

Original

Immunonutrition in clinical practice: what is the current evidence?

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Abstract

The clinical trials of immunonutrition that we have undertaken have often been small, single centre studies. They have often been of limited statistical power and have often included patients with a variety of underlying disease states and at different points in the disease process. Three meta-analysis and a consensus statement in conjunction with a systematic review, have been performed in an attempt to overcome many of these limitations and understand further the clinical place for immunonutrition. However, there are still many questions regarding the place of immunonutrition in clinical practice that we still do not understand or have definitive answers to.

For example, do we really know what is the optimal combination of nutrients and in what quantities they should be provided? Do we understand any potential interactions that might occur between these nutrients? What is the effect of the patients nutritional state? When and for how long should immunonutrition be provided? What is the impact of the patients' underlying disease process and how does this interact with the provision of immunonutrition?

At the present time whilst there is some indication and evidence as to which patients might benefit most, and as to those who may not benefit or even suffer detrimental effects from immunonutrition, we still can not answer these questions with any definitive authority. It is essential now that we undertake large well designed, well controlled multicentre studies with adequate statistical power to answer these questions. The indications are that immunonutrition has the potential to help patients but its place must be more clearly defined before its widespread acceptance into clinical practice is based on sound scientific evidence.

(*Nutr Hosp* 2004, 19:325-332)

Key words: *Clinical trials. Immunonutrition.*

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Recibido: 2-VIII-2004.
Aceptado: 10-IX-2004.

INMUNONUTRICIÓN EN LA PRÁCTICA CLÍNICA: ¿CUÁL ES LA EVIDENCIA ACTUAL?

Resumen

Los ensayos clínicos sobre inmunonutrición que se han realizado han sido en general pequeños y unicéntricos. Su poder estadístico se ha visto limitado y con frecuencia se han incluido pacientes con situaciones patológicas subyacentes múltiples y en diferentes puntos del proceso de la enfermedad. Se han realizado tres meta-análisis y una valoración de consenso, junto con una visión sistemática en un intento de superar muchas de las limitaciones y para entender mejor las situación clínica de la inmunonutrición. Sin embargo, hay todavía gran número de incógnitas en relación con el papel de la inmunonutrición en la práctica clínica, que todavía no entendemos y para los que no tenemos contestaciones definitivas.

Por ejemplo, ¿conocemos en realidad cuál es la combinación óptima de nutrientes y qué cantidades deben ser administradas? ¿Entendemos las interacciones potenciales que pudieran suceder entre estos nutrientes? ¿Cuál es el efecto sobre el estado nutritivo del paciente? ¿Cuándo y durante cuánto tiempo debe ser administrada inmunonutrición? ¿Cuál es el impacto de la enfermedad subyacente y cómo interactúa ésta con la de inmunonutrición?

En el momento actual, hay alguna indicación y evidencia en relación con los pacientes que se benefician más y en relación con cuales no se benefician o incluso puedan sufrir efectos detrimentales de la inmunonutrición, pero aún no podemos responder a estas preguntas con una autoridad definitiva. Es esencial que se lleven a cabo estudios multicéntricos controlados, bien diseñados con poder estadístico adecuado para responder a estas preguntas. La inmunonutrición tiene potencial para ayudar a los pacientes pero su lugar deberá ser clarificado aún más antes de su aceptación universal en la práctica clínica basada sobre una evidencia científica sólida.

(*Nutr Hosp* 2004, 19:325-332)

Palabras clave: *Ensayos clínicos. Inmunonutrición.*

Introduction

For the last 30 years, interest has focused on the effects of loss of body weight in patients with a variety of disease states, but particularly in those with severe and critical illnesses. The impairments of immune function and organ function that occur in these patients who have lost body weight have been well recognised for many years¹. The correlation between loss of body weight and morbidity and mortality in patients undergoing surgery has also been well documented previously^{2,3}. Therefore, in view of these many randomised trials have been undertaken to determine what impact nutritional supplementation, given enterally or parenterally, might have on both the incidence of complications and mortality in patients undergoing surgery or in those who have sustained a critical illness.

