Nutritional Support in Sepsis and Multiple Organ Failure

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The scope of this review is to provide practical guidelines for nutritional management of critically ill patients with sepsis with or without multiple organ failure (MOF). Basically, any nutritional intervention must be based on a better understanding of septic 'autocannibalism' [1]. Clearly, sepsis causes much the same metabolic disturbance as trauma or injury, but it must be stressed that sepsis is more often complicated by subsequent insults, which explains why in some instances nutritional or metabolic support should be modulated according to different post-inflammatory states, now termed systemic inflammatory response syndrome (SIRS), compensatory anti-inflammatory response syndrome and mixed adapted response syndrome. Finally, present definitions of sepsis, SIRS and septic shock are too broad and insufficiently specific: instead, mechanistic definitions should provide more homogeneous groups of patients [2] and favor the development of new modalities on nutritional and metabolic support.

What Is the Goal of Nutritional Support in Sepsis?

As long as the hemodynamic and respiratory status remains unstable, it is probably harmful to start complex nutritional support: the nutrient supply can consist simply of sufficient glucose (200–300 g/day) to meet the requirements of glucose-dependent tissues, and of 'critical' electrolytes and vitamins, such as phosphorus and folinic acid.

When the initial sepsis does not rapidly lead to death and the patient has stabilized, it seems reasonable to begin nutrition, thereby avoiding the onset of severe metabolic disorders and/or nosocomial infections which can engender
irreversible multiple organ dysfunction syndrome (table 1). Nutritional (metabolic) support is aimed at preventing or limiting the processes of malnutrition and immunosuppression which can be cofactors in the morbidity and mortality associated with sepsis states. However, nutritional support is at present one useful tool among others to help recovery in these patients in whom outcome clearly results from the combined effects of optimal therapeutic measures.

**Energy Supply in Sepsis: Is More Better?**

The estimation of resting energy expenditure (REE) by standard formulae (e.g., the Harris-Benedict equations corrected by stress factors) cannot be easily extrapolated to septic patients because of fluctuations according to fever, sedation, mechanical ventilation, etc. The measurement of REE by indirect calorimetry is possible, even in patients under mechanical ventilation if the inspired oxygen concentration is lower than 0.6–0.7, giving reasonable accuracy in the order of 5% [3]. Total energy expenditure (TEE) is generally no more than 1.2–1.5 higher than REE in patients with septicemia or peritonitis during 7–10 days, but progressively increases in severely septic surgical patients up to 1.7–1.8 higher than REE after 1 week [4], a fact that correlates with the results obtained during recovery from sepsis syndrome or septic shock. Calculation of VO_{2} using a Swan-Ganz catheter does not correlate well with indirect calorimetry, owing to the arbitrary choice of a fixed respiratory quotient, especially in unstable patients where underestimation of VO_{2} by the Swan-Ganz method can reach 20–30%.

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**Table 1. Nutritional or metabolic support in sepsis: A dynamic approach**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Duration</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early acute phase of stress¹</td>
<td>1–4 days</td>
<td>Glucose 200–300 g/day</td>
</tr>
<tr>
<td>Treat the cause of sepsis</td>
<td></td>
<td>Support vital functions</td>
</tr>
<tr>
<td>Support vital functions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged hypermetabolism</td>
<td>≥5 days</td>
<td>Nutritional/metabolic support (immunonutrition?)</td>
</tr>
<tr>
<td>High cardiac output state</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercatabolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovery phase</td>
<td>weeks</td>
<td>Anabolic nutrition (hormonal adjunctive treatment?)</td>
</tr>
<tr>
<td>Irreversible ARDS or MODS</td>
<td></td>
<td>Nutrition is useless</td>
</tr>
</tbody>
</table>

ARDS = Acute respiratory distress syndrome; MODS = multiple organ dysfunction syndrome.
¹ In case of preexisting malnutrition, minimal nutritional support may be initiated immediately.
In practice, total energy requirements in the septic patient are in the order of 25–35 kcal/kg/day (table 2). In the context of sepsis, the most important concern is not to do harm. Therefore, it is preferable to avoid excess, which cannot prevent the intense protein catabolism associated with sepsis and has well described detrimental effects [5]. However, during the recovery phase, it could be advisable to increase this amount to achieve energy balance, thus preserving endogenous fat stores.

Table 2. Proposed nutritional support for the septic patient

<table>
<thead>
<tr>
<th>Energy requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>25–35 kcal/kg/day (acute phase)</td>
</tr>
<tr>
<td>35–50 kcal/kg/day (recovery phase)? (see text)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Energy sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose &lt;6 g/kg/day</td>
</tr>
<tr>
<td>Lipids (LCT or MCT/LCT) 0.5 g/kg/day to 1 g/kg/day</td>
</tr>
<tr>
<td>Continuous administration over 24 h recommended</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Amino acids or proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2–2 g/kg/day (0.20–0.35 gN/kg/day)</td>
</tr>
<tr>
<td>Adaptation according to level of catabolism (BUN, nitrogen balance)</td>
</tr>
<tr>
<td>Conventional crystalline amino acid solutions (PN)</td>
</tr>
<tr>
<td>Polymeric diets (EN)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vitamins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard balanced formulas (PN)</td>
</tr>
<tr>
<td>+ Vitamin K (10 mg/day)</td>
</tr>
<tr>
<td>+ Vitamin B_1 and vitamin B_6 (100 mg/day)</td>
</tr>
<tr>
<td>+ Vitamins A, C and E (antioxidants?)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trace elements (provided normal renal function)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete standard solutions</td>
</tr>
<tr>
<td>+ Zn (15–20 mg/day plus 10 mg/l of liquid stool)</td>
</tr>
<tr>
<td>+ Se (120 mg/day)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Electrolytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Based on daily plasma concentrations (Na(^+), K(^+), Ca(^{2+}))</td>
</tr>
<tr>
<td>+ P(^{2-}) (&gt;16 mmol/day)</td>
</tr>
<tr>
<td>+ Mg(^{2-}) (&gt;200 mg/day)</td>
</tr>
</tbody>
</table>

LCT = Long-chain triglycerides; MCT = medium-chain triglycerides; PN = parenteral nutrition; EN = enteral nutrition.

