Clinical nutrition

— using nutraceuticals in critical care

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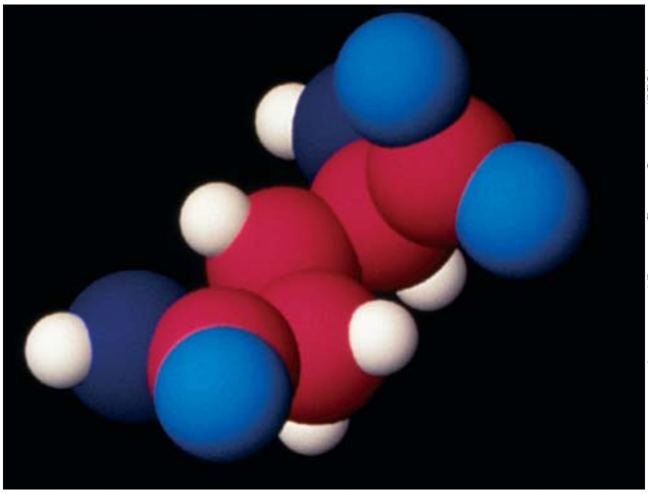
Various nutrients are believed to modulate the immune system and might therefore have a role in treating critically ill patients. The second part of this month's special feature examines the evidence for and against their inclusion in parenteral and enteral feeds



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Glutamine molecule: glutamine acts as a "nitrogen shuttle", protecting the body from high circulating levels of ammonia

Promoting survival and speeding up the recovery of patients are two of the main objectives of critical care. One potential way of achieving these is to modulate the patient's immune system. Among other benefits, this can help treat sepsis or reduce the likelihood of it occurring.

Certain nutrients, such as arginine, glutamine, omega-3 fatty acids, nucleotides and branched chain amino acids are believed to be immunomodulators. In particular, feeds containing glutamine have been advocated for critically ill patients being fed parenterally, with mixtures of arginine, glutamine and other nutrients being suggested for enteral use. The use of these compounds (dubbed "nutraceuticals") in feeds, however, remains controversial.

This article looks into the theories behind nutraceuticals and examines the main evidence for and against their use.

Glutamine

Glutamine is a five-carbon amino acid with two amino moieties — one from its precursor, glutamate, and one from free ammonia in the bloodstream.[1,2] It is estimated as accounting for 20–35 per cent of total circulating amino acid nitrogen, making it the most abundant free amino acid.[1,3] As a non-essential amino acid, glutamine is synthesised and stored in skeletal muscle by two enzymes — glutamate synthetase and glutaminase. Branched chain amino acids (ie, isoleucine, leucine and valine) can be metabolised to glutamine — hence their potential role in immunonutrition.[1]

Glutamine acts as a "nitrogen shuttle", accepting ammonia where there are high concentrations and donating it to other tissues where it is needed to form other amino acids, amino sugars, nucleotides and urea.[2] This protects the body from high circulating levels of ammonia, a neurotoxin associated with, for example, hepatic encephalopathy.

Glutamine is believed to help prevent or treat sepsis in two main ways:

- By protecting the integrity of the gut, thereby preventing microbes and endotoxins from passing into the blood and contributing to sepsis
- By promoting lymphocyte activation, thereby enhancing the ability of the immune system to fight infection

Further details of these mechanisms, together with information about some clinical studies that have been undertaken, are as follows:

Gut integrity The permeability of the endothelial lining of the gut wall is said to be increased in critical illness, allowing microbes and endotoxins to pass through the intestinal wall into the blood stream (ie, translocation). Evidence for this includes that *Candida albicans, Staphylococcus epidermidis, Escherichia coli, Pseudomonas aeruginosa* and *Enterococci* are seen frequently in patients with septic multiple organ failure syndrome, and are all routinely found in the gut flora.[1] Rapidly dividing cells such as those found in the gut use glutamine as their preferred fuel for regeneration,[3] and so glutamine supplementation could be expected to help the situation. In addition, as a precursor glutathione, an antioxidant involved in protecting tissues from free-radical injury, glutamine is also thought to protect the gut from mucosal damage following shock and post-ischaemia reperfusion.[4]

It should be pointed out that these mechanisms remain controversial. Most studies showing that parenteral nutrition causes beneficial morphological and functional changes to the intestine have been carried out in animals and it is not known whether the results can be extrapolated into humans. There is also controversy over whether bacterial translocation is an issue in humans.[5]

A clinical study has, however, shown that patients receiving glutamine-enhanced nutrition for nine days were significantly less likely to suffer mucosal atrophy (as assessed using a modified "D-xylose test") than those not receiving glutamine (mucosal atrophy being typically associated with long-term parenteral feeding).[6] It is worth mentioning that this was a small study, consisting of 12

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patients only. The appropriate daily glutamine requirement during critical illness remained unresolved in the study — 12–15g was considered as a physiological amount.