Although many studies have been undertaken, the results have often been difficult to interpret for various reasons. For example, different patient populations, differing nutritional interventions and for variable periods of time in the pre-operative, post-operative and perioperative periods, have all been studied. In trying to understand the role of nutritional support more clearly meta-analyses and detailed analyses have been undertaken in attempt to overcome some of these limitations of the studies^{4,6}. The most recent meta-analyses have suggested that such an approach can reduce the risk of post-operative complications in patients undergoing major surgery. However, any effect on mortality has been more difficult to demonstrate and, in fact, the evidence suggests that there is no reduction in mortality, in contrast to that in morbidity^{4,6}.

It is important to remember that such approaches to nutritional support have really focused on the provision of nitrogen and calories, together with other essential nutrients, to replace or supplement what it is expected to be a patient's normal oral intake, with or without considering the additional metabolic demands placed on the patient by their underlying illness. However, the recent developments in nutritional science have allowed a more full appreciation and understanding of the roles and function of a variety of nutrients. This knowledge is not only what is necessary to maintain health and organ function, but also what can happen if nutrients are given in amounts in excess of what was recognised previously as that being required for the maintenance of bodily function and homeostasis.

Certain key nutrients, if provided in excess of what is their normal daily requirement will effect a modulation of immune, inflammatory and metabolic pathways. The term "nutritional pharmacology" has been used to describe this approach. When nutrients are used specifically to modulate the immune system, although this is clearly interlinked with inflammatory and metabolic pathways, it is termed "immunonutrition"^{7,8}. Many nutrients will modify these processes but in this regard, most interest has focussed on amino

acids such as arginine and glutamine, fatty acids, ribonucleotides and certain trace elements. These individual nutrients have been discussed extensively elsewhere⁷⁻¹⁵ and will not be further discussed individually in this paper. Some of the key actions of these nutrients on the immune system are listed in table I.

It is not surprising that preliminary trials have been carried out to determine if any of these nutrients themselves can have clinically beneficial effects. However, at the present time, there is no evidence to support the use of any of these as single nutrients in clinical practice, perhaps with the exception of glutamine¹⁶. A recent meta-analysis of 14 clinical trials of glutamine supplementation which has been given to critically ill, or "surgical" patients, has suggested that there might be beneficial effects. The results showed that patients receiving glutamine supplementation had a reduction in their risks of developing an infectious complication and in the group of "surgical" patients there was a significant reduction in the length of their hospital stay¹⁷.

The most interesting results, however, have come from the clinical trials where combinations of these key nutrients have been combined together as commercially available immunonutritional regimens and which are for the enteral route. Most commonly, Impact[®] and Immunaid[®] have been evaluated. The key nutrients provided focused on arginine, glutamine, n-3 essential fatty acids and ribonucleic acid, but in diffe-

Table I
Modulatory effects of key nutrients

Arginine

- Increased responses of T cells to mitogenic stimulation and delayed type hypersensitivity responses
- Increases in NK and LAK cell numbers
- Increases in circulating cytokine levels
- Increased nitric oxide production
- Enhanced wound healing and collagen synthesis
- Stimulates release of prolactin, insulin and glucagon

Glutamine

- Increased responses of T cells to mitogenic stimulation
- Increased B lymphocyte differentiation and antibody production
- Increased macrophage phagocytosis and neutrophil function
- Increased cytokine production
- Maintenance of the intestinal mucosal barrier function

Fatty acids

- Suppression of T cell proliferative responses to polyclonal mitogens
- Reductions in NK and LAK cell activity
- Impaired cytokine production
- Decreased neutrophil and monocyte chemotactic responses and superoxide production
- Alterations in cell membrane function and intracellular signalling

ring compositions and quantities in the different formulations that are available (table II). The evidence base for the rationale of the composition of these immunonutritional regimens is unclear and the optimal combination and quantities for each of the nutrients is debatable. Perhaps, the 30g per day of arginine has some scientific basis in that a dose response study had indicated previously that this had a greater effect than did lower doses¹⁸. However, as regards other nutrients, the value of combinations when compared with single nutrients, the potential interactions between nutrients, and potential synergistic or antagonistic effects, there is even less evidence for their use in their current way.

