Nutrition and immunonutrition

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Nosocomial infections are common in critically ill patients and frequently lead to multiple organ failure and death. Such patients may be vulnerable to infection because of deficiency in immune function brought about by severe illness [32, 54, 66]. Requirement for prolonged ventilation is associated with the development of nosocomial pneumonias and sepsis, and the development of weakness and wasting of skeletal and respiratory muscles is a major cause of prolonged weaning from ventilatory support despite resolution of the underlying condition [15]. It is now recognized that nutritional support has a crucial role in maintaining immunological function and in the prevention of muscle wasting during critical illness. Failure to address the issues of muscle wasting and weakness in critical illness leads to delays in mobilization and prolongation of time to recovery [14, 15].

In this article we review recent work which has highlighted the potential importance of the route of administration, the use of specific nutrient substrates and the use of adjuncts to nutrition such as anabolic hormones in maintaining or augmenting immunological function and preventing muscle catabolism in critically ill patients. Nutritional support is a vital component of all preventive therapies available for multiple organ failure in critical illness.

Weight loss and wasting in critical illness

Despite good evidence that nutritional support in certain circumstances leads to reductions in morbidity and mortality [82], increased utilization of nutritional support has unfortunately led to little change in the rapid development of muscle wasting and consequent weakness associated with critical illness. This is important because it has been shown that the degree of weight loss occurring during acute illness is correlated with mortality [20]. Cachexia in critical illness may be explained by the combined effects of malnutrition, immobilization and the hypercatabolic state which occurs after stress, trauma and sepsis. Many patients in the intensive care unit (ICU) are malnourished on admission because of anorexia as the result of illness or fasting in preparation for surgery and this may be exacerbated by delays in commencing nutritional support after ICU admission.

Even hyperalimentation, however, fails to reverse muscle wasting and negative nitrogen balance during critical illness because the metabolic responses to uncomplicated starvation and to stress, trauma and sepsis are quite different. In starvation there is a fall in basal metabolic rate, resting energy expenditure and tissue oxygen consumption. Hepatic glycogen stores are sufficient for 24 h of glycogenolysis and after this a decrease in insulin secretion and increase in glucagon results in lipolysis and hepatic gluconeogenesis. There is then an adaptive phase during which gluconeogenesis falls and ketosis increases, with ketone bodies becoming the fuel for otherwise glucose-dependent tissues. In uncomplicated starvation, therefore, lean body mass is generally preserved until late, fat breakdown leading being the chief source of calories. The administration of sufficient nutrition will thus convert the starved catabolic patient to an anabolic state.

After stress, trauma or sepsis, however, the hypermetabolic state seen is distinct from that which follows simple starvation and in particular the adaptation to fat metabolism does not occur. There is a significant increase in caloric requirements, with increases in basal metabolic rate and tissue oxygen consumption and consequent negative energy balance. The circulating concentrations of many hormones (for example catecholamines, glucagon, cortisol and growth hormone) and cytokines are increased leading to rapid glycogenolysis, increased hepatic gluconeogenesis and a reduction in lipolysis. The ability to use glucose and fat is impaired and consequently there is an increased dependency on muscle breakdown for fuel. There is weight loss and muscle wasting which leads to an increased loss of nitrogen in the urine. Most of this nitrogen loss originates from muscle proteins because of increases in both whole body protein breakdown and synthesis [75, 80], with breakdown predominating over synthesis [3]. Weight loss of 30 % was common in burns patients before the introduction of routine nutritional support [94]. In sepsis proteolysis can cause nitrogen losses of up to 30 g (represents as much as 800 g muscle mass [52]) per day. Reversal of muscle wasting and negative nitrogen balance in these patients requires control of the effectors of hypermetabolism together with adequate nutritional support. Muscle loss is not prevented by hyperalimentation, however, this leading instead to hepatic steatosis, abnormal liver function and excess carbon
dioxide production which some authors believe may be detrimental to weaning from ventilatory support [24]. Over the past 20 years the energy intake prescribed to critically ill patients receiving parenteral nutrition has fallen, and it appears that the energy requirements of these patients are in fact similar to those of normal healthy subjects [24]. Energy requirements during critical illness have been overestimated in the past because measurements of resting energy expenditure were made at times of peak hypermetabolism and then extrapolated to longer periods, the effect of infused nutrients at time of measurement was not considered, and corrections for pyrexia were made inappropriately [23]. The lower energy requirements of these patients still reflect hypermetabolism, however, but this is balanced by the effects of reduced physical activity. It has now become clear that it is the quality rather than the quantity of nutrients provided that is of most importance in preventing muscle loss and supporting essential body systems such as the immune system during critical illness. In particular, the amino acid glutamine has been recognized to be of importance to muscles, the gut and to the immune system.

