Immunonutrition: current status

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Abstract

Nutritional support is now recognized as an essential component of care in all critically ill patients. Malnourished patients suffer from generalized reduction in both cellular and humoral immunity. Certain nutrients and their deficiencies may have specific effects upon the immune systems. Malnutrition and stress depresses immune system, adequate nutrition reverses this effect. Prevention of infection is a primary end-point of all nutritional support. Early enteral nutrition has gained increasing popularity due to host's immune response, maintenance of gut integrity and of course its lower costs. Animal studies have shown that fasting, injury and infection can lead to gut atrophy and increased mucosal permeability [1]. Bacterial translocation is linked to the development of post-operative sepsis and multiple organ failure [2,3].

The basic aims of immunonutrition are to modulate the immune response with naturally occurring nutrients so as to curb tissue injury, reduce infection rates and morbidity, and so eventually improve survival. Numerous clinical trials and three meta-analyses suggest that immunonutrition can be beneficial in specific groups of patients.

Keywords: glutamine; arginine; enteral nutrition; pre- and post-surgery feeding; critical care; pneumonia; burns; head injury; trauma; review; meta-analysis; randomized trials

Individual Immunonutrients

Glutamine

Glutamine is 'conditionally' essential amino acid in severe illness, synthesized in skeletal muscle. Primary fuel source for enterocytes and is required for lymphocyte and macrophage function. Major inter-organ nitrogen and carbon transporter. Glutamine is a precursor for nucleotide synthesis, glutathione a product of glutamine metabolism has an important role as an antioxidant [4].

Arginine

Arginine is a semi- essential amino acid becoming essential in catabolic states.

Arginine stimulates several hormones namely growth hormone, prolactin, insulin like growth factors, glucagons, somatostatin and norepinephrine [5]. Arginine is a precursor for nitric oxide, which is an ubiquitous molecule having important roles in immune system, motility of gastrointestinal tract, secretory functions, maintenance of vascular tone and an important role in coagulation. Nitric oxide is implicated as a factor in sepsis, hypertension and cirrhosis [6]. Arginine promotes wound healing. Role in Immune function consists of increased thymic size and cellularity, enhanced lymphocyte proliferation, augmented macrophage and natural killer cell lysis of tumor targets, increased lymphocyte interleukin (IL-2) production and receptor activity [7].

Nucleotides

Nucleotides are crucial for synthesis of RNA and DNA. They are important components of the energy transfer system and are essential for rapidly proliferating cell groups. Deficiency is associated with decreased immunity and supplementation improves T cell function[8].

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Omega-3 fatty acids

Polyunsaturated fatty acids mainly found in fish oil. Substitution of w-3 fatty acids for w-6 fatty acids shifts the balance of leukotriene and prostaglandin production. In general the inflammatory effects of the w-3 fatty acid mediators are less marked and less immunosuppressive than those derived from arachidonic acid [9].

Taurine

Biologic functions of taurine remain largely unknown. Taurine concentrations are remarkably high in human neutrophils and hence may play a key role in modulation. It may also \prevent oxidant induced lymphocyte damage and facilitate cellular protection by membrane stabilization [10].

Probiotic Bacteria

Lactobacillus plantarum tolerate a lower pH compared to any other microorganism. They preserve and increase w-3 fatty acids in food and also inhibit pathogens. These probiotic bacteria produce nitric oxide from arginine and tyrosine. Promotes mucosal proliferation by producing SCFA from fiber, production of vitamins and stimulates gut and systemic immune system [11].

Glycine

This molecule is unbranched, non-essential amino acid, and a condensed source of nitrogen. They are inhibitory neurotransmitter in the spinal cord and brain stem.

Cytoprotective effects have been demonstrated in animal models. It has been shown to protect organs against ischemic, hypoxic and reperfusion insults. Conditionally essential in stress and is therapeutic in high doses [12].

