British Journal of Nutrition (2007), **98**, Suppl. 1, S133–S139
doi: 10.1017/S0007114507832909

Immunonutrition in surgical and critically ill patients

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Surgery, trauma, burns and injury induce an inflammatory response that can become excessive and damaging in some patients. This hyperinflammation can be followed by an immunosuppressed state which increases susceptibility to infection. The resulting septic syndromes are associated with significant morbidity and mortality. A range of nutrients are able to modulate inflammation (and the associated oxidative stress) and to maintain or improve immune function. These include several amino acids, antioxidant vitamins and minerals, long-chain n-3 fatty acids and nucleotides. Experimental studies support a role for each of these nutrients in surgical, injured or critically ill patients. There is good evidence that glutamine influences immune function in such patients and that this is associated with clinical improvement. Evidence is also mounting for the use of long-chain n-3 fatty acids in surgical and septic patients, but more evidence of clinical efficacy is required. Mixtures of antioxidant vitamins and minerals are also clinically effective, especially if they include selenium. Their action appears not to involve improved immune function, although an anti-inflammatory mode of action has not been ruled out. Enteral immunonutrient mixtures, usually including arginine, nucleotides and long-chain n-3 fatty acids, have been used widely in surgical and critically ill patients. Evidence of efficacy is good in surgical patients. However whether these same mixtures are beneficial, or should even be used, in critically ill patients remains controversial, since some studies show increased mortality with such mixtures. There is a view that this is due to a high arginine content driving nitric oxide production.

Immune system: Inflammation: Surgery: Critical illness: Glutamine: Arginine: Fish oil: Parenteral nutrition: Enteral nutrition

The systemic inflammatory response syndrome, or SIRS, is the name given to the uncontrolled inflammatory response to an insult (e.g. surgery, trauma, burns) and involving excessive production of inflammatory cytokines, particularly tumour necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6 and IL-8[1]. Sepsis is the presence of SIRS in response to or in combination with an infection[1]. The mortality risk of sepsis is about 20 %, and it predisposes to organ failure, which carries an elevated mortality risk. Septic shock is the occurrence of multiple organ failures, metabolic acidosis and hypotension and it carries a mortality risk of 40 to 80 %[1]. Together SIRS, sepsis and septic shock are termed "septic syndromes". Septic syndromes are the leading cause of death in critically ill patients in Western countries[2].

Animal studies suggest a central role for inflammatory cytokines in the septic response (see 3 for references) and patients with sepsis show markedly elevated circulating concentrations of TNF-α, TNF-receptor 1, IL-1β and IL-6, with those patients having the highest concentrations being more likely to die[4–6]. In addition, circulating white cells from septic patients had high levels of activated nuclear factor kappa B (NFκB), a transcription factor that promotes the expression of numerous genes associated with inflammation, and levels of activated NFκB were higher in those patients who went on to die[6]. Mediators other than inflammatory cytokines are involved in the pathological processes that accompany critical illness. For example, prostaglandin E_2 is implicated in sepsis, burns and critical illness[7,8], while leukotriene B_4 and oxidants released by neutrophils are involved in acute respiratory distress syndrome[9].

In addition to hyperinflammation, patients with sepsis, burns and trauma can display immunosuppression, characterised by decreased monocyte expression of human leukocyte antigens (HLA), impaired ability of monocytes to stimulate T cells, impaired T cell proliferation, and low production of T helper (Th) 1-type cytokines (e.g. interferon (IFN)-γ) associated with host defence against bacteria and viruses but high levels of the Th2- and Treg-type cytokines (IL-4, IL-10) associated with inhibition of host defence against bacteria and viruses (see 10 for references). It is believed that the immunosuppressed phase of sepsis lags behind the hyperinflammatory phase (Fig. 1) i.e. initially sepsis is characterised by increased generation of inflammatory mediators but as it persists there is a shift towards an anti-inflammatory, immunosuppressed state sometimes called the compensatory anti-inflammatory response syndrome, or CARS although the precise timing of the two phases and the factors that influence their relative magnitudes are not entirely clear[11–13].