Lymphocyte activation Lymphocytes need glutamine in order to proliferate in response to antigenic challenge.[7] In particular, it is the latter phases of activation that require glutamine supplementation. Expression of the late-stage surface activation markers (ie, "C25", "CD45RO" and "CD71") and production of interferon gamma and tumour necrosis factor alpha (TNFα) required an exogenous glutamine supply of at least 0.5mmol/L, with higher concentrations of glutamine further enhancing proliferation.[7]

An improvement in lymphocyte counts and proliferation at "day 10" has been shown in rats with sepsis.[8] Improvements in the lymphocyte function of catabolic patients supported with exogenous glutamine have also been demonstrated.[9]

Other parenteral clinical studies The effects of parenteral glutamine on short- and long-term survival rates in critical care patients has been studied.[10] Researchers found a significant improvement in the six month survival rate in a group of critically ill patients who had APACHE II [Acute Physiology and Chronic Health Evaluation] scores of 11 or greater and who could not tolerate enteral feeding and who received glutamine-supplemented parenteral nutrition, as compared with a matched group receiving parenteral nutrition without glutamine supplementation. The total ICU (intensive care unit) and hospital costs per survivor were also reduced by 50 per cent in the group receiving glutamine. There were no significant differences in short-term survival rates.

This study was among those used to compile Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients.[11] These recommend that, where available, glutamine supplementation of parenteral nutrition be given to critically ill patients. According to the guidelines, there is currently not enough data to recommend giving intravenous glutamine to patients who are being enterally fed or enteral glutamine to patients other than burn and trauma patients in whom trial data suggest some reduction in mortality and infectious complications.

Arginine

Arginine is a non-essential amino acid that potently stimulates growth hormone, glucagon, prolactin, insulin release and collagen synthesis and is also a precursor for nitric oxide.[12] It is produced in the kidneys using citrulline (produced from glutamine metabolism in the gut) as a precursor.

In patients with sepsis, plasma arginine levels are decreased. The correlation is such that arginine levels have been used as an index for assessing the severity of sepsis and the survival of septic patients. A wide range of studies looking at the benefits of arginine (in combination with other immunonutrients such as omega-3 fatty acids and nucleotides) in enteral feeds given to critically ill patients have been published. These will be discussed later.

Nucleotides

Nucleotides are units made up of varying combinations of purine and/or pyrimidine with ribose and/or deoxyribose and a phosphate group. They are used in the synthesis of DNA, RNA, ATP, cyclic AMP and numerous other essential substances.

It is believed that nucleotides have immunomodulatory properties. Evidence for this includes various studies showing that immunosuppression in protein-depleted animals can be reversed by administering nucleotides.[12] However, in most of the experiments, nucleotide depletion was induced by starvation and, therefore, such studies might prove only that some nucleotides are required to be in the diet, and therefore do not necessarily provide evidence for supplementing standard diets with nucleotides.

Fatty acids

Omega-3 fatty acids are derived from alpha-linoleic acid (an essential fatty acid) and are precursor for eicosanoids (such as prostaglandins, leukotrienes and platelet-activating factor). Omega-6 fatty acids are derived from linoleic acid (another essential fatty acid). The eicosanoids produced from omega-6 fatty acids have more potent inflammatory effects than those produced from omega-3 fatty acids. Substituting omega-3 fatty acids (fish oil) for omega-6 fatty acids might therefore be expected to have anti-inflammatory effects,[12] inflammation being associated with shock, sepsis and organ failure.