Over twenty-five prospective randomized controlled trials and three meta-analyses about immunonutrition have been published during the past decade. While a good number of these studies show a positive benefit on patient outcome from use of immune-enhancing enteral formulas in a variety of disease states, certain discrepancy exist in the literature, which raise doubts in physician's mind. The effect of immunonutrition varies among patient populations with different disease processes. Evidence suggests a dose-dependent effect, requiring suitable timing with early commencement of feeds, an adequate volume, as well as a sufficient duration of feeds to achieve the therapeutic endpoints.

Numerous clinical studies have established that the administration of glutamine results in superior protein metabolism in muscle [13]. Studies have demonstrated that parenteral glutamine prevents gut atrophy, this has led to the idea that glutamine plays a key role in preserving the gut barrier and restricting the translocation of microorganisms and endotoxins from the lumen of the gut into the circulation [14]. An earlier study by Ziegler showed the benefits of TPN supplemented with glutamine in adult bone marrow transplant patients. In a double-blind prospective randomized trial evidence of clinical infection was significantly less in the glutamine-supplemented TPN group compared to control group receiving TPN without glutamine (12.5% vs. 42.8%, p=0.04). Likewise, hospital stay was reduced in the group receiving glutamine-supplemented TPN (26 vs. 29 days compared to controls, p=0.017) [15]. Houdijk compared enteral tube-feeding supplemented with glutamine to controls receiving standard formula alone in adult patients with severe trauma (Injury of Severity Score > 20).

In a prospective randomized trial, the study showed that pneumonia was significantly less in the glutamine-supplemented group (17% vs. 45% respectively, compared to controls, $p<0.02$). Bacteremia was reduced in the study group (7% vs. 42%, $p<0.05$), as was overall sepsis (3% vs. 26%, compared to controls, $p<0.02$) [16]. In critically ill patients who were unable to be fed enterally were given TPN or TPN+25gms Glutamine, six months survival in glutamine (57% vs 33% p=0.049) there was also a 50% reduction in total ICU & hospital costs [17].

In a meta-analysis published by Novak et al, 14 randomized trials comparing the use of glutamine supplementation in surgical and critically ill patients was analyzed. The results showed, with regards to mortality, glutamine supplementation was associated with a risk ratio (RR) of 0.78 (95% confidence interval [CI], 0.58 – 1.04). Glutamine supplementation was also associated with a lower rate of infectious complications (RR, 0.81; 95% CI, 0.64– 1.00) and a shorter hospital stay (-2.6 days; 95% CI, -4.5 to -0.7). Suggesting that in critically ill patients, glutamine supplementation may be associated with a reduction in complication and mortality rates, the greatest benefit was observed in patients receiving high-dose, parenteral glutamine [18]. Though many relevant sources were searched, it was not clear whether any language limitations had been applied. The duration of the intervention was not reported, and the influence of censoring from death on length of hospital stay was not mentioned... As the authors correctly state, the conclusions are not definitive in view of the heterogeneity among the studies.

In burns patients, glutamine supplementation improved measures of nutrition and decreased measures of

overall inflammation. Additionally, a trend toward lower mortality rate, decreased incidence of bacteremia, and the usage of antibiotics in the glutamine group was observed [19]. A more recent study from Beijing demonstrated that providing enteral glutamine to burns patients can normalize plasma glutamine concentration. The gut function was improved in terms of intestinal permeability and the length of stay in the hospital was shortened [20]. Both these studies had good survival as the patient population were comparatively young, hence effect on mortality could not be demonstrated since it would have needed large number of patients to be enrolled.

Recently in Western Australia influence of enteral glutamine on mortality and the incidence of severe sepsis was studied. This two arm single centre clinical trial was triple blinded (i.e. patient attending staff, research nurse). 363 patients requiring mechanical ventilation (median APACHE II score=14); of these, 85 had trauma. The intervention group received 20 g/l glutamine; the control solution was isojoulic and isonitrogenous. The outcomes were similar in the two groups, death within 6 months in the glutamine group was 15% (27 of 179) vs. control group 16% (30 of 184); *p*=0.75; relative risk, 0.95 (95% confidence interval, 0.71–1.28); and (b) severe sepsis: glutamine group 21% (38 of 179) vs. control group 23% (43 of 184); *p*=0.62; relative risk, 0.94 (95% confidence interval, 0.72–1.22) [21]. There was also no obvious difference in the secondary outcomes relating to infections, febrile period, antimicrobial therapy, and using up of inotropes. This clinical trial did not encourage the use of enteral glutamine supplements in similar cohorts of critically ill patients.

