Specialized Nutrition Support in the Critically Ill: For Whom and When?

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**Introduction**

For the purpose of this article, ‘specialized nutrition support’ means using nutrient formulations that have particular adaptations deemed either to alter the inflammatory response or correct a conditional deficiency. The term ‘immunonutrition’ is widely used. For ‘whom’ requires an understanding of the pathological processes patients are undergoing and ‘when’ implies there is some optimal intervention window. However, implicit in both is the need to understand the objectives of the nutritional intervention and the balance between the benefits and risks involved and how these relate to outcome. The focus will be on the survival of critically ill patients and how we can make decisions that are of practical consequence for the general clinician.

**Risks and Benefits**

Intensive care involves patients with a high risk of death. Benefit must be measured by preventing death and improving the quality of survival. Interventions that positively influence survival have an effect on the pathological processes that are leading to the risk of death. Risk of death in the intensive care unit (ICU) will eventually arise from starvation. The amount of body reserve on admission is independently related to outcome in multiple organ failure (MOF) and is apparent between the 25th and 30th day of an ICU stay [1]. This could imply that current nutrition therapies are of little effect within the ICU, but more likely that the consequences of malnutrition...
take time to arise and therefore the benefits from nutritional therapy can be expected to have longer time scales for effect. Balancing the benefits and risks is difficult in the ICU, because either the benefits of the therapy may appear small or have a long time scale, while the risks may be high or occur early on in the nutrition therapy, out of phase with the benefits. There is a serious potential risk, therefore, for nutrition therapy to do (or appear to do) more harm than good in the short term.

The risk can be broadly divided into three categories: (a) risks arising from abnormal delivery of nutrient through routes that carry a complication risk; (b) risks from disturbing physiological processes by abnormally altering substrate availability, either in an attempt to alter a pathological process, or in a misguided attempt to correct a perceived deficiency that may not be genuine, and risk from creating a nutrient deficiency by one’s actions or through the use of deficient substrate mixtures.

Theoretically, to whom could one do more harm than good? We would expect the malnourished or protein-depleted patients to suffer the risks more, but they would also have the most to benefit from the nutrition. Similarly, the fit well-nourished patients may suffer the risks better, but likewise be at the lowest risk from nutrient lack and therefore have the least to benefit. Such nutritional equipoise is probably related to the underlying genetic predisposition, the pathology, the intensity (or severity) and the phase of the illness that contribute to altering the risk/benefit ratio. Timing and duration of nutrition are of importance in this process.

**Risks Arising from Abnormal Delivery of Nutrition**

Within the ICU, the risks are often very different than in other clinical settings. For instance in ventilated patients there is good evidence that enteral feeding and being nursed in the supine position are independent risk factors for ventilator pneumonia [2]. The semi-recumbent posture for enteral feeding is therefore the best advice to reduce the risks, but they will still arise. This is important when it comes to consider the risk/benefits of immunonutrient feeds. Delivery is also an issue and studies show that the real practice of enteral nutrition is partial feeding [3]. The two largest nutrition studies, involving 648 patients and testing a formulation intended to enhance the immune system, suggested that the benefits were seen only in the 25% [4] and 30% [5] of patients who received ‘adequate’ yet modest early enteral feeds. Looking at this from the viewpoint of nutrition delivery, 7 and 28% were unable to even start feeding and overall 75–70% were underfed. These patients, regardless of feed, had a higher mortality of 48 and 15% *versus* 40 and 6% in the better-fed, respectively. Were they getting the risks without the benefits?
The use of parenteral nutrition has decreased and the majority of general ICU patients are fed via the enteral route, such that underfeeding is now the norm. There is a reluctance to supplement with parenteral nutrition for historical risk reasons. However, nowadays the complications of parenteral feeding are less likely to result in death, compared to those of enteral nutrition [6]. Recent studies in major surgery show that parenteral nutrition compared with early enteral nutrition [7] is risk neutral. When used with enteral nutrition as a supplement in the ICU [8], it seems also to be risk neutral or may even offer benefits. In the most severely ill of ICU patients with MOF, it is recognized that a dual feeding approach or total parenteral nutrition (TPN) alone is still required [9]. Is the reluctance to supplement with parenteral feeding increasing the risk for the most severely ill patients who are receiving days or weeks of insufficient enteral feeding?