Despite these considerations regarding the role of each individual nutrient, initial studies compared the effects of these combination of immunonutrients against readily available nutritional regimens which were commonly used in clinical practice^{19,20}. Although the amounts of nitrogen and calories were usually comparable between the formulations, it was the composition of specific nutrients that differed.

These immunonutritional combinations did modulate immune function in ways that would be expected to be beneficial. The provision of immunonutritional regimens resulted in enhancements of a variety of immune functions, particularly lymphocyte responses to mitogenic stimulation, phenotypic analyses suggesting enhanced lymphocyte sub-set numbers and functionally beneficial types of lymphocytes, in addition to increased levels of circulating antibodies^{19,22}. These key effects reported from these studies are summarised in table III. These results from these immunological studies were encouraging but the vital question regarding immunonutrition for use in clinical practice must be whether or not these changes in immunological parameters will translate into a better clinical outcome for patients.

Clinical trials of immunonutrition in patients

A series of randomised clinical trials have been undertaken to evaluate the role of these immunonutritional

Table II
Nutrient composition of two immunonutrition regimens used in clinical trials

	<i>Impact®</i>	<i>Immun-Aid®</i>
AID*		
Volume (ml)	1,000	1,000
Protein (g)	56	80
Arginine (g)	12.5	14
Glutamine (g)	-	9
Branched chain amino acids	-	20
Nucleic acids (g)	1.23	1
Fat (g)	27.8	22.0
N-3 EFA (%)	10.5	4.5
Selenium (ug)	46	100

Table III

The effect of immunonutritional regimens on immune function in clinical trials

- Increased activation of T lymphocytes
- Increased Natural killer cells
- Increases in Lymphocytes and percentage of T helper cells increased
- Polymorphonuclear phagocytosis enhanced
- Respiratory burst enhanced
- Circulating levels of IgG and IgM, and interferon gamma levels increased

nal regimens in a variety of clinical settings. Most commonly patients undergoing surgery for upper gastrointestinal cancer, patients with sepsis and critical illness and patients who have sustained major burns, have been studied and the results from these trials have been reported in detail previously^{20,22-44}.

Although the patient groups that have been studied have differed, the end-points of these trials have been comparable. In terms of morbidity, a key outcome measure has been the incidence of infectious complications that occur in these patients. Also, other outcomes that have been evaluated commonly in many of the trials, have included the effects on hospital stay, intensive care unit stay and patient mortality. Nevertheless, interpretation of the results is difficult because of the many variable features in each of these trials, particularly regarding patient type and immunonutritional provision. For example, the underlying pathophysiological states, the baseline nutritional status, the type and quantity of immunonutrition provided and the timing of provision of immunonutrition are all important factors which have the potential to affect the results of each trial.

Meta-analysis of clinical trials of immunonutrition which have evaluated clinical outcomes

In an attempt to further understand what effects immunonutrition has on clinical outcome, three meta-analyses⁴⁵⁻⁴⁷ and a more recent systematic review⁴⁸ and consensus statement have been reported during the last five years. These analyses have examined the published trials in some depth and try to draw some conclusions that can be applied to clinical practice.

In 1999, the first meta-analysis reported the results from 1,009 patients who had participated in eleven clinical trials⁴⁵. The underlying pathological states that these patients had were frequently different but the patients could be categorised as falling into two broad groups; those undergoing surgery for upper gastrointestinal cancer and those patients who were critically ill for a variety of other reasons including trauma, sepsis and major burns. Although there were differences in the methodological quality of the studies, three of

these 11 trials had a difference in the nutritional intake of the experimental and control groups of patients. There was an increased intake of nitrogen in the immunonutrition groups when compared with the control groups and clearly this may have affected the outcomes of the trials.