Immune-Modulating Diets in Surgical Patients

Post-operative feeding

Post-operative enteral feeding with immune-modulating diets in patients undergoing abdominal surgery has been widely investigated with positive outcomes compared to standard enteral feeding. Surgery places both nutritional and immunological stress on patients who may already be in a compromized nutritional state. Shorter hospital stay and fewer infectious complications have been widely reported in patients fed with immune-modulating diets. While the improvement in outcome may be greatest in patients who are malnourished prior to surgery even well nourished Patients will benefit [22-26].

Daly et al. conducted a prospective, randomized, double-blind trial of 85 patients undergoing upper GI surgery for malignant disease [23]. Enteral feeding was established soon after surgery with the immune-modulating diet Impact® (Novartis Nutrition) or an isocaloric but not isonitrogenous control, Osmolite HN® Ross Laboratories). Postoperative infections were significantly reduced in the patients fed with Impact® compared to those receiving the control diet (11% vs. 37%, p = 0.02). Length of hospital stay was reduced by 4.2 days in the study group compared to controls (15.8 ± 5.1 days vs. 20. 2 ± 9.4 days, p = 0.01). Three years later Daly reported on a group of 60 patients fed via jejunostomy following esophagectomy, gastrectomy, or pancreatectomy for upper Gl cancer [27]. Impact® was compared to Trauma Cal® (Bristol-Meyers Squibb), modified to be isocaloric and isonitrogenous to the study diet. Feeding with the immune-modulating diet was associated with significantly increased plasma and peripheral white blood cell omega 3 to omega 6 ratios and significantly decreased PGE_2 production. Infections and wound complications were significantly reduced in the study group compared to controls (10% vs. 43%, p<0.05) and mean length of hospital stay was 16 days in the study group compared to 22 days in the control group (p<0.05].

Patients undergoing surgery for gastric or pancreatic cancer mere studied by Braga et al. [24] 60 patients were randomized to receive Impact®, an isocaloric, isonitrogenous standard enteral Diet or Total Parenteral Nutrition(TPN) following the surgical Procedure. In subjects who received Impact®, favorable changes in both immunological and nutritional markers were observed. While there was no significant difference in postoperative infection rates among the three groups, the infections were less severe in the patients fed with the immune-modulating diet (p<0.005). Senkal et al studied 154 patients who underwent surgery for upper gastrointestinal malignancy and were randomized to receive either Impact® or an isocaloric and isonitrogenous control [28]. There were significantly fewer infectious complications after the fifth post-operative day in the immune modulating diet group (6% vs. 17%. p <0 05). This reduction in late phase complications was reflected in a substantial reduction in treatment costs for the patients receiving Impact®.

Schilling et al studied 45 patients undergoing major abdominal surgery [29]. Patients were randomized to receive either Impact®, a standard enteral formula (Fresubin®, Fresenius AG), or an IV fluid containing only glucose and fat. The immune modulating diet was associated with an improvement in a number of Immunological markers. A reduction in C-reactive protein levels by day four implied that the inflammatory response was ameliorated in the patients fed with the enhanced formula. Infectious complications were less frequent in the Impact® group but this did not reach statistical signifi-

cance. Hospital and ICU length of stay did not differ between the three groups.