Fish oils have been shown to be beneficial in humans with chronic inflammatory conditions, such as psoriasis and rheumatoid arthritis. Similarly, healthy volunteers given a diet supplemented with omega-3 fatty acids have been shown to produce less interleukin(IL)-1a, IL-1b and tumour necrosis factor, all of which are contributors to the systemic inflammation and hypermetabolism associated with sepsis. A burn model using guinea pigs suggests that the "post-burn" reduction in metabolic rate and weight loss can be reduced by substituting fish oils for safflower oil in the diet. Such a substitution also raises serum transferritin levels and cell-mediated immunity and lowers levels of serum complement (C3).[12]

Enteral studies

As mentioned above, various reports about the use of enteral feeds containing arginine in combination with other immunonutrients have been published. These studies, however, are of variable quality and often include only a small number of patients from specific cohorts, making it difficult to extrapolate findings to other situations.

Because of the limitations of the separate studies, several authors have published systematic reviews or meta-analyses of the available data on enteral immunonutrition. The pooling of a number of similar small studies aims to identify real trends and improve the power of the statistics in order to draw conclusions. The findings of these various reviews are set out in Panel 1 (p16).

Even with such reviews and meta-analysis studies, the evidence for forming a decision on whether or not to use immunonutrition is far from perfect. In particular, most of the work has been done by enthusiasts for the particular substance under consideration[13] and so there is a tendency for published results to show a variety of positive effects on a variety of end points, with authors being less likely to publish work showing negative outcomes. In addition, where there are no statistically significant differences between treatment and control groups, a number of authors have chosen to use subgroup analysis. Restricting the data assessment to a small part of the original cohort runs against the principles of "intention to treat" analysis and may disrupt the demographic matching of the treatment and control groups. It should be noted that it is difficult to carry out good quality clinical trials in a critical care setting — especially in terms of blinding staff to the treatment they are giving.

The results of the meta-analysis and other studies are also conflicting. In particular, there is a question mark over the safety of using enteral feeds containing immunonutrients in critical care patients, especially those suffering from sepsis. Provision of arginine might worsen hypotension by increasing the capacity of inducible nitric oxide synthase in the endothelium of peripheral organs. It might also inhibit the synthesis of endogenous glutamine available for the gut, glutamine potentially having a role in preventing and treating sepsis (see above). In addition, suppressing inflammation (eg, using omega-3 fatty acids) might not always be of benefit because it can leave the host unable to fight invading micro-organisms.[13] Moreover, because all these studies have been carried out with combinations of immunonutrients, it is not known if harm is associated with one nutrient or a particular combination.[14] Much more work needs to be done on the optimum mix of nutrients, the concentrations of nutrients and the total doses required, not least

Panel 1: Main conclusions from systemic reviews or meta-analysis studies about the use of enteral feeds supplemented with immunonutrients in critically ill patients

A
- No overall effect on mortality rates
- Significant reduction in the relative risk of acquiring an infection
- Significant reduction in the number of days of mechanical ventilation patients need
- No significant reduction in length of ICU stay, but the overall length of hospital stay was reduced by 2.9 days
- No increase in diarrhoea
- On average the control group received 1.6kcal/kg/day more than the treatment group but the treatment group received 0.04g/kg/day more nitrogen than the control group
- Benefits were most marked in the surgical subgroup

B
- "Grade A" recommendation made for using immunonutrition to reduce infectious complications and length of stay in ICU patients
- "Grade B" recommendation made for using immunonutrition to decrease mortality
- Methods of predicting which patients will benefit from immunonutrition need further work

C
- No mortality advantages
- Reduction in the number of patients having infectious complications
- Reduction in the length of hospital stay
- Subgroup analysis showed that feeds with a high arginine content performed better that other formulas (other formulations might actually be associated with higher mortality and complication rates)
- Effects of immunonutrition in critically ill patients may differ from those in elective surgical patients
- Stimulating the immune system of critically ill patients might do more harm than good
- Although it might be useful in elective surgical patients for decreasing infectious complications and length of hospital stay, enteral immunonutrition cannot be recommended for all critically ill patients

D
- Enteral feeds with arginine and other nutrients show a lack of treatment effect with respect to mortality and infection
- Because there are concerns about increased mortality in patients with sepsis and because immunonutrition is expensive (compared with standard feeds), enteral immunonutrition should not be routinely given to critically ill patients. Enteral glutamine should be considered for those with burns and trauma
- Evidence in ARDS patients shows decreased oxygen requirement and reduction in mortality
- The use of products with fish oils, borage and antioxidants should be considered in patients with ARDS (this cannot be extrapolated to fish oils alone)

Study A is reference 15, study B is reference 16, study C is reference 17 and study D is reference 11. "ICU" means intensive care unit and "ARDS" means adult respiratory distress syndrome. Gradings in study C are those used in the Pulmonary Artery Consensus conference, grade A being highest.

because feeds supplemented with immunonutrients are considerably more expensive than "standard" feeds.