The concept of immunonutrition

The ability of nutrients to influence the activities of cells of the immune system has been termed "immunonutrition", although this term has most frequently been associated with the use of specific nutrients or combinations of nutrients in surgical, trauma, burned or critically ill patients[14]. These patients typically receive artificial nutrition, through the parenteral or enteral routes. The overriding notion of immunonutrition is that nutrients can improve cell-mediated immune responses in a

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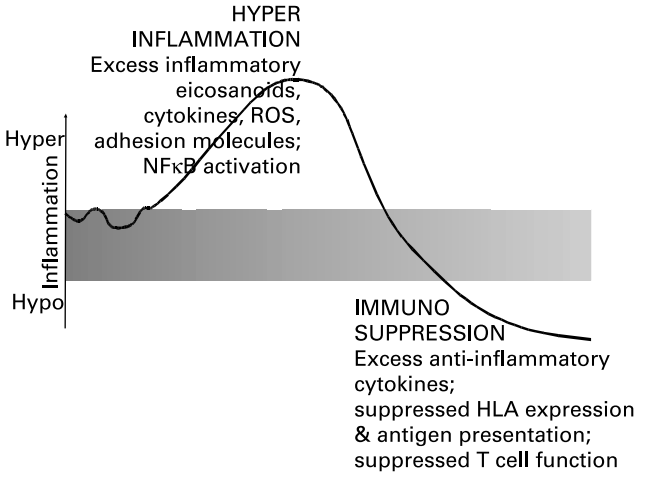

Fig. 1. Hypothetical biphasic immuno-inflammatory response to a traumatic insult. HLA, human leukocyte antigen; NFκB, nuclear factor κ B; ROS, reactive oxygen species. The grey area represents the physiological range.

way that is clinically meaningful, but in the context of patients requiring artificial nutrition this concept is extended to include modification of hyper-inflammatory processes (including oxidative stress) and improvement in gut barrier function, so preventing bacterial translocation (Fig. 2).

Scientific rationale for the nutrients included in immune-modulating artificial nutrition

Nutrients considered for inclusion in immune-modulating artificial nutrition are generally those that have been shown to act in relevant animal models to improve immune function, regulate inflammation, maintain or improve gut barrier function, or improve antioxidant defences, and which have been shown to be safe and efficacious (assessed according to the defined study outcome which has not always been a clinical endpoint) in clinical trials in the relevant patient groups. In addition, theoretical considerations, experimental data from in vitro studies and healthy volunteer studies, and clinical findings in other patient groups have played a role in influencing the makeup of immune-modulating artificial nutrition. It is important to appreciate that artificial nutrition contains macro and micronutrients including carbohydrate, lipid, protein and/or peptides, and the full range of vitamins and minerals; immune-modulating artificial nutrition contains additional nutrients or increased amounts of nutrients normally present. Nutrients that have been identified as potentially important as components of immune-modulating artificial nutrition are:

- Glutamine
- Arginine
- N-acetyl cysteine (as a cysteine precursor)
- Branched chain amino acids
- Nucleotides
- Long-chain n-3 fatty acids
- Antioxidant vitamins
- Trace elements
- Taurine

The scientific rationale for the inclusion of these nutrients is summarized in Table 1.

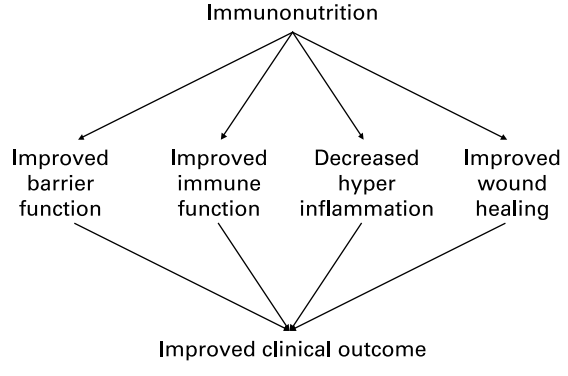

Fig. 2. The concept of immunonutrition in the context of surgical or critically ill patients.

Trials of immunonutrition in surgical and critically ill patients

Glutamine

Enteral glutamine increased the blood ratio of $CD4^+$ to $CD8^+$ cells in intensive care patients[26], whilst parenteral administration in post-colorectal surgery patients increased mitogen-stimulated proliferation of blood lymphocytes[27]. Another study in post-operative patients who received glutamine parenterally also showed increased blood lymphocyte numbers[28] and more recently, parenteral glutamine for 48 hours after major abdominal surgery was shown to result in better maintenance of the HLA-DR expression on circulating monocytes[29]. Patients with oesophageal cancer being treated with radio-chemotherapy also had higher blood lymphocyte counts and better lymphocyte proliferative responses if they consumed glutamine for 28 days[30]. Furthermore, in addition to a direct immunological effect, glutamine, even given parenterally, appears to improve gut barrier function in patients at risk of infection[31], an effect that is likely to decrease translocation of bacteria from the gut and hence eliminate a key source of infection.