One study failed to show improved outcome with immune modulating diets Heslin et al. studied 195 patients undergoing surgery for upper gastrointestinal cancer who were randomized to receive either Impact® or lV fluids alone [30]. The investigators found no difference in the number of infections, length of hospital stay or mortality between the two groups. Concerns have been expressed however, with regards to a number of study issues. The study was neither double-blind nor effectively controlled. There were considerable imbalances between the study groups with more pancreatico- duodenectomies performed in the immune modulating diet group (53 of 97 vs. 38 of 98), requiring significantly longer anesthesia time (310 mins vs. 260 mins. P<.003) In addition, the Impact® patients aid not receive adequate levels of the diet with less than 40% of daily energy requirements provided by the formula. This under-dosing of what was a sicker group of patients would explain a lack of beneficial effect.

Pre- and post-surgery feeding

Recently a number of studies have been designed to investigate the effects of feeding with immune modulating diets from 5 – 7 days prior to surgery. Patients undergoing elective surgery for upper gastrointestinal malignancies have been the subjects of two Studies [22,31]. In the Braga study of 206 patients, peri-operative immunonutrition was compared with standard enteral feeding. Feeding was commenced orally seven days prior to surgery with Impact® (1 liter/day) or an isocaloric, isonitrogenous control. Jejunal feeding with the same compound continued from 6 hours postoperatively for 7 days. Intention-to-treat analysis showed pre-operative feeding with Impact® resulted in halving of the post-operative infection rate from 30% (32/104) to 14% (14/102) (p=0 009) The length of hospital stay was also significantly reduced from 12.9 ± 4 6 days in the control group to 11.1 ± 4.4 days in patients fed with the immune modulating diet (p=0.01). Both malnourished and well nourished patients benefited and the authors proposed that feeding with immune modulating diets prior to surgery resulted in optimal modulation of the immune system at the time of surgery.

Senkal et al. also studied patients with gastrointestinal malignancy undergoing elective surgery [31]. Feeding was commenced 5 days pre-operatively with Impact® or a control diet (isocaloric and isonitrogenous). There was a 48% reduction in total complications in the Impact® group compared to controls (14/78 vs. 27/76, p=0.05). In addition, fewer patients in the Impact® group developed complications after post-operative day three compared to controls (7/78 vs. 16/76, p=0.04), suggesting a faster recovery of immune function after surgical stress. There was a trend towards lower treatment costs in the supplemental diet group

Preoperative immunonutrition is not only beneficial to patients undergoing upper gastrointestinal surgery. Snyderman studied 136 patients being operated on for head and neck malignancy [32]. Subjects were randomized to receive oral Impact® for five days pre-surgery plus enteral Impact® post- operatively, or just post-operative Impact®. Controls received a standard formula pre- and post-operatively or just post-operatively. There was a 49% reduction in postoperative infections for the two Impact® groups combined compared to controls (9/40 vs. 14/31, p=0.04), but no difference between the two Impact® groups. Because length of stay in lCU was increased in patients with post-operative infectious complications, there was a trend towards shorter stay in the Impact® group. The authors suggested this could translate into significant cost savings for patients fed immune modulating diets.

High-risk cardiac patients were the subjects of a study reported by Tepaske et al. [33] . Forty-five patients received either Impact@ or an isocaloric, isonitrogenous control 5 to 10 days prior to surgery. Improved cell-mediated immunity in the peri-operative period was seen in the patients fed Impact®. Overall, significantly fewer Infections were reported in the Impact® group compared to controls (18% vs. 52%, p=0.009) and significantly fewer patients fed with lmpact® developed lower respiratory tact Infections (0% vs. 22%, p=0.022).

Immunonutrition has been shown to improve outcome in patients undergoing gastrointestinal tract surgery. While mortality is not altered, infection rates are reduced and length of stay in hospital is shortened. There is now strong evidence to support pre-operative feeding with immune modulating diets in elective cases. Commencing administration of the immune modulating diet prior to surgery has been shown to benefit not only patients undergoing surgery on the upper GI tract, but also those with head and neck malignancy and high-risk cardiac disease. Both malnourished and well-nourished patients will benefit from this approach because immunonutrition prior to the operation prepares the immune system for the stress of the surgical procedure. Post-operative infection rates are reduced and patients spend less time in hospital after surgery.