**Nutritional assessment**

A number of variables can be measured to assess a patient’s nutritional status. These include serum concentrations of albumin and transferrin, the triceps skinfold thickness and the cutaneous responses to recall antigens [27]. In practice, however, these measurements are relatively insensitive when used for individual patients, and malnourished patients are generally accurately identifiable on the basis of a subjective clinical assessment [20].

Although it is possible to estimate energy requirements using standard equations such as the Harris-Benedict equation or by indirect calorimetry, these measurements are rarely required in the clinical setting. The majority of ICU patients require 25–30 kcal kg⁻¹ day⁻¹. Energy intake greater than this may result in complications associated with overfeeding, except in certain situations such as after severe burns, where greater quantities may be required. Protein requirements for catabolic patients are 1.2–2.0 g kg⁻¹ day⁻¹ if renal function is normal. Additional supplementation does not result in increased protein synthesis and may contribute to ureaemia. Protein dose may need alteration in light of changes in renal and hepatic function, as many catabolic patients are unable to utilize administered nutrients efficiently until they are in a recovery phase. A non-protein calorie to nitrogen ratio of between 100 : 1 and 150 : 1 must be administered to permit utilization of the protein load for protein synthesis. For patients requiring parenteral feeding it is recommended that dextrose should provide 70–80 % of non-protein energy and lipid the rest, despite the concerns about the immunosuppressive effects of lipid emulsions discussed below [43, 73].

Many critically ill patients require fluid restriction as a therapeutic approach, but will often be given large fluid volumes including antibiotics, vaso-pressors and other drug infusions. One of the problems encountered in administering nutritional support during critical illness is allowing adequate volume to deliver sufficient quantities of energy and protein. In many cases a balance has to be accepted between the desired nutritional intake and the volume space available.

**Route of nutrition in critical illness: enteral vs parenteral**

Along with the move away from hyperalimentation in critical illness, there has been a change in emphasis from parenteral to enteral administration of nutrients. This has been driven by increased understanding of the pathology of nosocomial infections in the critically ill and the role of the gut in their development. Infection is the most common cause of mortality in critically ill patients irrespective of the underlying cause of their critical illness. The development of nosocomial pneumonia is associated with a mortality exceeding 30 % [57]. Interest has centred on the gut as a reservoir of bacteria and endotoxin which may be the cause of nosocomial infections and sepsis syndrome [59]. Tracheal and nasogastric intubation, the use of H₂-receptor antagonists as stress ulcer prophylaxis and the cessation of enteral nutrition all predispose to bacterial overgrowth in the upper gastrointestinal tract. It has been demonstrated that bacteria can be isolated from the stomach of critically ill patients some days before their appearance in the tracheal aspirate [5]. Furthermore, gut mucosal atrophy occurs in the absence of enteral feeding because enterocytes normally obtain some of their nutrients directly from the intestinal lumen. Mucosal atrophy may allow translocation of bacteria or endotoxin to the portal circulation. Translocation of bacteria and endotoxin has been shown to occur in animal models of critical illness [96], but has as yet not been convincingly demonstrated to occur in humans. Circumstantial evidence in support of translocation occurring in humans is provided by the demonstration of increased gut permeability after trauma [50], burns [100] and in critical illness [34, 37], and the finding of significant amounts of endotoxin present in the peritoneal cavity and bacteria present within organ specimens from organ donors without intra-abdominal injuries [90]. Interestingly, 95 % of the organ donors in this latter study received no feeding. The use of total parenteral nutrition (TPN) is also associated with atrophy of gut-associated lymphoid tissue (GALT) [51]. The translocation of bacteria into the circulation may stimulate macrophages to release cytokines which generate the hypermetabolic response seen in sepsis, and may be responsible for producing hypoxia and multiple organ failure [12].