The improvements in immune function with glutamine administration appear to result in clinical advantage. Parenteral glutamine following bone marrow transplantation reduced infections and length of hospital stay[32], with a later report showing that glutamine resulted in higher total blood lymphocyte, T lymphocyte and $CD4^+$ lymphocyte numbers after patients' discharge[33]. Very low birthweight babies who received a glutamine-enriched premature feeding formula had a much lower rate of sepsis than babies receiving a standard formula[34], and in a study of patients in intensive care, glutamine decreased mortality compared with standard PN and changed the pattern of mortality[35]. In a more recent study, in which patients received enteral glutamine vs. standard enteral feed from within 48 hours of the initiation of trauma, there was a significant reduction in the 15-day incidence of pneumonia, bacteremia and severe sepsis in the glutamine group, although this was not associated with reduced mortality[36]. This improved clinical outcome in patients receiving glutamine was associated with increased monocyte expression of HLA-DR[37] and increased

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Table 1. Scientific rationale for inclusion of nutrients in immune-modulating artificial nutrition

Nutrient	Rationale	Reference
Glutamine	The most abundant amino acid in the blood and in free amino acid pool; An important fuel for cells of the immune system; Intramuscular and plasma glutamine concentrations decrease post-surgery, in sepsis, cancer cachexia and following burns; In animal experiments glutamine improved T cell function and enhanced resistance to infectious pathogens; In animal experiments glutamine improved gut-associated immune tissue weight and cellularity and maintained intestinal integrity (infections; endotoxaemia)	15,16
Arginine	Involved in protein, urea, and nucleotide synthesis and ATP generation; Precursor of nitric oxide, a potent immunoregulatory and blood flow mediator, which is cytotoxic to tumour cells and some microorganisms; Precursor for synthesis of polyamines, which have a key role in DNA replication, regulation of the cell cycle and cell division; In animal experiments arginine decreased thymus involution associated with trauma, promoted thymus cellularity, lymphocyte proliferation, natural killer cell activity, and macrophage cytotoxicity, and improved delayed-type hypersensitivity, resistance to bacterial infections, survival to sepsis and burns, and wound healing; In healthy human subjects arginine supplementation increased blood lymphocyte proliferation in response to mitogens and promoted wound healing	16,17
N-acetyl cysteine	Cysteine is a component of the antioxidant glutathione; Glutathione concentrations in the liver, lung, small intestine and immune cells fall in response to inflammation and this fall can be prevented in some organs by provision of cysteine; Glutathione enhances the activity of T cells, improves cell-mediated immune function and decreases production of inflammatory cytokines	16
Branched-chain amino acids	Glutamine precursor; Some (limited) evidence of improved immune function and increased resistance to infection from animal studies	18
Nucleotides	Involved in DNA and RNA structure, energy metabolism, signal transduction, biosynthesis of phospholipids, and regulation of enzyme activity; Activation of lymphocytes causes a rapid increase in demands for nucleotides to cover an early increase in energy requirements and a later need to synthesize RNA for protein production and DNA for cell division; In animal experiments nucleotides improve T cell functions, antibody responses, delayed-type hypersensitivity and resistance to pathogens	19,20
Long-chain n-3 fatty acids	Excessive arachidonic acid (long-chain n-6 fatty acid) may promote inflammatory processes and suppress cell-mediated immunity; Arachidonic acid-derived eicosanoids associated with trauma, burns and acute respiratory distress syndrome; Long-chain n-3 fatty acids oppose the action of arachidonic acid; In vitro, animal and healthy volunteer experiments show that they are anti-inflammatory (decreased production of inflammatory eicosanoids and cytokines; increased production of anti-inflammatory resolvins); In animal experiments increased resistance to endotoxin; Generally associated with human health	10,21–23
Antioxidant vitamins	Maintenance of antioxidant defences; Prevention of oxidative stress and lipid peroxidation (oxidative stress induces inflammation and lipid hydroperoxides are immunsuppressive); Vitamin E has been shown to improve T cell responses and cell-mediated immunity	24
Trace elements	Zinc, copper and selenium are components of the major antioxidant enzymes; Maintenance of antioxidant protective mechanisms; Post-surgical and critically ill patients lose trace elements; Deficiencies in zinc, copper or selenium are associated with immune impairments and increased susceptibility to infections, while zinc, copper and selenium have all been shown to improve immune function in individuals with a low status	25
Taurine	Taurine is present in high concentrations in most tissues and particularly in cells of the immune system; It contributes 50 % of the free amino acid pool within lymphocytes and is the most abundant free nitrogenous compound therein; Animal studies show that taurine prevents the decline in T cell number seen with ageing and enhances the proliferative responses of T lymphocytes; In neutrophils taurine maintains phagocytic capacity and microbicidal action through interaction with myeloperoxidase; In humans, plasma taurine concentrations are decreased by trauma and sepsis	16