Immune modulating diets in Bum Patients

Early enteral feeding in burns patients is safe and well tolerated [34]. In this group of patients it is especially

important that enteral feeding be established within 24 hours of the injury, before edema of the gastric wall leads to gastroparesis. Enteral feeding has been commenced as early as 4 – 6 hours after the burn, with excellent results [35].

Only two studies looking specifically at the use of immune modulating diets compared to standard diets in burns patients have been published. These clinical trials were prospective, randomized and double-blind, with 50 subjects included in each study. Gottschlich compared 2 standard formulas to a Shriner's solution that had been modified by the addition of immunonutrients [36]. Patients receiving the immune modulating diet showed a significant reduction in wound infection ($p<0.03$) and length of stay per percentage total body surface area (TBSA) burned ($p<0.02$) compared to the other formulas. Trends toward reduced frequency of diarrhea and improved glucose tolerance were also reported. Saffle et al. compared Impact® to Replete® (Clinitec) [37]. They found no difference in mortality, days on ventilation or length of hospital stay for the two diets. However, in this study the parents were stratified based on TBSA. The small sample size that resulted raises the possibility of a Type II error. Furthermore, the control diet, Replete®, does contain a significant amount of omega-3 fatty acid. 0mega-3 fatty acids are anti- inflammatory and potentially immune enhancing [38] and are a component of the study compound, Impact®. In this respect, the control diet was also potentially immune-modulating

Ten burns patients were included In the 26 subjects studied by Cuntrasakul et al. [39] to asses the metabolic and immune effects of supplementation with immune-modulating agents. Patients were fed an immune formula via naso-gastric tube. Intravenous parenteral nutrition was given to the burns patients if clinically indicated. Significant improvement of nutritional parameters was reported along with significant improvement in a number of Immunological markers. The formula was generally well tolerated

There may be rational arguments for the use of immune modulating diets in burns patients despite the relative lack of clinical trial support. Burn Injury is associated with a hyper-metabolic state and immuno-suppression is well documented with high risk of infection [34, 40,41]. Immune-modulating diets would seem appropriate in this setting.

Immune modulating diets in Head Injury Patients

Clinical trials on enteral feeding with immune modulating diets in isolated head injury are rare because many patients with severe head injury have other trauma and are therefore classified as trauma cases. However, it is generally accepted that early enteral nutrition improves outcome in head injury patients [42,43]. Patients with head injury enter a hypermetabolic state equivalent to those suffering burns to 20-40% of the body [44]. Delayed gastric emptying secondary to raised intracranial pressure may lead to reduced tolerance to enteral feeding in this group of patients [45]. However, this difficulty can be overcome by various techniques including feeding via the naso-jejunal route [42].

One study has been published on the use of enteral immune modulating diets in head injury [46]. Thirty patients were started on Impact® "early" (prior to 72 hours post injury, n = 15) or "late" (after the resolution of injury-induced ileus, n = 15). No differences in outcome were reported between the two groups Conclusions are difficult to draw however, because the small sample size could result in a Type 11 error. Also, there was considerable overlap between the "early" and "late" groups in that 6 of the 15 "late" patients were commenced on Impact® prior to 72 hours. Nearly one third (4/15) of the patients in the late group died, an outcome that contributes further concern with regards to the validity of the study.

In theory, immune modulating diets may be helpful in head injury patients. The risk of infection is between 50-75% in this group [47]. Pneumonia is the most common infection, secondary to the prolonged intubation and chemical paralysis required in many cases [48]. While evidence from human clinical trials is limited, immune modulating diets in head injury patients are well tolerated. Animal data in head injury models support the use of immune modulating diets however more evidence is needed in humans to recommend its use in this sub-group of patients [49].

Immune modulating diets in Trauma Patients

Early enteral nutrition is an integral part of supportive care for trauma patients, with proven advantages over TPN [50-53]. A number of studies have been carried out to investigate the use of immune modulating diets in trauma patients. Results have suggested improved outcome with improved cellular immunity parameters, reduced infectious complications and shortened stay in lCU. However, immune modulating diets and control diets have varied between studies as have the patient populations.