In addition to these concerns about the advisability of substituting TPN for enteral feeds there is some evidence that TPN itself has deleterious immunological effects. TPN appears to accentuate the metabolic response to stress, trauma and sepsis by increased pro-inflammatory cytokine and stress hormone release, by the effects of hyperglycaemia and by a specific immunosuppressive effect of lipid emulsions [73]. Omega-6 polyunsaturated fatty acids...
(PUFAs) are the form found in Intralipid used in TPN and may have significant immunosuppressive effects, mainly through stimulation of production of prostaglandin E₂. Prostaglandin E₂ has a direct suppressant effect on delayed cell-mediated immunity, suppresses complement synthesis, increases the generation of superoxide radicals and increases suppressor T-cell activity. In addition, omega-6 PUFAs cause increased production of thromboxane A₂ which results in vasoconstriction and thrombosis [1]. TPN also depresses pulmonary macrophage function [81], and depresses local and systemic immune responses to intraperitoneal infection [28, 43]. The use of TPN has been shown to increase the incidence of intra-abdominal abscesses and septic complications after pancreatic resection for malignancy [8], and to increase mortality three-fold in burns patients [38]. In the clinical situation, however, it is likely that the major adverse immunological effect of TPN is due to the cessation of enteral feeding with the consequent development of mucosal atrophy and bacterial overgrowth.

Animal studies have demonstrated that continuous tube feeding started immediately after burn injury reduces the post-burn hypermetabolic response, and prevents the gut mucosal atrophy seen in a comparative delayed enteral feeding group [64]. Enteral feeding resulted in fewer septic complications in high-risk surgical patients [65] and after abdominal trauma [47]. Enteral nutrition has been shown to prevent bacterial and endotoxin translocation in experimental animal models [96], and a recent study in humans has demonstrated a significant decrease in gut mucosal permeability occurring in critically ill patients receiving glutamine supplemented enteral nutrition when compared with a group receiving standard TPN [34].

In addition to providing the mucosa with essential nutrients and preventing the development of mucosal atrophy, the provision of enteral nutrition may also increase gut blood flow. Reduction of oxygen and nutrient delivery to the gut mucosa because of microcirculatory disturbances is thought to be common in sepsis, and may also play a part in the breakdown of the mucosal barrier to bacteria and endotoxins. Enteral feeding has been shown to ameliorate the decrease in splanchnic blood flow associated with the institution of positive end-expiratory pressure ventilation for acute lung injury [74]. This effect may occur even with only small volumes of feed. Enteral feeding also results in improved hepatic synthesis of albumin compared with parenteral nutrition [19].

For a significant benefit to be seen from the use of enteral rather than parenteral feeding the enteral feed must be started as soon as possible after the insult. No difference in infectious complications were seen in head injury patients begun on enteral feeds 5 to 7 days after injury when compared with a group who were given early TPN; however, if the enteral feed was commenced within 3 days of the injury infectious complications were significantly reduced [48]. It is now generally accepted that enteral feeding can be started almost immediately after operation even in patients undergoing abdominal surgery, and in critically ill patients who are sedated, paralysed and ventilated on the ICU. Gastric stasis may be a problem, but this can be overcome by the use of prokinetic agents, nasojejunal tubes or feeding enterostomies.

It is often not possible to achieve comparable energy delivery by the enteral route to that which can be obtained by TPN; however, although TPN guarantees a certain nutrient delivery utilization may be incomplete. TPN will be required in those patients in whom enteral feeding is contraindicated or fails because of malabsorption, ileus or intractable diarrhoea. Supplemental parenteral nutrition may be needed when it is not possible to provide adequate energy enterally. It is likely, however, that if even small amounts of nutrients can be given enterally this will help maintain mucosal integrity, prevent bacterial overgrowth and help maintain splanchnic blood flow.