ex vivo IFN-γ production by T cells[38]. Enteral glutamine was found to decrease infection rate, *Pseudomonas aeruginosa* bacteremia, and mortality in adult burned patients[39].

Novak *et al.*[40] conducted a meta-analysis of 14 studies of glutamine (parenteral or enteral) in surgical or critically ill patients excluding bone marrow transplantation and premature infant studies. Glutamine use was associated with decreased infectious complications (RR = 0·81) and length of hospital stay (2·6 d shorter) and a trend towards lower mortality (RR = 0·78). In surgical patients, glutamine decreased infections and length of hospital stay, but did not affect mortality. Mortality benefits were seen in the critically ill, especially when glutamine was used parenterally at high dose. Murray and Pindora[41] conducted a meta-analysis of parenteral glutamine in bone marrow transplantation and showed decreased length of hospital stay (6·2 d shorter) and reduced development of positive blood cultures (RR = 0·23). They concluded that bone marrow transplant patients with gastrointestinal failure should receive parenteral glutamine.

Arginine

Oral arginine supplementation for 7 days post-surgery was associated with an increased number of circulating $CD4^+$ cells and an enhanced response of peripheral blood lymphocytes to mitogens by day 7[42]. Although the arginine-supplemented

group achieved a positive nitrogen balance (by day 6), there was no difference in clinical outcome compared with the placebo group. Intravenous arginine has been given in various conditions including in surgical and intensive care unit patients, although these did not evaluate immune outcomes (see 43 for references).

N-acetyl cysteine

Infusion of N-acetyl cysteine infusion into patients with sepsis increased blood glutathione concentration, decreased plasma concentrations of IL-8 and soluble TNF receptors, and improved respiratory function with a decreased number of days in intensive care[44,45]. While not affecting mortality rates, N-acetyl cysteine also shortened hospital length of stay.

Fatty acids

The lipid typically used in parenteral nutrition is soybean oil, in which n-6 linoleic acid comprises about 50 % of fatty acids present. A meta-analysis of total parenteral nutrition suggested that inclusion of lipids might be detrimental as far as complications are concerned[46], at least in very ill patients. A recent study in gastrointestinal surgery patients showed that the amount of n-6 fatty acids infused was one of two predictors of the length of hospital stay, the other being the delay in starting nutrition support[47]. Despite this, clinical trials with soybean oil based lipid emulsions provide conflicting evidence with some showing immunosuppressive effects, perhaps linked to poorer patient outcomes, while others show no effect on immune outcomes (see 23 for references). Nevertheless, there is an increasing view that using lipid emulsions entirely based upon soybean oil is not optimal. One approach to decreasing the linoleic acid content in lipid emulsions is partial replacement of soybean oil with long-chain n-3 fatty acid rich fish oil. This not only decreases n-6 fatty acid content but increases n-3 fatty acid provision. Several studies with fish oil containing lipid emulsions have been conducted in post-surgery patients, demonstrating decreased production of some inflammatory mediators (leukotriene B_4, TNF-α, IL-6) and better preservation of some immune functions (e.g. monocyte expression of HLA-DR, IFN-γ production) (see 10,23 for references). Some studies have also reported shorter post-operative stays in intensive care and in hospital with parenteral fish oil but most report no differences in infection rates or mortality (see 10,23). One study reported that perioperative fish oil decreased need for mechanical ventilation, readmission to intensive care, mortality and length of hospital stay[48] and similar findings were seen in the 230 post surgical patients within a large study of over 650 patients[47].