**Risk from Disturbing Physiological Processes**

Nutrition delivery in the ICU is on the background of a changing and evolving patho-physiological state. A feature of most patients is an evolving inflammatory response, where the decision to commence nutrition may not arise at the same time in the process. The importance of the inflammatory response to activate defense mechanisms against infection, to direct cell movement and induce endogenous cytoprotective mechanisms must be balanced by the collateral damage that occurs to various tissues. The rest of this article will examine the clinical attempts through nutrition to modulate these events.

Studies on new formulations have arisen from a better understanding of the metabolic changes occurring during severe illness, such that nutrition formulations have been modified to enhance or optimize tissue function. We are sold the concept that these enhanced formulations represent a ‘pharmaceutical’ approach, where the nutrient is the driving force for altered function. This imposes a risk, because a forced change may or may not be beneficial. However if they are merely optimizing metabolism by correcting a conditional deficiency that arises from traditional feeds being unable to meet altered metabolic demands, then the risks should be minimized. A deficiency state has only been implicated for glutamine (see below, p. 207).

**Immunonutrient Formulations – Objectives of Therapy?**

How should the ICU clinician use these new ‘immunonutrient’ formulations? Since there is no study that shows improved hospital or long-term survival for general ICU patients, how should the ICU clinician decide? There is only one unblinded study using an immunonutrient cocktail that shows an improved within ICU survival in septic patients, where 7 of the 11 additional survivors were those who were less ill [10]. However, since the follow-up
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did not extend into the hospital or longer (say 6 months), we cannot tell if this is not simply a postponement of death, given that only about 60–75% of mortality in ICU admissions occur within the ICU. Table 1 lists the ICU mortality and hospital mortality of the largest ICU studies. The mortality risk and benefits should be looked at using the decision to feed (intention to treat) as one does in practice. Taking the two largest studies that contain hospital mortality data collectively, the same immunonutrient feed produces a significant excess mortality (OR 1.45; CI 1.06–2.11; \( p = 0.02 \)). This is disturbing, since it suggests that more harm than good may occur. Since benefits were said to occur in sub-sets of patients, it could be that some patients might benefit while others suffer harm. As mentioned earlier, is this due to the feed or the failure to feed? The two largest studies used questionable sub-group analysis to infer a benefit in reduced infection and length of stay. These studies have been extensively reviewed and also exposed to meta-analyses that are confusing to interpret, because of the inclusion of studies from less ill or non-ICU populations and a variety of different formulations as test or control [11, 12]. The collective wisdom was that there was no overall treatment effect on outcome, but that benefit can be described in terms of reducing infection and shortening stay. In post-operative studies where the population has no mortality this is a measure of benefit. However in intensive care with its high mortality, if a nutrition therapy does not reflect on outcome and could possibly even make some patients worse, there is good reason to hold a serious reservation and not deliver it indiscriminately.

<table>
<thead>
<tr>
<th>Study</th>
<th>Impact deaths</th>
<th>Control deaths</th>
<th>( \chi^2, p ) value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>% (number/total)</td>
<td>% (number/total)</td>
<td></td>
</tr>
<tr>
<td>Bower et al. [5] 1995</td>
<td>15.7 (24/153)</td>
<td>8.4 (12/143)</td>
<td>0.055</td>
</tr>
<tr>
<td>Died in hospital (ITT)</td>
<td>25 (11/44)</td>
<td>8.9 (4/45)</td>
<td>0.04</td>
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<tr>
<td>Septic sub-set</td>
<td></td>
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<tr>
<td>Atkinson et al. [4] 1998</td>
<td>40.6 (80/197)</td>
<td>38.3 (74/193)</td>
<td>0.64</td>
</tr>
<tr>
<td>Died in ICU (ITT)</td>
<td>48 (95/47)</td>
<td>44 (85/193)</td>
<td>0.41</td>
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<tr>
<td>Died in hospital (ITT)</td>
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<tr>
<td>Galban et al. [10] 2000</td>
<td>19 (17/89)</td>
<td>32 (28/87)</td>
<td>0.047</td>
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<tr>
<td>Died in ICU (ITT)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bower and Atkinson</td>
<td>34 (119/350)</td>
<td>25.6 (86/336)</td>
<td>0.02</td>
</tr>
<tr>
<td>Total died in hospital</td>
<td>33.9 (97/286)</td>
<td>36.4 (102/280)</td>
<td>0.53</td>
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\( \text{ITT} = \text{Intention to treat.} \)
How should we reflect on the evidence that the same or similar formulations have shown striking positive results in some populations of trauma [13, 14] and post-operative cancer patients [15, 16]? What might be the reason? Was this fortuitous or does it reflect an astute patient selection by the investigators targeting those most likely to benefit? The hypothesis at the basis of the use of these immunonutrients is dependent on a theory of acute inflammation (systemic inflammatory response syndrome, SIRS) and concurrent counter-regulation (counter-regulatory anti-inflammatory response syndrome CARS; Fig. 1).