Nevertheless, when these trials were analysed together, there did appear to be clinical benefits in those patients who received immunonutrition. In particular, immunonutrition was associated with a reduction in the risks of developing an infectious complication (defined as intra-abdominal abscess, major wound infection, septicaemia, pneumonia). The magnitude of this effect was substantial, with the relative risk being reduced to 0.47 (95%CI 0.32-0.70) by the use of immunonutrition. A sub-group analysis also examined separately at those patients with gastrointestinal cancer, but not including those with critical illness. Again, there was a significant reduction in infectious complications in patients receiving immunonutrition (relative risk 0.47, 95%CI: 0.30-0.73). Another benefit to accrue in these patients from immunonutrition was that their length of stay in hospital was also reduced. Although this was only by 2.5 days (95% CI, -4.0 to -1.0 days), nevertheless, there is a potential financial saving which may also be important⁴⁵.

Did the provision of immunonutrition have any effect on mortality in these patients? Of the 11 studies, only seven of these reported effects on mortality. The overall relative risk in patients receiving immunonutrition was 1.77 (95% CI, 1.00 to 1.32)⁴⁵. Although this was higher in these patients it was not statistically significant. Furthermore, there were no deaths in either the experimental or control groups in four of the trials and only one showed a significant difference, with there being an increase in patients receiving immunonutrition. Closer examination of this latter study revealed that there had been a randomisation error with an increased number of patients with higher APACHE II scores in the immunonutrition group. It should also be remembered that the patients in this study were those with sepsis or a systemic inflammatory response syndrome and the potential significance and importance of this with respect to immunonutrition will be highlighted later.

As reports of more trials of immunonutrition began to appear in the literature it wasn't surprising that an update of the first meta-analysis were published⁴⁶. As an interim step, Beale et al⁴⁶ then included four more trials to give a total of 15 then available for statistical analysis. The results were compared to those previously reported⁴⁵ in that immunonutrition was associated with a reduction in infectious complications by approximately one half, but there was no significant effect on mortality⁴⁶.

More importantly, by 2001, a total of 22 randomised controlled trials of 2,419 patients were suitable for another more detailed, examination⁴⁷. The trials had included patients who had either undergone elective

surgery or who were critically ill, which was defined as being cared for in a "critical care environment". The immunonutrition given to patients had to include at least two of the four most commonly used immunoenhancing nutrients (arginine, glutamine, n-3 fatty acids or nucleotides). There were also a large enough number of studies to be able to carry out subsequent sub-group analyses which compared the methodologically better studies with the remainder, and also compared those trials where patients received immunonutritional regimens which had higher arginine contents with the others who did not.

When considering the results of this analysis in terms of all trials together and the effect on infectious complications, similar effects as noted before emerged⁴⁷. In the 18 trials where infectious complications were reported, patients receiving immunonutrition had less infectious complications (pneumonia, wound infections, intra-abdominal abscesses, urinary tract infection, intravenous line sepsis). Their relative risk of infectious complications was 0.66 (95% CI, 0.54 to 0.80). Furthermore, the provision of immunonutrition was also associated with a reduction in their length of stay in hospital by some 3 days (95% CI, -5.6 to -1.0 days) from the 17 trials where this was reported. As observed previously, when mortality was examined there was no difference between those patients receiving immunonutrition or those in the control groups (Relative risk 1.10, 95% CI, 0.93 to 1.31) (see table IV).

An important sub-group analysis separated out and examined those patients who had a critical illness and then compared them with those who had undergone elective surgery. Here, a different picture emerged because in the critically ill patients there was no reduction in infectious complications associated with the provision of immunonutrition (RR, 0.96, 95% CI, 0.77 to 1.20)⁴⁷. In contrast, there was a significant reduction in infectious complications in the elective surgical patients who were given immunonutrition (RR, 0.53, CI, 0.42 to 0.68). Interestingly, in both groups of patients there was a significant reduction in hospital stay which was of comparable length between the two groups, but there was no effect on mortality in either type of patients⁴⁷.