Fish oil containing parenteral nutrition has also been examined experimentally in septic patients[49,50]. Anti-inflammatory effects including lower blood leukocyte counts, serum C-reactive protein concentration and production of inflammatory cytokines by isolated endotoxin-stimulated mononuclear cells and increased production of leukotriene B_5 by stimulated neutrophils were reported. No clinical outcomes were reported in these studies. Koch and Heller[47] included 268 patients with abdominal sepsis in their study of n-3 fatty acid infusion. They found a significantly lower rate of infection, shorter lengths of intensive care unit and hospital stay and lower mortality in those patients receiving the highest amounts of fish oil.

A novel enteral formula used in patients with acute respiratory distress syndrome included n-3 fatty acids[51,52]. By 4 days of treatment the numbers of total leukocytes and of neutrophils in the alveolar fluid declined significantly in the n-3 fatty acid group and were lower than in controls[51]. Alveolar fluid IL-8 was lower in the experimental group compared with controls and leukotriene B_4 and TNF-α tended to be lower[52]. Arterial oxygenation and gas exchange were also improved and the treated patients had a decreased requirement for supplemental oxygen, decreased time on ventilation support and a shorter length of stay in intensive care[51]. Total length of hospital stay tended to be shorter in the experimental group and fewer patients developed new organ failure[51]. Mortality was 12 % in the experimental group and 19 % in the control group, but this difference was not statistically significant[51]. However, the experimental n-3 fatty acid formula also contained more medium chain triglycerides, β-carotene, taurine, carnitine, vitamin C and vitamin E than the control formula and hence it is not possible to ascribe the benefits to any particular nutrient. Two more recent studies also report benefits from n-3 fatty acid containing enteral formulae in acutely ill patients[53,54]. In one of these studies patients with acute lung injury received a control formula or a formula enriched in n-3 fatty acids and the n-6 γ-linolenic acid for 14 days[53]. By days 4 and 7 patients receiving the experimental formula showed improved oxygenation and a reduction in length of ventilation; there was no difference between the groups in mortality[53]. Most recently a formula similar to that used by Gadek et al.[51] was trialed in ventilated patients with severe sepsis and septic shock[54]. Patients receiving the experimental diet had significantly better oxygenation, more ventilator-free days, more intensive care unit-free days and less development of new organ dysfunctions. These improvements were associated with significantly lower mortality in the experimental group.

Antioxidant micronutrients

Several studies investigating parenteral or enteral (mainly parenteral) antioxidant micronutrients in post-surgery, burned or critically ill patients have been conducted and eleven were included in a recent meta-analysis looking at clinical outcomes[55]. The nutrients studied were zinc, copper, selenium, vitamin E, vitamin C, and *N*-acetyl cysteine alone or in various combinations. Most studies did not evaluate immune markers although some did. One study showed that parenteral zinc, copper and selenium did not influence blood lymphocyte subsets, neutrophil chemotaxis or T lymphocyte proliferation in burned patients in the ICU, although there was a decrease in IL-6 levels[56]. Several studies show improved clinical outcome with antioxidant micronutrients including fewer infections in burned patients[56,57] and fewer infections and organ failures in trauma patients[58]. The meta-analysis[55] showed reduced mortality (RR = 0·65) with antioxidants, but no effect on infectious complications. Parenteral antioxidants reduced mortality (RR = 0·56) but enteral did not, and effects on mortality were only seen when selenium was administered either alone or in combination (RR = 0·59). Although the lack of effect of antioxidant micronutrients on infectious complications suggests that they do not act via immune modulation, their anti-inflammatory actions might contribute to improved survival since hyper-inflammation is linked to organ failure. It is worth noting however that some individual studies do

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report reduced infections[56–58] an effect confirmed by a recent study in burned patients, which also found improved wound healing and reduced requirement for regrafting[59].

Mixtures of nutrients

Several enteral formulas using a combination of nutrients have been developed, typically including arginine, nucleotides and long-chain n-3 fatty acids. The majority of trials in surgical and critically ill patients have used the commercially-available product IMPACT® and a number of these studies reported immune and/or inflammatory outcomes (see 60 for references). Most studies reporting circulating lymphocyte numbers and subsets, and circulating immunoglobulin concentrations showed little difference between IMPACT® treated patients and controls, although some studies reported benefits on phagocytosis, respiratory burst, lymphocyte proliferation, HLA-DR expression on monocytes and cytokine production (see 60). These effects could be due to any single specified nutrient (i.e. arginine, nucleotides, long-chain n-3 fatty acids) or to a combination.