There is much interest in alterations in the composition of TPN solutions in an attempt to ameliorate some of the adverse effects associated with their use. Glutamine is a non-essential amino acid with poor stability in solution so is not normally included in parenteral feeds. However, in times of physiological stress blood glutamine concentrations decrease and the amino acid may become “conditionally essential”. Glutamine is an important nutrient for enterocytes, and parenteral nutrition containing glutamine has been shown to maintain intestinal barrier function in patients with inflammatory bowel disease [89], and maintain intestinal absorptive capacity in a small group of critically ill patients [88]. There is as yet no clinical evidence that glutamine-supplemented TPN reduces morbidity and mortality caused by infection in critical illness however. The molecular mechanism underlying the beneficial effect of glutamine on gut mucosa is not known, but glutamine has been shown to augment heat shock protein messenger RNA and protein expression in rat enteric crypt cells after injury in vitro [22]. Heat shock proteins are stress-response genes that protect cells from various injuries. Escherichia coli sepsis in rats causes selective damage to enteric crypt cells, and the morphological abnormalities seen can be partially prevented by parenteral administration of glutamine [95]. In health, gut mucosal cells derive glutamine from luminal contents [84]. If enteral nutrition is better than TPN because of its effects on the gut, and addition of glutamine to TPN offsets some of its deleterious effects on the gut, it is tempting to extrapolate this to recommend the inclusion of glutamine in enteral nutrition for critically ill patients. There are as yet, however, no published studies demonstrating increased efficacy of glutamine-enriched enteral nutrition over standard formulas in reducing infectious complications in the heterogeneous intensive care population.

**Preventing muscle loss**

**GLUTAMINE**

Protein loss from muscle during critical illness may occur in response to depletion of plasma amino acids (increased demand), or alternatively increased...
Muscle protein turnover may be stimulated by circulating mediators (hormones or cytokines). The loss of muscle protein may have short-term advantages such as providing substrate for the manufacture of acute phase proteins and fuel for more essential body processes. This may include provision of amino acids such as glutamine for protein synthesis within the cells of the immune system and intestine, for repair processes and for hepatic gluconeogenesis. However, consequential plasma glutamine depletion may be central to the failure of traditional nutritional regimes to reverse muscle catabolism in critical illness. Glutamine constitutes 60% of free intracellular amino acids in skeletal muscle [77]. It is the most important carrier of ammonia from the peripheral tissues to the splanchnic area, and serves as an oxidation fuel during cell division [83]. It is also a donor of nitrogen for DNA and RNA synthesis and hence is essential for the proliferation of cells [79]. Glutamine is the principal metabolic fuel of gut mucosal cells [61, 85], lymphocytes and monocytes [2, 7]. Glutamine also has important roles in generation of ammonia by the kidney and in gluconeogenesis in the liver. Lung, adipose tissue and the liver are all sources of glutamine, but skeletal muscle is thought to be the major site of glutamine storage, synthesis and release. Animal and human studies have demonstrated a net flux of glutamine from peripheral to splanchnic tissue with increased hepatic and intestinal uptake after operative stress or in sepsis [21, 83]. In illness glutamine requirements increase markedly [4], and utilization may exceed endogenous production.

If adequate dietary glutamine is not provided net catabolism of skeletal muscle will occur to supply the requirements of glutamine-dependent tissue. Plasma and muscle glutamine concentrations decrease in catabolic states [4, 70, 77]. In patients with sepsis, depleted muscle glutamine was associated with increased concentrations of glutamine precursors [77]. It is therefore suggested that muscle glutamine depletion in illness may be due to both reduced intracellular synthesis and increased efflux to supply glutamine dependent tissues. A positive correlation between glutamine concentration and rate of protein synthesis has been demonstrated in perfused rat skeletal muscle [41, 55], and protein breakdown was inhibited by glutamine in the same model [55]. Recent studies in humans have suggested that addition of glutamine to nutritional regimes may restore depleted plasma and muscle concentrations and improve nitrogen balance in patients with sepsis [77], after bone marrow transplant [101] and after surgery [86]. In addition, the reduction in muscle protein synthesis seen after operation (as assessed by ribosome analysis) was counteracted [36]. Traditionally, glutamine has not been included in parenteral or enteral feeds for critically ill patients because of difficulties with solubility and stability. Heat sterilization causes glutamine to break down to ammonia and pyroglutamic acid. Recent work has demonstrated that degradation is minimized with cold sterilization; however, solubility problems persist. Glutamine in parenteral nutrition requires large volumes which may not be practical for use in critically ill patients. This problem may eventually be overcome by the use of glutamine dipeptides which are soluble in smaller volumes. Until these issues are resolved the addition of glutamine to parenteral nutrition remains essentially a subject for further research.