Perhaps the most interesting and thought-provoking data to emerge from this meta-analysis was the

Table IV
Effects of immunonutrition on clinical outcome in all patients considered together

	Number of trials evaluated	Relative risk	95% Confidence interval (CI)
Mortality effect	22	1.10	0.93 to 1.31
Infectious complications	18	0.66	0.54 to 0.80
Length of hospital stay effect	17	-3.3 days	-5.6 to -1.0 days

Taken from Heyland et al (47).

effect of immunonutrition on mortality. As already discussed, there was no effect on mortality overall, or in the sub-groups of patients with critical illness or those in the elective surgery group. However, when the patients who had received immunonutritional formulations with higher arginine contents were examined then a different picture emerged. The relative risk of mortality was 2.13 (95%CI, 1.08-4.21) in patients receiving a higher arginine content type of immunonutrition. In contrast, patients with lower arginine immunonutritional regimens had a relative risk of death of 1.03 (95%CI, 0.75-1.41). Furthermore, this former group of patients also had a reduction in risk of infections complications and a shorter hospital stay than did patients in the latter group (see table IV)⁴⁷.

The other major subgroup analysis which was of those studies with the better methodological designs and performance. Again, of some concern was that the mortality analysis from these studies gave a relative risk of 1.46 (95%CI, 1.01-2.11). Whilst these results are of some concern, it is important to remember that they are from a subgroup analysis with all the attendant statistical limitations. Nevertheless, as discussed previously, it is important to consider the implications of this further and this will be discussed later in this paper.

Further understanding of the effect of the patients underlying disease state on clinical outcomes

In trying to take the understanding of the role and potential for immunonutrition to affect the clinical outcomes from the treatment of critically ill patients, most recent systematic review analysed the results from 26 clinical trials of enteral immunonutrition⁴⁸. However, the results from this analysis were then subjected to review by a panel of experts. These experts then considered the appropriateness of these results for clinical practice and made recommendations for the use of immunonutrition. The general overall results from this analysis are shown in table V, but patients receiving immunonutrition had reductions in infection rates, intra-abdominal abscesses, nosocomial

pneumonia and bacteraemia. Furthermore, these patients also had reductions in their length of time in hospital, length of stay in the intensive care unit and length of time for which they required mechanical ventilation but there was no effect on mortality⁴⁸.

These authors then attempted to answer five questions which were thought to be of major importance for clinical practice and with respect to certain categories and subgroups of patients categorised according to their underlying pathology. Their findings and interpretations are summarised below:

In response to the question as to what effect of immunonutrition had on nosocomial infection in critically ill patients, then there was a reduction in patients undergoing elective surgery (bacteraemias, intra-abdominal abscesses) but no effect on wound infection or nosocomial pneumonia. In addition, in patients who had sustained a major burn, there was a reduction in the incidence of nosocomial pneumonia.

The effect of immunonutrition in reducing hospital stay times was beneficial in the patients who were undergoing surgery and intensive care unit stay was also reduced in both patients who had undergone surgery and those who had sustained a major trauma. The authors also concluded that there was no convincing effect of immunonutrition on the incidence of multiple organ dysfunction or adult respiratory distress syndrome, and no effect on in-patient mortality. Finally, there was no evidence to answer the question as to the effect of immunonutrition on reduction of the financial costs in patients with critical illness⁴⁸.