Meta-analyses of controlled, randomized clinical studies using IMPACT or similar immunonutrition formulae have identified significant reductions in infections and length of hospital stay but these effects are more evident in surgical rather than critically ill patients[61–65] and none of the meta-analyses shows a significant effect on mortality. Despite some clear statements to the contrary in the earlier meta-analyses[61–63], concern has been raised that these formulae may actually be detrimental in the seriously ill[66–68]. This is because some studies of immunonutrition mixtures in critically ill patients reported increased mortality[61–63]. The source of the concern is the high arginine content, which is thought to drive excessive production of nitric oxide[43,68]. A consensus recommendation for the use of enteral immunonutrition mixtures was made following a US summit[69]. The recommendations are as follows:

- Clearly established benefit in elective gastrointestinal surgery and in blunt or penetrating torso trauma
- Probable benefit in elective major surgery, severe head injury, burns $>$ 30 % body surface area, ventilator-dependent non-septic intensive care unit patients
- No benefit in patients able to resume oral intake within 5 days or in patients in intensive care unit for monitoring only

More recently the European Society for Clinical Nutrition and Metabolism (ESPEN) has established guidelines for use of enteral nutrition that included a consideration of "immunonutrient" mixes[70,71]. The guidelines for surgical patients[70] included:

- Use enteral nutrition with immuno-modulating substrates (arginine, nucleotides and long-chain n-3 fatty acids) perioperatively in:
- patients undergoing major neck surgery for cancer
- patients undergoing major abdominal surgery for cancer.

The guidelines for patients in intensive care[71] included:

- Immune modulating formulae (formulae enriched with arginine, nucleotides and long-chain n-3 fatty acids) are superior to standard enteral formulae in:
- Elective upper gastrointestinal surgical patients
- Patients with mild sepsis
- Patients with trauma
- Patients with acute respiratory distress syndrome (formulae containing omega-3 fatty acids and antioxidants)
- No recommendation for immune-modulating formulae can be given in burned patients due to insufficient data.
- ICU patients with very severe illness who do not tolerate more than 700 ml enteral formula per day should not receive an immune-modulating formula enriched with arginine, nucleotides and omega-3 fatty acids.
- Glutamine should be added to standard enteral formula in:
- Burned patients
- Trauma patients

Conclusion

Surgery, trauma, burns and injury are insults that can induce an excessive inflammatory response, which may be associated with a later immunosuppressed state. Hyperinflammation can lead to organ damage and failure while immunsuppression increases susceptibility to infection. The resulting septic syndromes are associated with significant morbidity and mortality. A range of nutrients are able to modulate inflammation and its partner oxidative stress and to maintain or improve immune function and the intestinal barrier. These include several amino acids, antioxidant vitamins and minerals, long-chain n-3 fatty acids and nucleotides. Experimental studies support a potential role for each of these nutrients in surgical, injured or critically ill patients. There is good evidence that parenteral or enteral glutamine influences immune function in such patients and that this is associated with clinical improvement. This conclusion is supported by meta-analyses and recent guidelines. Evidence is also mounting for the use of long-chain n-3 fatty acids in surgical and septic patients, but more evidence of efficacy is required in these groups and there is a lack of studies in other patient groups that might benefit. Mixtures of antioxidant vitamins and minerals are also clinically effective, especially if they include selenium. Their action appears not to involve improved immune function, although an anti-inflammatory mode of action has not been ruled out. Enteral immunonutrient mixtures, usually including arginine, nucleotides and long-chain n-3 fatty acids have been used widely in surgical and critically ill patients. Evidence of efficacy is good in surgical patients; this conclusion is supported by meta-analyses and recent guidelines. However whether these same mixtures are beneficial, or should even be used, in critically ill patients remains controversial. While some studies show decreased mortality with such mixtures, several show increased mortality. There is a view that this is due to a high arginine content driving nitric oxide production. It is interesting that these mixtures do not typically include glutamine, which is clearly of benefit. It seems likely that novel immunonutrient mixtures will be developed in the future. Clearly more research using larger, better designed trials will be needed to see whether these benefit immune function, with an improved clinical benefit in vulnerable patients.

Conflict of interest statement

The author has research funding from B. Braun Melsungen, receives consultancy fees from Royal Dutch Numico and speaking fees from B. Braun Melsungen and Fresenius Kabi.

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