In two clinical trials the effect of Perative®@ (Ross Laboratories) compared to Osmolite HN® supplemented with ProMod® (Ross Laboratories) was investigated [54,55]. The Brown study was prospective and randomized but the investigators were not blinded. Infectious

complications were significantly reduced in the study group (3/19 vs. 10/18, p<0.05) but there was no difference in length of stay in ICU or hospital, or in days on ventilation. However, there was a significant difference between the study and control group in that the patients given the standard diet were fed later and failed to reach the caloric goal more often. Mendez et al. [55] found no significant difference in outcome between the two groups in their prospective, randomized, blinded trial of 43 trauma patients. Trends were reported towards longer lCU and hospital stay, and more ventilator days in the study group, related to a higher incidence of ARDS in patients receiving the immune modulating diet. On investigation of cellular immunity parameters, significantly increased monocyte production and neutrophil oxidant burst activity was found in the patients receiving the study diet. The authors expressed concern that immune modulating diets may stimulate the inflammatory response resulting in more frequent or more severe ARDS but this concern has not been supported by other clinical studies[56].

Significant improvement in clinical outcome was reported in two studies of the immune modulating diet Immun-Aid® [57]. Ninety-eight trauma patients were studied in a prospective multi-center trial of Immun-Aid® compared to Vivonex® (Novartis Nutrition), an isocaloric but not isonitrogenous control [58]. Patients fed with the immune modulating diet had a significantly higher total lymphocyte count (p=0.014) with increased T lymphocytes (p=0.04) and T-helper cells (p=0. 004). Overall septic complications were significantly reduced in the study group (22% vs. 43%), in particular, intra-abdominal abscess was reported in none of the 51 patients fed Immun-Aid®, but in 5 of the 47 control patients (p=0.023). Multiple organ failure (MOF) was also significantly less frequent in the study group compared to the control (0/51 vs. 5/47, p=0.023). No difference in mortality between the two groups was reported.

Kudsk et al compared 17 patents fed with Immun-Aid® to 18_fed an isocaloric, isonitrogenous control (Promote® Ross Laboratories and Casec, Mead-Johnson Nutritionals) [57]. Nineteen patients in whom early enteral access could not be established served as unfed controls Significantly fewer infectious complications occurred in the patients fed the immune modulating diet compared to patients fed the control diet (6% vs. 41%, p = 0.02) or not fed at all (6% vs. 58% p = 0.002). In particular, intra-abdominal abscesses and pneumonia were less frequent in the study group. As a result, study patients used fewer antibiotics and stayed in hospital fewer days. These advantages were reflected in reduced costs for the patients receiving the immune modulating diet.

Impact® was compared to an isocaloric, isonitrogenous control in 32 severe trauma patients studied by Weimann [59]. While there was no difference in the rate of infectious complications or sepsis, the 16 patients fed with the immune modulating diet had a significantly lower incidence of systemic inflammatory response syndrome (SIRS) during the first 28 days than patients fed the control diet (8.3 ± 6.3 vs. 13.3 ± 6.7) Multiple organ failure score were lower in the immune modulating diet group on day 3 and days 8 to 11. There were lower levels of C-reactive protein and fibrinogen in the Impact® group, indicating a more rapid resolution of the hypermetabolic state in patients receiving the enhanced diet.

Overall, results from studies of immune modulating diets in trauma patients suggest improved clinical outcome with fewer infectious complications and shorter ICU stay. Immunological studies show enhanced cellular immune function with increased T -cells and enhanced cellular responsiveness [56,58]. Differences in the diets studied, and endpoints evaluated make it difficult to reach concrete conclusions and further clinical trials are necessary to resolve this. However, the evidence does suggest immune modulating diets offer benefit this group of patients.