There are available, however, proprietary preparations of enteral feeds containing glutamine. Unfortunately, there is little work yet published on the efficacy of glutamine-enriched nutrition in heterogeneous groups of critically ill patients. Preliminary results from a randomized study of glutamine-enriched parenteral nutrition in critical illness have been reported [33]. Plasma glutamine concentrations taken before feeding were significantly depressed in both study and control groups in comparison with normal volunteers. Glutamine-enriched feeding (TPN including 25 g glutamine a day) resulted in partial restoration of plasma concentrations towards normal on day 5, significantly different from the control group. Muscle glutamine concentrations were severely depressed in all patients undergoing muscle biopsies before feeding; however, 5 days of glutamine-enriched feeding did not affect muscle glutamine concentrations when compared with the control feeding group. There is still some debate as to the optimum daily amount of glutamine needed to maintain plasma and muscle concentrations during critical illness. Most workers have used 25 g a day, however, Zeigler has reported a series of dose-response studies conducted to evaluate the clinical safety, efficacy and metabolic effect of glutamine-enriched feeding in humans [98]. Glutamine was administered orally and parenterally in two doses (0.285 g kg⁻¹ day⁻¹ (approximately 20 g day⁻¹) and at 0.57 g kg⁻¹ day⁻¹ (approximately 40 g day⁻¹)) to normal volunteers and to patients after bone marrow transplant (parenteral only). In the patient study plasma glutamine decreased from pretreatment concentrations in both control and low-dose glutamine groups over the first 2 weeks, whereas plasma glutamine increased in the high dose group. Muscle glutamine was not studied; however, nitrogen retention was enhanced in the high dose group, there being no difference between the low dose group and control group. It may be that a higher dose of glutamine is required to restore plasma and muscle glutamine concentrations in the critically ill, and the results of further studies are awaited.

It is interesting to note that normally little dietary glutamine reaches the circulation as a substantial amount is utilized by intestinal cells. Consequently, although there are theoretical reasons to believe that glutamine-enriched enteral nutrition may be the optimum nutritional regime to protect the gut in critical illness, it may not be possible to deliver sufficient glutamine via the enteral route to obtain beneficial effects on muscle catabolism or immune function.

**OTHER NUTRIENTS AND GROWTH FACTORS**

Some other amino acids which, in certain situations may become essential, are also deficient or absent from parenteral nutrition solutions because of their
poor stability. These include cysteine and tyrosine. In some patients with liver disease, the hepatic conversion of phenylalanine to tyrosine and methionine to cysteine is inadequate, and unless sufficient cysteine and tyrosine are included in the nutritional regime wasting of lean tissue will occur [78].

The availability of human anabolic hormones synthesized by recombinant techniques has raised interest in their use in the amelioration or prevention of muscle catabolism during critical illness. It has been postulated that derangement of the growth hormone/insulin-like growth factor 1 (IGF-1) axis may partly explain muscle loss and negative nitrogen balance in critical illness. Growth hormone has both direct fuel regulating effects (lipolysis and insulin antagonism) and indirect growth promoting actions (anabolism) which influence amino acid uptake and protein synthesis. Its anabolic actions are mediated through IGF-1, which is secreted principally by cells of the liver under the control of growth hormone, although synthesis may occur in many other tissues. Critically ill patients are relatively resistant to growth hormone, and circulating concentrations of IGF-1 are reduced despite increased basal secretion of growth hormone [76]. Studies of the therapeutic use of growth hormone in seriously ill humans have mainly involved those with burns [102], although recently there have been reports of the use of growth hormone after surgery [62, 63], sepsis [91] and pancreatitis [99]. These studies confirm that a positive nitrogen balance can be promoted, even in the presence of hypocaloric nutrition [42, 58]. After operation protein synthesis is stimulated in patients, along with an increase in the concentration of free glutamine in muscle [35, 53]. It is possible that the effect of growth hormone therapy on muscle protein synthesis is related to preservation of muscle free glutamine concentrations [55]. It is unclear whether the preservation of muscle glutamine is due to decreased efflux from muscle, increased synthesis in muscle or repletion of the plasma pool by increased hepatic or pulmonary release of glutamine [93]. Growth hormone may also have direct effects on immunological function. In a study of daily s.c. injections of growth hormone (GH) after elective cholecystectomy fewer septic complications were reported in the GH group in comparison with placebo-treated controls [63]. Growth hormone administration to critically ill patients does not appear to be associated with any significant adverse effects, and a multicentre trial of its use in critical illness is currently in progress. IGF-1 has also been administered to patients after operation and to critically ill patients without adverse effects, but as yet there is insufficient information on its use therapeutically in these groups.