The magnitude of the SIRS, which can have infective and noninfective origins, appears to dictate the extent and severity of the initial organ tissue injury. If death is prevented by organ support therapy at this stage, it is followed by an immunosuppressed state characterized by macrophage inactivity, Th1 helper cell suppression and reduced cell-mediated immunity. In this environment of a weakened innate immune response and inappropriate acquired immune response, invasive infections occur often in normally nonpathogenic organisms. For instance colonization and subsequent invasive candida infections are a clinical indication of this poor immune state. This second insult (the secondary hit) is thought to be responsible for progressive MOF and death.

The immuno-modulatory ingredients are intended to (a) reduce the extent of the initial inflammatory response and (b) prevent or restore an appropriate immune response to avoid immunosuppression. Why is it that this objective appears to be achieved in cancer patients fed pre-operatively and trauma patients fed soon after admission? Could it be a matter of dose of ingredients in a fixed regimen or their timing of administration relative to the pathological

![Fig. 1. Inflammation and organ failure in the ICU – is it a matter of timing? SIRS = Systemic inflammatory response syndrome; CARS = counter-regulatory anti-inflammatory response syndrome; MOF = multiple organ failure.](image-url)
process? The rationale for the relative proportions of the added constituents is not clear. The key ingredients are increased n-3 lipids and arginine (and in some trauma studies glutamine). The rationale for the presence of additional nucleotides has no clinical evidence base in man. The altered lipid profile is intended to reduce the magnitude of the inflammatory response, while the arginine is intended to restore immune cell function. The ability of different lipid formulations to alter the inflammatory response may be related to prior lipid consumption and underlying differences in the human gene pool. The most striking results in cancer surgery occur when the feed is given before the operation, suggesting that the substrates should be available or incorporated before the stress event [16]. Similarly post-operative studies show delayed benefits giving a suggestion that a number of days is required for efficacy [17]. In these studies the benefits are manifested by reduced infective complications. The benefits seen in trauma subjects may be similar and revolve around the process of the inflammatory response. In trauma cases it is not unusual for the inflammatory state to be initially low and increase over the subsequent days. This is more in keeping with a surgical stress response; indeed many of the trauma studies include a post-operative stress response, as they have needed early surgery for penetrating injuries. Key to these positive studies has been effective feed delivery to the majority of the study patients and the use often of the jejunal route. This may be important to achieve rapid nutrient delivery at an effective dose.

Following trauma or surgery, giving a nutrient that can suppress the initial immune response will possibly do benefit and not harm, since the inflammatory state is not required initially to fight an infection. When the time comes to deal with an acquired infection, the degree of immunosuppression is less, because the magnitude of the SIRS was less. These populations of trauma patients are probably much nearer to the surgical model and may not have the same response as other kinds of trauma (e.g. burns, blunt injury, head). A worse outcome was suggested by one study of patients with blunt trauma [18].

A feature of the two largest ICU studies was that feed delivery was via the naso-gastric route and poor for some 70–75% of patients who had a worse mortality. The populations were different, with the US study in a low-risk-of-death trauma group and the UK study in a higher-risk-of-death general ICU population. In both studies, the start of feeding would not have been so closely linked to the onset of the injury response and the dose of active agents was probably less. However the disturbing pattern of mortality difference remains across all groups and is significant in the patients with sepsis in the study of Bower et al. [5], where 11/44 (25%) died on Impact versus 4/45 (8.9%) who died on the control feed, $\chi^2 (p = 0.04)$. But this observation does not match that of the only study to show possible survival benefits [10]. In this study from Spain, the patients were all septic at recruitment, with the overwhelming majority having pneumonia (Fig. 2). Feed delivery was more aggressive with naso-jejunal tubes being used in many patients. The lung was
already involved on admission and the treatment did nothing to alter this organ injury response. There was no reduction in days of ventilator use or length of ICU stay. There was a nonsignificant trend to a reduced number of acquired nosocomial infections. Consistent with a time effect, however, this was seen as a reduction in the number of second acquired intensive care infections. A significant reduction in bacteremias was observed. Since the majority of admitting events were pneumonia, it is likely that the patients were in similar stages of their inflammatory response. The survival advantage was seen in the patients with a lower illness severity. Does this mean that only less ill patients have the ability to tolerate the immune modulation to their advantage? Similarly, one can only speculate on the failure to alter the outcome of the sicker patients. This could be because their death was already determined by overwhelming pathology or possibly because a key nutrient was deficient, that of glutamine.