Immune modulating diets in critically ill Patients

Studies of immune modulating diets in critically ill patients have suggested positive effects on many parameters, in particular infection rates. Galban et al reported a significant reduction in mortality in 176 septic ICU patients fed with Impact® as compared to standard enteral nutrition (17/89 vs. 28/87, p<0.05) [60]. Bacteremias were reduced in patients receiving the immune modulating diets (7/89 vs. 19/87, p=0.01) as were the number of patients acquiring more than one nosocomial infection (5/89 vs. 17/87, p=0.01). Interestingly, the improvement in mortality was most pronounced in the less severely ill patients (APACHE score <15). This indicates that aggressive enteral feeding with immune modulating diets is helpful in the less critically ill.

Patients studied by Bower et al were classified as critically ill but in fact 84% (248/296) were trauma patients [61]. Overall mortality in the study was low, at only 11.8% which does not suggest these were in fact critically ill patients. Subjects were divided into subgroups based on levels of feeding achieved, and sepsis. Significant reductions in length of hospital stay were seen in the study patients with sepsis and in those who were classified as optimally fed. The septic subgroup fed with Impact@ also had significantly fewer nosocomial infections.

A trend towards increased mortality was reported in this study, with the mortality rate in the septic subgroup

higher for patients who received the study feed than those who received the control feed (11/44 vs. 4/45, p=.051).

However, on review this trend related to patients who were not successfully fed and who did not therefore receive an adequate level of nutrition or dose of immunonutrients. The trend disappeared in the more successfully fed groups [62].

In a large study of 390 critically ill subjects, Atkinson et al found that patients who received successful early enteral nutrition with Impact® (>2.5L within 72 hours) spent significantly less time on ventilation (medians 6.0 vs. 10.5 days, p=0.007) and in the ICU (medians 15.5 vs.20, p=0.03) than patients receiving the control diet [63]. A non-significant trend towards higher mortality was seen in the study group. This was accounted for by statistically significantly higher APACHE II scores in the patients fed Impact® who were therefore a more severely ill group. Overall mortality was high in this study (46%) because many of the patients were transferred to the study unit at a late stage and already had multiple organ failure on entry to the trial.

Recently thirty-three general ICU in Italy conducted randomized unblinded controlled clinical trial. Among the 237 recruited patients, 39 had severe sepsis or septic shock; 21 of them received parenteral nutrition. Eligible patients received either total parenteral or enteral nutrition, the latter containing extra L-arginine, omega-3 fatty acids, vitamin E, beta carotene, zinc, and selenium. The primary endpoint for the subgroup analysis on patients with severe sepsis was mortality on ICU. The ICU mortality of patients with severe sepsis given enteral nutrition was higher than for those given parenteral nutrition (44.4% vs. 14.3%; p=0.039). More patients given enteral nutrition than patients given parenteral nutrition still had severe sepsis when they died (38.9% vs. 9.5%, p=0.055). Recruitment of patients with severe sepsis was subsequently stopped.

Some concern remains however, as to possible limitations to the use of immune modulating diets in patients with severe systemic infection. An exaggeration of the acute inflammatory response may occur in these patients, potentially worsening clinical outcome. Further studies are therefore required to assess the effectiveness of immune modulating diets in critically ill patients with severe sepsis

Meta-Analyses of Arginine containing immune modulating diets

Meta-analyses of clinical trial data on immunonutrition have been published by 3 groups Heys et al. [65], Beale et al. [66], Heyland et al. [67]. Heys et al included 11 prospective, randomized controlled trials carried out between 1990 and 1998 with a total of 1009 trauma, surgical or critically ill patients. The diets studied included Impact® (8), Immun-Aid® (2) and a third diet containing L- arginine with glutamine (1). Immune-modulating diets were associated with a significant decrease in infection (OR 0.47, 95% CI 0.32-0.70) and length of hospital stay (reduction of 2.5 days, 95% CI1.0-4.0) for critically ill and surgical patients with GI malignancy. No differences were found for length of ICU stay or the incidence of hospital-acquired pneumonia. There was a non-significant increase in mortality seen in the patients fed immune modulating diets (OR 1.77, 95% CI1.00-3.12, p=NS), all relating to the Bower study [61]. As discussed earlier, the mortality rate in this study was complicated by failure to achieve adequate enteral feeding with immune modulating diet in many patients.

