutamine demand, increased glutamine metabolism, and/or baseline deficits.<sup>132</sup> This subgroups of surgical patients may be more similar to critically ill and trauma patients in whom glutamine supplementation has been proven to decrease morbidity and mortality.<sup>133-135</sup>

The use of lipids in AN, particularly long-chain triglycerides (LCT), is not without metabolic effects. In fact, LCT may affect the physiologic response of the arterial vascular bed. Moreover, the consequences of n-6 poly-unsaturated fatty acids (PUFAs) administration on immune and inflammatory response remain controversial. A recent meta-analysis<sup>136</sup> did not support an immunosuppressive effect of n-6 PUFAs while other systematic review showed that they have a pro-inflammatory effect and trials tend to show lower complication rates in patients receiving PN containing fewer of these fatty acids.<sup>137,138</sup>

In view of these considerations attempts have been made to reduce the long-chain PUFA content without a

net loss of lipid calories. This has been obtained by replacing part of the lipid by medium-chain triglycerides (MCT), by administering synthetic lipids which consist of a glycerol backbone randomly esterified with MCT or LCT, or by a substantial replacement with n-9 LCT (olive oil). All such emulsions contain lower amounts of n-6 fatty acids and appear to have fewer immunological effects.<sup>138</sup>

Most of research has been focused on n-3 PUFAs which have a proven anti-inflammatory effect. In a blinded randomized trial by Kenler et al.<sup>139</sup> studied 50 patients who were jejunally fed either an enteral diet containing a fish oil/medium-chain triglyceride structured lipid or a isocaloric diet for 7 days postoperatively. A 50% decline in the total number of gastrointestinal complications and infections as well as an improved liver and renal function was observed in the treated group.

When associated with gamma linolenic acid and given enterally in ICU, n-3 PUFAs have been shown in prospective randomized trials to improve pulmonary inflammation, to shorten days on the ventilator and overall ICU stay.<sup>140-142</sup> In open label cohort studies, increasing dosage of n-3 PUFAs has been associated with reduced ICU stay following major abdominal surgery,<sup>143</sup> and in a randomised trial inclusion of n-3 PUFAs in PN was associated with reduced overall hospital stay.<sup>144</sup>

Thus, at present there is some evidence that increasing the percent of lipids in favour of n-3 fatty acids particularly during TPN may benefit organ function and reduce length of stay in patients undergoing major surgery or admitted to the surgical ICU.<sup>145</sup> However, these trends will need to be substantiated in adequately powered randomised trials.

#### *The use of prebiotics, probiotics and synbiotics*

Prebiotics, probiotics, and synbiotics may all be beneficial for the host by improving the characteristics of indigenous microflora. The composition and the equilibrium of microbiota are known to influence important host activities among them the local immune response and several intestinal metabolic traits.<sup>146-151</sup>

Despite, the effects of their administration has been intensively investigated *in vitro*, in animal models, in healthy volunteers, and in some human gastrointestinal diseases (i.e. inflammatory bowel diseases, alimentary allergy, infectious diarrhea, pouchitis, etc.)<sup>147-151</sup> little is known on the possible cross-interactions among treatment, changes of intestinal flora and local immune response in surgical patients. Prebiotics, probiotics and synbiotics enriched enteral formulas were used in patients candidate to gastrointestinal operations with the aim of affecting microbiota that contains bacteria responsible for postoperative infections. The results of randomized clinical trials are conflicting with significant reduction of infection rate in upper gastrointesti-

nal surgery<sup>152-154</sup> and lack of clinical benefits in other type of operations and clinical settings.<sup>155-157</sup> One trial by Reddy et al.,<sup>158</sup> was selective for colorectal patients. They reported a synergistic positive effect of synbiotics, neomycin and bowel preparation on the prevalence of enterobacteriaceae colonization and bacterial translocation but these events were not associated with a significant reduction of septic morbidity. These studies have been reviewed by Van Santvoort and colleagues.<sup>159</sup> Part of the inconsistency in surgical outcome may be the substantial difference in study design, dose and strain, duration, period and combination of treatments.

We recently evaluated whether probiotics given perioperatively in patients undergoing colorectal resection for cancer may adhere to the colonic mucosa, reduce concentration of pathogens in stools and modulate intestinal immunity.<sup>160</sup> Thirty-one subjects were randomly and blindly assigned to receive two doses/day either of placebo (group A; n = 10), or a mixture of *Bifidobacterium longum* (BB536) and *Lactobacillus johnsonii* (La1) (concentration 10<sup>7</sup> CFU/dose; group B; n = 11), or the same mixture at a concentration of 10<sup>9</sup> CFU/dose (group C, n = 10) for three days before and three days after operation. During operation colonic mucosa and stool samples were harvested to evaluate the presence of BB536 and La1 by random amplified polymorphism DNA method.

The results showed that BB536 was never found at any of time-point studied. At surgery, La1 was recovered in 6 of 10 patients in either stools or biopsy in group C, in 3 of 11 in group B, and none in group A (p = 0.02 C vs. A). There was a linear correlation between dose given and number of adherent *La1* (P = 0.01). The rate of mucosal colonization by enterobacteriaceae was 30% in C, 82% in B and 70% in A group (p = 0.03 C vs. B). Enterobacteriaceae count in stools was 2.4 ± 0.3 (log<sub>10</sub> scale) in C, 4.2 ± 0.4 in B, and 4.5 ± 0.2 in A. Same trend was observed for colonizing enterococci. We observed greater expression of CD3, CD4, CD8, naive and memory lymphocyte subsets in group C than A with a dose response trend (C > B > A). Treatment did not affect dendritic cell phenotype or activation, but after *ex vivo* stimulation with lipopolysaccharides, groups C and B had a lower proliferation rate compared to group A (P = 0.04). Moreover, dendritic phenotypes CD83-123, CD83-HLADR, and CD83-11c (markers of activation) were significantly less expressed in patients colonized with *La1* (p = 0.03 vs. not colonized).

At present there are stimulating but insufficient results to show consistent and reproducible benefits of prebiotics, probiotics and synbiotic administration in surgical patients. Further trials are warrant to understand if better results may be obtained by different single or mixture of probiotic strains, increased dose, prebiotics alone or synbiotic preparation, longer treatment period or different timing of administration. The future results should be taken in consideration before designing phase III trials.

## Summary

Patients undergoing major abdominal operation may be safely and effectively managed with new protocols that avoid preoperative fasting and allow early return to oral feeding, enhance recovery and well-being, reduce hospitalization and improve outcome after surgery. These new strategies have substantially reduced the need of perioperative artificial nutritional support.

Evidences that nutritional formulas enriched with specific substrates may improve surgical outcome when compared to standard feeds, has profoundly changed the classic thought of simple perioperative energy and nitrogen support. The augmentation of the host immune response, the reduction of oxidative stress, the control of glucose metabolism, the protection of organ/tissue function, and the modulation of inflammatory response in the perioperative period should represent the new targets of nutritional therapy .

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