Can recommendations be made as to the use of these fixed formula commercial immunonutrients? They do not all have the same composition. The worrying excess mortality seen in the studies using non-glutamine-containing feeds via the naso-gastric route suggests that the overall risks did not outweigh the benefits. The most recent more comprehensive meta-analysis has confirmed this hypothesis [19]. It should be noted that despite the results indicating a reduction in infective morbidity, there was no survival advantage demonstrated and even as suggested considerable cause for concern regarding
excess mortality. At present until we understand the cause of these risks, these feeds cannot be recommended for indiscriminate general use within ICUs. To be certain of no risk of harm (death), it should be reserved for: (a) pre- and peri-operative use for elective surgery; (b) use in trauma where surgery is involved, and (c) on condition delivery can be assured and that probably means using jejunal feeding.

**Specific Disease Modification**

A move beyond the general immunonutrient approach has been the development of a more specific approach to disease modification. From a background of detailed animal work an hypothesis was recently tested that the severity of the initial inflammatory response in the lungs of patients developing moderate acute respiratory distress syndrome (ARDS) could be modified by a regimen containing an altered lipid profile and enhanced antioxidants [20]. Feeds with enhanced antioxidants alone have shown little discernible benefit [21]. The combination of eicosapentaenoic acid (fish oil) and γ-linolenic acid (borage oil) had been shown to modulate membrane phospholipid composition with a shift towards a less inflammatory eicosanoid pattern. This is a remarkable study, since it demonstrates disease modification through a nutritional intervention predominantly given intra-gastrically. Patients were recruited with firm pathological diagnosis, bronchoalveolar lavage was used to show a reduction in lung inflammation, and outcome measures showed improved parameters of gas exchange, reduction in duration of ventilation, decreased ICU stay and decreased new organ failures (Fig. 3). The bulk of the results are presented for the 98 patients who achieved 75% of the target feed for at least 4 days. Similar clinical outcome data was included on the full 142 intention to treat patients. Mortality, although impressively less 16 versus 25%, did not achieve significance. These mortality figures suggest that the population chosen to study, however, was not that at highest risk of death. A 17% reduction in incidence of infection was not significant. The mortality on both feeds and the difference in mortality was less in those 98 patients who received the target amounts, suggesting that the less ill patients had been preferentially selected. The question remains how applicable are these results to patients with more severe ARDS or patients with other disorders? Would this feed be of benefit given to patients at risk of ARDS like the pre-operative feeding studies mentioned earlier? Is the benefit seen in the patients overriding a risk that might be greater in other patients? The underlying genetic status of the patients may not only determine the severity of their ARDS, but also their response to lipid modification. The control group received a commercial high-fat feed and not necessarily a standard ICU enteral feed. For the moment, this is the best evidence for a particular nutrition support for patients with ARDS, but it is not the complete answer. There is no evidence to support its use more widely.
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**Fig. 3.** Randomised control study of an enteral feed ‘Oxepa’ (7 g eicosapentaenoic acid +6 g γ-linolenic acid) *versus* ‘Pulmocare’ control started within 24 h of diagnosis and increased until a minimum of 4 days at 75% target calories (BEE x 1.3) achieved in 98/146 patients with ARDS, most fed naso-gastrically. Results presented for those achieving target feed intake. ICU LOS = ICU length of stay; MVD = mean ventilator days; EPA = eicosapentaenoic acid; GLA = γ-linolenic acid; OSF = organ system failure. Adapted from Gadek *et al.* [20].

*Risk from Nutrient Deficiency by One’s Actions or through the Use of Deficient Substrate Mixtures*

Omission of nutrients is the greatest risk. Strong evidence suggests that glutamine supply becomes deficient in the critically ill intensive care patient. One probable target tissue for deficiency is cellular defense and the immune system with glutamine replacement restoring an optimized immune defense system. This was discussed in a recent large review along with the current evidence for glutamine use in the critically ill [22]. Other reviews discuss the background and extensive past evidence [23, 24].