Techniques to predict which cohort of patients will respond well also need to be honed. Some studies have already been carried out with this in mind, and suggest that patients with APACHE II scores of between 10 and 15 respond better than those with scores of lower than nine or greater than 16 (the greater the score, the more severe the illness and percentage risk of death associated with it). However not all ICUs will have access to a patients' APACHE II scores until well after the patient has arrived there. A possible alternative method that has been suggested is to target patients who have endotracheal tubes and who are likely to require intubation for several days.[16]

There is a need for well designed, large scale, double-blinded randomised controlled trials to clarify the safety and efficacy issues. Until these have been performed, the case for using immunomodulators in enteral regimens for critically ill patients does not seem to be made out. There appears to be more reason to consider them in surgical and trauma patients.

Conclusion

Immunonutrition remains controversial. There is some evidence that this type of feed may decrease infectious complication rates and reduce length of hospital stay, particularly in surgical and trauma patients. However, there are cost implication, with feeds supplemented with immunonutrients being substantially more expensive than standard feeds.

References

1. Hall JC, Hell K, McCauley R. Glutamine. British Journal of Surgery 1996: 83;305–12.
2. Miller AL. Therapeutic considerations of L-glutamine: A review of the literature. Alternative Medicine Review 1999;4:239–47.
3. Ziegler TR, Szeszycki EE, Estívariz CF, Puckett AB, Leader LM. Glutamine: from basic science to clinical applications. Nutrition 1996;12(suppl):S68–70.
4. Fürst P, Pogan K, Stehle P. Glutamine dipeptides in clinical nutrition. Nutrition 1997;13:731–7.
5. Buchman A. Glutamine: is it a conditionally required nutrient for the human gastrointestinal system? Journal of the American College of Nutrition 1996;15:199–205.
6. Tremel H, Kienle B, Weilemann LS, Stehle P, Fürst P. Glutamine dipeptide–supplemented parenteral nutrition maintains intestinal function in the critically ill. Gastroenterology 1994;107:1595–601.
7. Heberer M, Babst R, Juretic A, Gross T, Hörig H, Harder F, Spagnoli G. Role of glutamine in the immune response in critical illness. Nutrition 1996;12(suppl): S71–72.
8. Yohida S, Hikida S, Tanaka Y. Effect of glutamine supplementation on lymphocyte function in septic rats. Journal of Parenteral and Enteral Nutrition 1992;16(suppl):S30.
9. O'Riordan M, De Beaux A, Fearon K. Effect of glutamine on immune function in the surgical patient. Nutrition 1996;12(suppl):S82–4.
10. Griffiths RD, Jones C, Palmer TE. Six-month outcome of critically ill patients given glutamine-supplemented parenteral nutrition. Nutrition 1997;13:295–302.
11. Heyland DK, Dhaliwal R, Drover J, Gramlich L, Dodek P. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. Journal of Parenetral and Enteral Nutrition 2003;27:L355.
12. Barton R. Immune-enhancing formulas: are they beneficial in critically ill patients. Nutrition in Clinical Practice 1997;12:51–62.
13. Rennie M. Critical to feed - but what? British Journal of Intensive Care 2000;10:77
14. Heyland DK. Immunonutrition in the critically ill patient: more harm than good? Journal of Parenetral and Enteral Nutrition 2001;25:S51–5.
15. Beale RJ, Bryg DJ, Bihari DJ. Immunonutrition in the critically ill: a systematic review of clinical outcome. Critical Care Medicine 1999;27:2799–2805.
16. Oltermann MH, Rassas TN. Immunonutrition in a multidisciplinary ICU population: a review of the literature. Journal of Parenteral and Enteral Nutrition 2000;25(suppl):S30–5.
17. Heyland DK, Novak F, Drover JW, Jain M, Su X, Suchner U. Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. Journal of the American Medical Association 2001;286:944–53.