**Nutrition and the immune system**

It has long been recognized that immune function is depressed in seriously ill patients [32, 54, 66]. The metabolic response to stress, trauma and sepsis is closely interrelated with the immunological changes seen after such events. Consequently it has been proposed that nutritional support would be likely to improve host defence mechanisms and reduce morbidity. It appears, however, that unless there is severe protein-calorie malnutrition the provision of traditional nutritional support has little effect on immune function. Patients receiving TPN are, in fact, probably more likely to suffer infectious complications [9] for the reasons we have outlined above. Enteral feeding may be beneficial when compared with the parenteral route in preserving immune competence, but recently interest has also centred on the use of specific nutrients which may confer unique immunological benefits. These nutrients include glutamine, arginine, RNA, omega-3 fatty acids and trace metals such as zinc.

**GLUTAMINE AND IMMUNONUTRITION**

The net flux of glutamine from peripheral to splanchnic tissue seen after operative stress and in sepsis in animal and human studies [21, 83] is thought to occur at least in part in response to increased demand from immunological tissue. Glutamine is utilized at a high rate by lymphocytes [2] and macrophages [67], both as an oxidative fuel and to provide intermediates for synthesis of purine and pyrimidine nucleotides which are essential for DNA and RNA synthesis [46]. Lymphocyte and macrophage proliferation depend upon glutamine concentration in culture media [2, 71, 87]. Differentiation of both B- and T-cells cultured in vitro [16] and the appearance of interleukins 1 and 2 [10] in cell culture have been shown to be glutamine dependent, as have antibody production and macrophage phagocytic capacity [92]. It appears that the rate of utilization of glutamine by these cells depends upon the external concentration of glutamine. It is possible, therefore, that some of the immune dysfunction seen after stress, trauma and sepsis is due to glutamine deficiency. Increased lymphocyte proliferation and increased macrophage activity have been reported after glutamine feeding in septic rats [49, 95], and in humans glutamine-enriched TPN appeared to maintain immune function after bone marrow transplant in that there was a reduction in incidence of infectious episodes and shorter stay in hospital [101]. There are, as yet, no published studies addressing the effect of glutamine-enriched feedings on immune function during critical illness in humans. Gottschlich and colleagues administered glutamine enterally in varying concentrations to patients for 4 weeks after burn injury and failed to demonstrate any positive benefits; however, the total daily intake of glutamine was not stated [30]. As we have already noted, however, it may not be possible to provide sufficient glutamine by the enteral route to increase plasma concentrations and thus to produce specific changes in immune function during critical illness.

**ARGININE, OMEGA-3 FATTY ACIDS AND RNA**

Animal studies have supported the use of nutritional supplements such as arginine, omega-3 PUFAs and RNA to boost immune responsiveness after surgery or trauma. There is no published work evaluating the effect of nutrition supplemented with any of
these substances alone on infectious morbidity or mortality in patients; however, they are marketed together commercially in an enteral feed (Impact, Sandoz Nutrition, Bern, Switzerland) which has been evaluated in postoperative patients. Arginine is an essential amino acid during growth, and may become essential in catabolic states. Supplementary dietary arginine has been shown to have useful effects on cellular immunity in laboratory animal studies, resulting in increased thymic size, enhanced lymphocyte proliferation to mitogen and alloantigen, augmented macrophage and natural killer cell lysis of tumour targets and increased lymphocyte interleukin 2 production and receptor activity [45]. Arginine is the precursor for nitric oxide which is now recognized to be a ubiquitous cellular messenger with important immune functions. Rats fed an arginine-enriched diet survived longer after an intraperitoneal bacterial challenge than control animals [69], and arginine-enriched TPN improved survival in rats after caecal ligation and puncture [56]. In postoperative cancer patients, diet supplemented with arginine resulted in recovery to baseline levels of the proliferative response of lymphocytes to concanavalin A and phytohaemagglutinin by day 4, and increased responses by day 7. Patients fed a glycine-supplemented diet showed no such recovery of response [17]. Of interest, patients receiving arginine supplemented feeding also had increased IGF-1 concentration and improved nitrogen balance. No differences in infection rates or outcome between groups were seen in this study, however.