*Summary Evidence for a Deficient Endogenous Supply of Glutamine*

The classic observation by Vinnars *et al.* [25] 26 years ago was that following surgery, trauma or sepsis, the free glutamine pool is depleted. Despite the rapid fall in the intramuscular concentration of free glutamine, transport out of muscle is maintained and clearance from the plasma by other tissues increased [26]. Stable isotope studies of glutamine metabolism in critically ill patients appear to support the extensive and robust large animal studies that show net flux of glutamine from skeletal muscle to vital organs. Jackson *et al.* [27] demonstrated in newly admitted ICU patients a similar production rate, but increased the metabolic clearance rate from plasma,
consistent with increased utilization by other tissues and only modest correction of low plasma levels with 28 g/day of glutamine infusions [28]. Similar findings in malnourished gastrointestinal surgical patients receiving glutamine-supplemented TPN (12–15 g/day) pre-operatively show that endogenous glutamine production is not suppressed, the plasma glutamine does not rise significantly and tissue utilization appears increased [29].

Later on during an intensive care stay with a severe sustained inflammation, the efflux of glutamine cannot be maintained and plasma delivery declines. In children with burns, the plasma levels of glutamine were reduced, the whole body flux of glutamine was 40% greater, but the turnover in the skeletal tissues was reduced maintaining the net efflux near normal [30]. This observation implies a decrease in muscle glutamine production that has been confirmed in a large study of 20 severely burned patients 2 weeks into their critical illness [31]. Competing demands for intracellular glutamate are suggested to be at the heart of the problem.

**Glutamine, Immune Function and Infective Morbidity in the Critically Ill**

In the critically ill ICU patient acquired infections are common. Along with intravascular catheters, the presence of a naso-gastric tube and endotracheal tube alters bacterial and fungal colonization, while disturbances in enteral nutrition and gastrointestinal function alter the micro-flora. Most infections in the ICU are acquired from flora abnormally colonizing various mucus membranes or skin entry sites. Approximately half of the patients acquire infection on the ICU [32], which is significantly associated with mortality rate. Patients with pneumonia, laboratory-proven blood stream infection and clinical sepsis had increased risk of death. Not surprisingly, multiple factors were associated with new infections including mechanical ventilation, diagnosis of trauma and the use of invasive devices. The duration of stay within the ICU is most important, but not the length of hospital stay before the ICU admission. This implies that it is the combination of opportunities for infection and the failure to correct the deficiencies in our support of these patients that result in infection. Although preventing infection is important, the key to understanding survival particularly in intensive care is the ability of the patient to overcome and recover from infection. Indeed, as mentioned earlier, simply reducing infective morbidity in some of the enteral ‘immunonutrient’ studies has not been able to improve mortality. Survival requires the complete working of all the defense and repair mechanisms.

Along with the mucosal barrier protective mechanisms, the maintenance of an effective innate immune system response (phagocytosis and active monocytes) is essential for the initial prevention and control of the infection. Cell protective mechanisms are important in the early phase of an illness and the production of the cellular antioxidant glutathione and heat shock proteins
are important. Low intramuscular glutathione levels are correlated with low glutamine and glutamate levels in the critically ill, but surprisingly the cysteine and glycine levels are maintained [33]. In the presence of protein breakdown, there should be plenty of substrate available, except when alternative demands for glutamate predominate, leading to limitation of glutathione production. Tissue studies on hepatocytes suggest that glutamine working through the maintenance of glutathione is protective against the oxidative mitochondria damage that would arise during sepsis [34]. Mice fed supplemented enteral diets and then challenged with endotoxin showed maintenance of glutathione levels with increased numbers of T cells and glutamine prevented the apoptosis of B cells in the Peyer’s patches but not arginine, glycine or n-3 fatty acids [35]. Acute glutamine infusion in endotoxin models shows striking protection against end-organ tissue damage, probably mediated via heat shock protein expression and glutathione [36]. The generation of cysteiny1-leukotrienes from polymorphonuclear neutrophil granulocytes is enhanced by glutamine [37], probably by increasing glutathione, which is a necessary co-factor in the production of leukotriene C4 (LTC4). Nonsurviving critically ill patients show an inability to generate LTC4, compared with those that survived [38]. This is an interesting conundrum since increased LTC4 appearance in body fluids is a feature of ARDS [39], yet it is the failure to generate sufficiently that is associated with death.

After the initial phase, the ultimate recognition and subsequent controlled resolution of infective inflammation requires an optimal function of the acquired (adaptive) immune system dependent on T- and B-cell control. The clinical sepsis response combines pro-inflammatory and counter-regulatory or anti-inflammatory signaling to ensure an optimal balance, which intimately effects the T-cell response.