Importance of timing of the provision of immunonutrition

An important consideration when examining these clinical trials is what effect the timing of the provision immunonutrition might have on clinical outcome. This might be extremely important in determining what clinical outcomes may occur in such patients. Immunonutrition differs from conventional nutritional support in that it is not just simply the provision of nutrients, nitrogen, calories etc., to patients who are either not able to take in nutrients normally or who are

Table V
Effect of immunonutrition in "critically ill" patients considered alone

	Odds ratio	95% Confidence interval
Intra-abdominal abscesses	0.26	0.12-0.55
Nosocomial pneumonia	0.54	0.35-0.84
Bacteraemia	0.45	0.35-0.84
Mortality	1.10	0.85-1.42
Reduction in time on mechanical ventilation	2.25 days (mean)	0.5-3.9 days
Reduction in time in ICU stay	1.6 days (mean)	1.9-1.2 days
Reduction in hospital stay	3.4 days (mean)	4.0-2.7 days

Data from Montejo et al. (48).

malnourished. That is, immunonutrition is not designed or intended to maintain "normal" metabolic processes or to cause an anabolic response in a patient. It is conceptually and fundamentally a different approach to nutritional provision in the surgical or critically ill patient. Immunonutrition is a provision of nutrients with the specific aim of modulating the immune, metabolic and inflammatory processes and it could be considered, therefore, to be a "pharmacological" intervention.

This point regarding the potential importance of timing of the provision of immunonutrition has been developed in key studies reported by Braga et al⁴¹ in patients undergoing surgery for colorectal cancer. A large, randomised, controlled study of such patients evaluated the clinical effects of immunonutrition (Impact[®]) when it was given perioperatively, including the pre- and post-operative periods. Overall, immunonutrition provision resulted in a reduction in post-operative complications and patients had a reduction in their length of stay in hospital. These effects also had a tangible benefit in terms of a reduction in the financial costs of treatment associated with the provision of immunonutrition^{42,49}.

A post-hoc analysis was also carried out subsequently to determine if there was any effect on outcome which could be attributed to the timing of the provision of the immunonutritional intervention. Interestingly, this indicated that the provision of nutrients pre-operatively was probably as good as administration in the whole of the peri-operative period in terms of effects on clinical outcomes. Clearly, subgroup analyses do have limitations in the validity of the conclusions that can be drawn from them, but they do allow the generation of a hypothesis for future testing.

To answer this question definitively as to whether immunonutrition given in the pre-operative period is as effective as that given in both the pre- and post-operative patients, Braga et al⁵⁰ undertook another large clinical trial. This study was designed not only to look at clinical outcomes but also to examine carefully what effects there were on basic physiological functions. More than 200 patients with colorectal cancer undergoing surgical resection were randomised to one of four experimental groups; this was either (i) to receive pre-operative immunonutrition for 5 days, (ii) pre-operative immunonutrition but then continued for 5 days post-operatively (jejunal infusion), (iii) oral intake of a standard isonitrogenous, isocaloric formula for 5 days period to surgery, and (iv) a group of patients who were treated conventionally with no supplementation before or after surgery.

It was demonstrated in this study that those patients receiving immunonutrition in either the pre-operative period and the peri-operative period, had improved immunological functions, better gut oxygenation and microperfusion than did the patients who were not receiving immunonutrition⁵⁰. This may

have an important clinical relevance in these patients undergoing intestinal resections because of the adverse effects on the healing of gastrointestinal anastomosis that occurs with inadequate oxygenation. In fact, there was almost a halving of the anastomotic leak rate in those patients who received peri-operative or pre-operative immunonutrition when compared with the other patients (although this was not statistically significant)⁵⁰.

Is the provision of immunonutrition appropriate for all patients?

The previously discussed data suggests that there are clinical benefits to be gained by providing immunonutrition to patients undergoing elective surgery for gastrointestinal tract cancers. However, not all patients may benefit, particularly those with critical illness and there is also a concern that there may be a potential for harm in some patients⁵¹⁻⁵³. In particular concern has focussed on the role and effects of arginine as a component of immunonutrition. This is because it was the studies using the immunonutritional regimens that patients had an increased mortality⁴⁷. In trying to understand this further, perhaps the precursor role of arginine for nitric oxide (NO) synthesis via the nitric oxide synthase (NOS) enzyme system provides a reason as to why there may be some concern. During inflammatory conditions there is an increased production of NO via the inducible (iNOS) enzyme system. One of the key effects of NO is to cause a vasodilatation, which can be substantial, and indeed has been shown to be of therapeutic benefit in patients with hypertension, claudication and coronary artery disease^{54,55}.