Prostaglandin E₂ (PGE₂) is thought to be an important factor in the generalized immunosuppression which follows major injury. Leucocyte function is suppressed by PGE₂ in culture [29], and high concentrations of PGE₂ are found in the serum of burns patients [68]. When PGE₂ production is blocked by administration of indomethacin after major surgery there is restoration of the immune response and decreased opportunistic infections [25]. Omega-3 and omega-6 PUFAs are essential dietary constituents as they are the sole precursors of eicosanoid metabolites, which include prostaglandins, lipoxins, thromboxanes and leukotrienes. If the diet is rich in omega-3 PUFAs there is suppression in the production of a number of dienoic eicosanoid metabolites with increased production of trienoic metabolites which have lower biological potency. Of particular importance, PGE₂ is replaced by PGE₃, TXA₂ by TXA₃, and PGI₂ by PGI₃. Enteral feeds rich in omega-3 PUFAs lead to suppression of PGE₂ production, an action which is probably as effective as pharmacological administration of cyclooxygenase inhibitors such as indomethacin.

Guineapigs recovering from burn injury fed an enteral diet rich in omega-3 PUFAs showed improved immune and metabolic function [1]. Improved survival was seen in guineapigs after exposure to endotoxin challenge [60] and in rats after intra-abdominal implant of a faecal agar pellet [6] who were fed with omega-3 PUFAs commencing before the insult. In burns patients omega-3 PUFAs improved survival, reduced infectious complications and diminished immunosuppression secondary to blood transfusion [31]. Some other animal studies have failed to show an advantage of omega-3 PUFAs in sepsis, however, especially when treatment is started after the insult [39]. Blocking the production of PGE₂ may not always be desirable as the precise role of PGE₂ in the immune response after major insult has not been fully defined. In the early stages after trauma or sepsis PGE₂ may actually have advantageous immunomodulatory effects, perhaps through suppression of the release of other cytokines such as tumour necrosis factor (TNF). After these first stages of injury or infection there is at least some evidence that a reduction in PGE₂ levels may reduce immunosuppression [72]. There may also be some disadvantages to the use of omega-3 PUFAs. In addition to reducing PGE₂ activity, TXA₂ activity is also reduced. This eicosanoid is of importance in the maintenance of vascular tone and in platelet aggregation. PGI₂ which is produced rather than PGI₁ however, has similar biological potency and is both an important inhibitor of platelet aggregation and a vasodilator.

Theoretically, therefore, a diet high in omega-3 PUFAs may predispose to vasodilatation and prolonged bleeding times. Indeed, Greenland eskimos, whose diet is high in fish oils rich in omega-3 PUFAs do have a prolonged bleeding time [72]. The risk of platelet dysfunction remains a concern despite there being no demonstrable increase in bleeding times in critically ill patients given omega-3 PUFA diets. Those studies addressing the issue however have only included small numbers of patients. A more serious concern associated with the use of omega-3 PUFAs is the recognition that diets high in PUFAs can lead to generation of lipid peroxides and consumption of the natural free-radical scavenger, vitamin E. Free radicals and lipid peroxides produce cellular and tissue damage, which raises the possibility that the administration of omega-3 PUFAs may exacerbate the pathological processes associated with the development of multiple organ failure. It is not known whether these concerns are valid in clinical use, or whether any potential increase in lipid peroxide stress could be prevented by concomitant vitamin E administration.