The demand for glutamine is high in the immune system for production of receptors, cytokines and rapid clonal expansion of lymphocytes. Lymphocytes demonstrate a striking dose-response relationship at physiological plasma glutamine concentrations critical for the T-lymphocyte function [for detailed discussion of the evidence see 22]. Can this concept of immune paralysis (or imbalance), which is thought to occur and predispose to progressively worse infections, MOF and death be a result of glutamine deficiency and inadequate systemic glutamine availability? A study in multiple-trauma patients of glutamine at 30 g/day required jejunal delivery and led to a significant reduction in the development of pneumonia, bacteremia, and severe sepsis [40].

**Survival and Exogenous Glutamine Replacement in Intensive Care**

Early death in the ICU is due to the magnitude of the initial pathology and usually involves a failure of a single organ system. The survivors are then exposed to intensive care acquired infections and, if recovery does not occur, death results due to progressive MOF. This means that the mortality risks of the initial illness are overtaken by the risks of a sustained ICU stay. If glutamine
supply becomes limiting, one would expect the benefit of its exogenous replacement to be seen by a reduction in the risk of deaths, the longer the ICU stay, and duration of deficiency. This hypothesis was examined in a very high-risk group of MOF patients with gut failure dependent only on parenteral nutrition using a robust inclusive end-point of survival to 6 months [41]. Survival was significantly better with glutamine 57% versus control 33% ($p = 0.049$; Fig. 4). Differences in mortality increased with time on parenteral nutrition. Subsequent analysis to explore the relationship between infection and outcome showed that there was no significant reduction in the number of acquired infections but glutamine patients were able to survive infections. The incidence of infection and mortality was the same in those fed for less than 5 days. In those fed for 5 days or more, there was a trend for repeated acquired intensive infections in the control patients, particularly line-related infections and yet they encountered the same risk with a similar duration of parenteral nutrition and stay on the ICU. Those fed 5 or more days described the overall difference in mortality in the intention-to-treat population almost completely. Of these, 18/27 control patients vs. 9/25 glutamine died ($p = 0.05$) most within the ICU from MOF (16/18 control vs. 8/9 glutamine). Consistent with a possible impaired cell-mediated T-lymphocyte function, control patients not given glutamine had more systemic candida infections and higher associated mortality [42].

If the risk in the critically ill related to glutamine is one of failing to correct the deficiency, there is no logic to omit it now that dipeptides of glutamine have
overcome pharmaceutical problems of delivery. How much should be given remains open to debate and has been reviewed [43]. There is a lack of clinical evidence showing that enteral supplements can significantly raise plasma or tissue glutamine levels for a sustained period. The enteral route may be sufficient, when given early to the noninfected patient (e.g. following trauma) to improve gut-associated immunity, but adequately delivery is a challenge. Bio-availability may be questioned in the current glutamine enhanced enteral feeds that use glutamine-rich protein sources [44]. It has still to be shown whether, in the already severely stressed or infected ICU patient, enteral supplements alone can be adequate and that parallel parenteral support may not also be required.

It is encouraging to see nutritional studies having an effect on intensive care survival. The glutamine study showed a reduction in late deaths from MOF. The same results have recently been shown in a large study, where full nutrition was accompanied by intensive insulin therapy to reverse insulin resistance [45]. Interestingly, parenteral glutamine has been shown to ameliorate insulin resistance [46] and facilitate glucose utilization [47], so the mechanisms of action may not be so different.

Conclusion

We remain ignorant about the many varied and alternative stages in the pathological cascade that eventually lead to death in an intensive care patient. Any intervention to alter the pathological process must be entertained with caution. The story of growth hormone use within intensive care is one where initial studies using measures of physiological improvement in less ill patients did not predict the worse mortality in the studies in the very sick. To maximize the benefit-to-risk of nutritional interventions, it is likely to be more rewarding, if one seeks to correct nutrient deficiencies that are connected to the pathological events. The replacement of a single nutrient, vitamin C, corrected the diverse symptoms of the multisystem disease of scurvy and saved many lives on long voyages at sea. We already know about a conditional deficiency of glutamine and there are likely to be others such as selenium. It is not fanciful, therefore, that correcting deficiencies arising during the ‘long-voyage’ in intensive care may be manifest across a number of systems, which can impact in various ways on the risk of death.