Beale et al. published an intention-to-treat analysis of 12 prospective, randomized, controlled trials of patients suffering trauma, sepsis or undergoing major surgery [66]. These studies included 10 of the 11 covered in the Heys analysis, plus trials conducted by Atkinson et al [63] and Galban et al. [60]. Impact® was the immune modulating diet used in 10 of the 12 trials, Immun-Aid® in the other two. Novartis Nutrition supported this meta-analysis and made the data bases from the three largest studies [60,61,63], available to the authors. Beale et al were therefore able to censor for mortality in their analysis. Even allowing for the fact that not all control diets were isonitrogenous, significant reductions in infection rate (RR 0.67, CI 0.50 - 0.89, p=0.006) days on ventilation (2.6 days, CI 0.1 - 5.1, p=0.04) and length of hospital stay (2.9 days, CI 1.4 - 4.4, p=0,0002) were noted. These benefits were most marked in surgical patients, and were present before and after censoring for death. Mortality was not found to be different between the immune modulating diets and standard diet patients (RR 1.05, CI 0.78 - 1.41, p=0.76).

Heyland et al. [67] in their meta-analysis included 22 randomized trials, immunonutrition was found to be associated with a significantly lower risk of infectious complications (RR 0.66, 95% CI 0.54 - 0.80) Length of hospital stay was significantly reduced (-3.33 days, 95% CI -5.63 to -1.02 days). However, it was noted that the studies were heterogeneous with regard to diet and population groups. A prior subgroup analyses found that the immune modulating diets Impact® and Immun-Aid®, which contain high levels of arginine were significantly more effective in reducing infectious complications(RR, 0.55; 95% CI, 0.46 – 0.67 vs. RR, 1.27; 95% CI 0.74 – 2.22, p=0.01) and shortening hospital stay than other products (ES, -0.77; 95% CI, -1.09 to -0.45 vs. ES, 0.37; 95%

CI, -0.09 to 0.83, p=.008) While immunonutrition overall was not associated with a significant mortality advantage (RR 1.10, 95% CI 0.93 - 1.31) use of Impact® and Immun-Aid® was associated with a trend towards lower mortality compared to other products.

On review of these meta-analyses, considerable evidence exists to support the use of immune modulating diets, although one should be aware that not all immune modulating diets are equal. Reduction in infection rate and shorter time on ventilation, plus reduced length of stay in hospital are demonstrated. There is no significant effect on mortality.

Disease specific nutrition

Patients with acute respiratory distress syndrome (ARDS) were the subjects of a prospective, double-blind, multicentre randomized controlled trial reported by Gadek et al. [68]. One hundred and forty-six patients with mild to moderate ARDS (PaO2:FiO2 <250 but> 100 mmHg) were fed with a low carbohydrate, high fat immune-modulating formula or an isocaloric, isonitrogenous control. Patients who received the study diet exhibited decreased pulmonary neutrophil recruitment, improved oxygenation, fewer ventilation days, and shorter stay in ICU. Mortality was lower in the immune modulating diet group but this was not statistically significant (16% vs. 25%). Overall mortality in the study was low for a group of patients with ARDS suggesting that these patients had only mild disease. This study however, raises the possibility of a specific approach to nutrition in certain diseases, tailoring the immune modulating diet according to the pathogenesis of the condition.

In conclusion, evidence is growing that immunonutrition may put forth favorable effects on the inflammatory response in critically ill patients and that these may favorably influence outcome. However more research should be dedicated to the potential side effects of this nutritional approach, since immunonutrition is turning basic nutritional support into a form of therapy and hence may be referred to as "nutriceuticals". Due to the added cost, cautious optimism and a careful thought of various important issues are needed, before universal recommendations of the use of immunonutrition is considered.

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