Dietary RNA may be necessary to maintain normal immune function. Nucleotides increase protein synthesis, and are involved in the regulation of several T-cell-mediated immune responses [11]. In an animal model, administration of RNA significantly improved host immune responsiveness and host survival to a septic challenge whereas a diet free of nucleotides resulted in decreased interleukin 2 production, decreased cell-mediated immunity, decreased allograft rejection and reduced resistance to infection [26]. Heyland, Cook and Guyatt, however, in a review of the evidence from all published studies concluded that there is as yet little evidence to support the use of dietary RNA supplementation to prevent infectious complications in critically ill patients [39]. Impact, the commercially available enteral feed supplemented with RNA, arginine and omega-3 PUFAs together has been evaluated in postoperative surgical patients. Ni-
trogen balance was greater, lymphocyte responsiveness restored, and infectious and wound complications reduced (11% vs 37%) in patients given Impact when compared to a group receiving a standard diet after surgery for upper gastrointestinal malignancy; however, the Impact group received a higher daily nitrogen intake [18]. Mean length of hospital stay was also reduced for patients in the supplemented group (16 vs 20 days). In another study involving post-surgical patients receiving Impact vs an isonitrogenous control diet, T-lymphocyte counts, B-lymphocyte indices, mean immunoglobulin M and G concentrations and mean interferon-gamma after phytohaemagglutinin stimulation were higher in the supplemented group [44]. Cerra and colleagues randomized critically ill trauma patients to Impact or a standard feed and demonstrated greater immune cell proliferative responses in vitro [13]. There were no differences in infections or mortality; however, the sample size was small. In a much larger group of critically ill patients Bower, Lavin and LiCari failed to demonstrate a reduction in the overall number of infections in the Impact-treated group, although the number of urinary tract infections was reduced [7]. Length of stay in the ICU was significantly shorter in those patients receiving Impact. Impact appears, therefore, to have some immunological advantages over standard feeds; however, further controlled trials of its use in critically ill patients are needed.

OTHER 'IMMUNONUTRIENTS'

Zinc has an important role in the maintenance of immune function, in promotion of wound healing and in maintenance of intestinal mucosal integrity. Zinc deficiency is associated with reduced concentrations of IGF-1 and reduced rates of protein synthesis [40]. In certain conditions, zinc deficiency is particularly likely. These include severe burns, pancreatitis and patients with excessive loss of gastrointestinal fluid. Urinary excretion of zinc increases with the degree of catabolic stress. Supplemental zinc therapy is recommended during critical illness, guided by regular monitoring of serum zinc concentrations [97]. Some workers have recommended the use of branched chain amino acids or increased doses of antioxidants such as vitamins E and C. There is no evidence in patients with critical illness to support the therapies currently advocated by some workers. Indirect evidence of efficacy is present for some nutritional manipulations from studies in elective surgical patients. The relevance of studies in animal models and in elective patients to patients with critical illness is unclear, however, and large randomized controlled trials are needed before definite pronouncements can be made.

From the evidence that is available can any conclusions be drawn? The enteral rather than parenteral route should be chosen for nutritional delivery in critical illness when possible. The use of enteral nutrition appears to be associated with a reduced incidence of sepsis and likelihood of developing multiple organ failure. At present, there is a fairly convincing evidence that glutamine deficiency is a significant problem in critical illness. Addition of glutamine to parenteral nutrition solutions may ameliorate or even prevent the deleterious effects of glutamine deficiency on the gut, the immune system and on muscles. Addition of glutamine to TPN may offset some of the disadvantages demonstrated to be associated with the use of TPN. The efficacy of glutamine-enriched enteral feeding is less clear, however, and unfortunately only enteral glutamine-enriched feeds are widely available commercially. The enteral feed Impact, which contains arginine, omega-3 PUFAs and RNA appears to have useful effects on immunocompetence in elective surgical patients, and it is tempting to extrapolate these to the critically ill. The potential adverse effects of increased lipid peroxide generation in patients with multiple organ failure associated with the use of omega-3 PUFAs is of concern, however, and the results of formal trials should be awaited before PUFA-enriched feeds are used routinely in the ICU.

There is much exciting work to be done in the field of nutrition and immunonutrition in critical illness, and it is likely that future improvements in intensive care outcomes will depend at least in part upon choice of nutrients and their route of supply.

Acknowledgement

Dr O’Leary is supported by the Joint Research Board of St Bartholomew’s Hospital and a grant from the British Journal of Anaesthesia.

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