References

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**Discussion**

*Dr. Meier:* In Heyland’s meta-analysis [1], he compared the high quality trials with the low quality trials and found that there was a higher mortality and a lower infection rate in the high quality trials. How can this be explained? And there was also a trend to lower mortality on high arginine diets, but you didn’t mention beneficial substrates in your talk.

*Dr. Griffiths:* I was very careful not to go into specific detail, because of the need to avoid overinterpreting meta-analyses and drawing unjustified conclusions. They are hypotheses generating exercises. You are right in saying that the greater mortality was in the higher quality studies, but of course that just reflects the fact that the higher quality studies got their marks, because they were the studies with the greatest statistical power. Some of them were in patients in intensive care, and of course you can only look at mortality in such patients who have a high risk of mortality. There were some high quality studies among the ones on surgical patients, but they were not dealing with a population in which you can examine mortality; you can only examine that as an outcome in a high risk population. The real concern I have with this sort of meta-analysis is that it is virtually impossible to do good intention-to-treat analysis studies with enteral feeding, because you only have a subset of those whom you decide to feed, who, you can actually end up analyzing.

*Dr. Meier:* Yes I think that is true. When you look at the mortality in the surgical groups, it is between 0 and 5%, but in the intensive care unit (ICU) it was between 0 and 50%.

*Dr. Chioléro:* You correctly stressed that when we assess the performance of a new diet, we have to compare it with a good existing product, in both the parenteral and the enteral domain. But what is a good standard formula for ICU patients, either enteral or parenteral? It is a difficult point.

*Dr. Griffiths:* That’s exactly what we are trying to find out. The study I cited [2] looks very good: it was built on a laboratory-based series of animal experiments, targeting the composition of the feed to a specific pathology in the lung, and the investigators were able to show clinical changes that matched the same pathological evolution of the disease, which they saw in the animal populations. It was all extremely encouraging. I wanted to point out, though, the two features that are of concern to me. One is that it still does not help me to decide whether giving that feed is better than what I do at the moment, because it was not tested against what I do at the moment. Secondly, it is only studying a subset of that pathological population.

I am trying to avoid answering your question directly, because I don’t know what is the best or right feed to compare it against! I would suggest, though, that we do know enough about glutamine, so maybe we should be looking at studies that actually contain glutamine in them, when we are trying to determine the advantages and
disadvantages. As was said at the beginning, this is all about doing something abnormal vs. doing something very abnormal.

**Dr. Grimble:** With all these issues we are adopting a pharmacological approach to the way we interpret how effective things are. We demand the meta-analyses and the statistical differences that we would get from drug trials, to show whether they are efficacious or not. However, the problem with nutrition is that there is more than one source of nutrition for the patient. Endogenous sources of nutrients are probably far more important than those we put down the tube, and it is very difficult to remove that factor from what is happening in these meta-analysis. We’ll get no further with this issue, unless we characterize our patients more thoroughly, looking at the things you mentioned, the genotype, for example: do some patients intrinsically have a potential for a stronger inflammatory response than others and are they, therefore, more likely to run into problems? Are some patients more depleted in antioxidant defenses, in other words do they have a much lower level of endogenous nutrition available to them? These are the issues that we need to look at and characterize before we can move forward with this whole issue of immunonutrition.

**Dr. Griffiths:** I agree. One of the concerns I have is that when we look at nutritional data we must pay careful attention to where the patients have come from. For example, well-nourished people have vast nutrition stores inside them, so no effects of varied diet could possibly be expected to show differences over short periods of study.

**Dr. Shenkin:** You returned to a point that has been referred to several times over the past couple of days – the whole issue of manipulating physiological responses for the benefit of the patient. I am confused again about this question of manipulating the acute phase response. You were talking about suppressing the inflammatory response to protect the later immune response, whereas we heard earlier about sustaining the early inflammatory response to protect the later immune response. I think there is a real concern about whether, in a severely ill patient, there is any benefit whatsoever in dampering down the acute phase response in the early period, rather than making sure that everything is maintained, so that you get a full-blown protective immune response later on.

**Dr. Griffiths:** If you start off well and experience a timed programmed insult, all the evidence suggests that dampening down the immune response is beneficial; that is the principle of Lindqvist giving glucose, and of the preoperative immunonutrient studies. You need to have an active inflammatory process to fight off infections, but you don’t necessarily need to have an exaggerated response to overcome a controlled stressful event. The trouble is that there is a vast array of different processes involved in what we call the ‘disinflammatory response’, which all have different time courses and different components. Their effects on subsequent processes are also at different time phases, and that represents the complexity of what we are dealing with. What I think we should be doing is trying to correct the disimmune function, so that the balance at any single time is appropriate and things are in the phase and sequence.