Is it possible that this resultant vasodilatation might have harmful effects in patients who are critically ill? It is certainly a possibility because experimental clinical studies has shown that an intravenous bolus injection of arginine can have marked effects in patients with sepsis⁵⁶. This bolus administration of arginine effected a large reduction in the patients mean blood pressure with concomitant reductions in systemic and pulmonary vascular resistances, together with an increased cardiac index. However, within ten minutes of the arginine bolus having been given, these effects had reversed and returned to the pre-treatment indices for the patients⁵⁶.

There are also other effects of arginine which could be potentially harmful to critically ill patients. For example, NO can affect cellular oxygen consumption and utilisation, possibly by inhibiting the mitochondrial enzymes that are key to the process of electron transfer⁵⁷. In the clinical situation there is evidence to support this possibility. The partial pressure of oxygen in skeletal muscle has been shown to increase with increasing severity of sepsis in critically ill patients which is in proportion to the severity of sepsis which patients are experiencing⁵⁸. Whilst this is important

circumstantial evidence for a block in oxygen utilisation, in animal studies there is more direct evidence. Reduced levels of the cytochrome c enzyme systems have been documented in an animal model of sepsis⁵⁹ and furthermore, this reduction was proportional to the degree of the sepsis and septic shock⁵⁹.

NO is also important in the critically ill patient because it is essential in the physiological situation for the maintenance of the gut-mucosal barrier and for ensuring that its functions are optimal⁶⁰. As already discussed, in inflammatory states where there is an increased iNOS system, then the administration of arginine can result in the production of large amounts of NO with resultant damage to the intestinal mucosa. If this occurs there will be a failure of the gut-barrier function with ensuing translocation of bacteria and endotoxin and their adverse effects on critically ill patients.

Given these issues regarding arginine that may give rise to some concerns, is there any more clinical evidence that might support these being clinically relevant effects? Certainly, the last meta-analysis⁴⁷ suggested that high arginine-containing diets did have a higher mortality but this was a subgroup analysis. Of interest in this respect is the interim analysis of a recent study which was reported by Bertolini et al⁶¹. Included in this trial were 39 patients with severe sepsis or septic shock who were randomised to receive either immunonutrition enterally (Impact®) or total parenteral nutrition (TPN). There was a significant difference in mortality between the two groups of patients; 44.4% in the immunonutrition group but only 14.3% in the group receiving TPN⁶¹. Whilst there may be other reasons for this difference, it may well be related to the arginine content and clearly requires further investigation.

Whilst the focus on immunonutrients has centred on arginine, it is also important to consider other immunonutrients in relationship to the patients underlying and dynamic pathophysiological changes, especially in those patients with sepsis. Initially these patients experience an inflammatory response. However, as the sepsis process continues this may be superseded by an anti-inflammatory response which may be of even greater magnitude⁶². Although the mechanisms of this remain to be fully clarified it appears that the balance of cytokines produced by Th1 and Th2 cells is crucially important in this "switch"⁶³. The result of this is that there may be an immunosuppressive state in these patients⁶² which would then be expected to result in an increased susceptibility of these patients to developing infectious complications.

Taking this into consideration, it is clear that inflammation and sepsis are constantly changing and dynamic states which may at different times have an enhanced inflammatory phase and a second phase where there is impaired inflammation and immunity. Therefore, immunonutrition with immunoenhancing nutrients may not be appropriate to give to all patients because the underlying and dynamic physiological

changes are different. Indeed, in those patients in whom there is immunosuppression then immune enhancement is appropriate. In contrast, in those patients in an inflammatory phase, immunonutrition with immunoinhibitory nutrients may be theoretically more appropriate. This needs to be considered further and in much detail if we are to understand further these potential benefits of immunonutrition.

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