**Dr. Soeters:** I think there are components to the acute phase response that are deleterious, but nobody knows exactly which ones and to what extent. What we do know is that the work of Kehlet [3–5] has shown that if you treat pain adequately and pay attention to the psychological aspects of the patient’s state, this will dampen down parts of the acute phase response. So there is some substance to the view that dampening down the response in that way is indeed useful, but I don’t believe that dampening down the metabolic response and the production of acute phase proteins is also useful. Take the case of edema. Local edema may be of value in a circumscribed wound, but if the whole body is edematous the edema is no longer useful and starts interfering with many functions. Of course that has to do with the fact that in such
cases the insult is much greater than the body was ever meant to survive, but it does not mean that the response is inadequate.

**Dr. Griffiths:** I could respond by pointing out a recent study in the *New England Journal of Medicine* [6], which is going to influence how we think about managing patients with severe sepsis. This is for emergency room doctors. The basis of this impressively well-structured study was a comparison between patients with severe sepsis who either stayed in the emergency room for 6 hrs for absolute fine tuning of their fluid balance and oxygen delivery, or who had initial good management but were then rushed off the ICU, to the theater, or to have other things done. So the investigators were examining the golden period of the inflammatory shock process, and how it should be got under control. They did that by having a catheter that measured the oxygen debt in the central venous system, so they are able to find the 20% of patients whose circulation hadn’t been fine tuned. These patients need a little extra blood, a little extra fluid, and a slightly larger dose of inotropes to get things right. They found that, though the pre-illness severity score measures were very similar, after 6 hrs of treatment the index group had a significant reduction in their measurement of illness severity risk. These patients had improved base deficits at 6 hrs, and a better coagulation status. So the management was altering the pathology of the early septic disease response, and this was reflected in a considerable reduction in hospital mortality. The punch line is that they significantly reduced sudden early cardiovascular death, and this is the same type of death that the activated protein C affects. So with this population of patients we are able to show effects with treatments and effects on survival.

**Dr. Segal:** When we speak of immunonutrition, do you have any data on associations with particular bacteria?

**Dr. Griffiths:** A study in *Lancet* [7] illustrates where Alexander’s concept of an immunonutrient cocktail has been taken correctly. This is about optimizing the gut-associated immune system, suppressing the severity of the inflammatory response, but also providing things like arginine to help prevent immune suppression. Essentially, the investigators randomized elective cardiac surgery patients with a planned short ICU stay to 5–7 days of preoperative oral supplementation. They then looked at the measurement of how that supplementation had affected the subsequent surgery. It was found that more blood needed to be given in the control group and there was a reduction in infective episodes in the index group. The types of organisms in many such studies have been gut-related pathogens and Gram-negative organisms. The trouble we face later on in intensive care is that we are dealing with organisms that are not necessarily present in the gut of healthy people. They are organisms that colonize patients in hospital, and they can be Gram-positive or fungal. In the study I have just cited, the patients who had the immunonutrient feed before surgery were able to cope with the surgical stress process better than the controls, so that their cells were able to mount their immune response despite the stress of the surgery, and that was sufficient to reduce the incidence of infection.

**Dr. Rössle:** For some immunonutrients, you have the option of providing them directly or of providing their precursors. This is the case, for example, with eicosapentaenoic acid, where you could provide ω-3 fatty acid, or with arginine, where you could provide glutamine. Do you think a substantial supply of a precursor is the safest option? In that case, the body can regulate how much of the immunonutrients it wants to produce in particular situations.

**Dr. Griffiths:** I will confine myself to your specific example. I am biased in favour of the view that if you supply enough glutamine you will manufacture enough arginine, and that seems a much more physiological way to proceed, but we can’t get away from the fact that arginine is very easy to make into an enteral feed and it does not have the problems of providing such a high quality bacterial growth medium.
So for enteral delivery I can see the appeal of arginine, but as it is now so easy to incorporate glutamine into parenteral feeds, I can’t see the advantage of using arginine in that situation.

_Dr. Soeters:_ There is a pathway allowing arginine to be produced from glutamine in the kidney, but it has never been demonstrated that it is a pathway that is very significant in humans. Most of the arginine produced comes from net catabolism of protein. The question is whether the renal production of arginine can be upregulated.

**References**