In practice, total energy requirements in the septic patient are in the order of 25–35 kcal/kg/day (table 2). In the context of sepsis, the most important concern is not to do harm. Therefore, it is preferable to avoid excess, which cannot prevent the intense protein catabolism associated with sepsis and has well described detrimental effects [5]. However, during the recovery phase, it could be advisable to increase this amount to achieve energy balance, thus preserving endogenous fat stores.

**A Classical Dilemma: Glucose or Lipids as Optimal Energy Source?**

We think this question should be addressed in terms of anabolic drive in septic patients [6], but few studies have been dedicated to this problem.
Taking into account that a prevalent glucose system (70–80%) seems to be the most efficient tool to optimize protein metabolism [6, 7], glucose infusion can be progressively increased to maximal tolerance in so far as, during sepsis, the defect is not in glucose oxidation (providing endogenous release of insulin is adequate), but rather in declined nonoxidative disposal of glucose. The maximum rate of glucose oxidation is in the order of 5–6 mg/kg/min, therefore, the recommended supply of glucose for septic patients is about 3–5 g/kg/day [7].

The maximal effectiveness of insulin is decreased to approximately 50% below normal in sepsis [7]. Therefore, the addition of insulin when the endogenous blood insulin is elevated does not appear to be justified, except for avoiding hyperglycemia and osmotic polyuria. Hyperglycemia is common in critically ill patients, and this situation can predispose to nosocomial infections [8]. In a recent study by Van den Berghe et al. [9], at the time of admission to the intensive care unit (ICU) surgical patients were randomly assigned either to strict normalization of blood glucose (4–5.5 mmol/l) with intensive insulin therapy or to conventional treatment in which insulin was given only when the blood glucose level exceeded 11 mmol/l. Mortality in the group assigned to intensive insulin therapy was lower than that in the control group (4.6 vs. 8.0%; \( p < 0.04 \)). Benefit was achieved mainly through a reduction in the incidence of MOF with a proven septic focus. In-hospital mortality and morbidity were also lower in this group. However, the value of these impressive results is restricted to patients undergoing surgery (most often cardiac surgery) at a single institution. Further studies in other groups of critically ill (septic) patients is essential to confirm its benefits. Until then, widespread adoption of this treatment would be premature.

Although there is theoretically no impairment in the ability to oxidize fatty acids during sepsis, the oxidation and clearance rates of lipids from the blood fall rapidly as the severity of sepsis increases, further suggesting poor utilization and peripheral adipose tissue storage. In addition, controversy remains surrounding the possible immunosuppressive effect of lipids in the septic patient because long-chain triglycerides (LCT) reduce the functions of the reticuloendothelial system, neutrophils, and the ratio of T-helper to T-suppressor cells. Finally, alterations in alveolar macrophages could partially explain the transient desaturation seen during intermittent infusion of lipid emulsions. However, Druml et al. [10] found no side effects in septic patients, with or without hepatic failure, during a low-rate LCT lipid infusion, suggesting that the deleterious effects of LCT emulsions are unlikely as long as the infusion rate is not excessive.

With regard to these problems, medium-chain triglycerides (MCT) have been proposed because of their potential advantages in septic patients, i.e. more even balance of n-3 and n-6 fatty acids, rapid clearance from the plasma, limited storage, and more rapid oxidation than LCT. However, recent clinical data are inconsistent and suggest that MCT-LCT emulsions do not offer
clear-cut advantages over LCTs in terms of the lipid oxidation rate [11], pulmonary hemodynamics and gas exchange in septic acute respiratory distress syndrome (ARDS) [12], and do not support the systematic use of such emulsions in septic patients.

In practice, lipids can safely contribute 20–35% of nonprotein calories in septic patients or even less in patients who are very seriously septic (table 2). In any event, it is best to give a continuous 24-hour infusion, for example, with a glucose-lipid-protein mix.

**Low or High Nitrogen Supply?**

In the context of sepsis, equilibrium or positivity of nitrogen balance is not the goal and can even be detrimental if it leads to a rise in the metabolic stress. Correctly adapted nitrogen supply can, however, reduce the myofibrillar breakdown and stimulate synthesis of certain proteins, especially hepatic proteins involved in immune defenses. Ishibashi et al. [13] suggested that even the current recommendation of 1.2–2.0 g protein/kg/day does not take the overhydration (up to 15 liters) of resuscitation into account, and proposed 1.0–1.2 g protein/kg/day as a fair approximation of optimal protein requirements. Interestingly, the same group showed that, despite an adequately mixed energy intake, patients lost about 13% of their total body protein over the 3 weeks following peritonitis, and this loss occurred early from the skeletal muscle, and later from visceral organs, likely leading to some loss of function.

In practice, a nitrogen supply of 200–300 mg/kg/day, i.e. 1.2–1.8 g protein/kg/day appears to be adequate (table 2), so that the ideal nonprotein calorie to grams of the nitrogen ratio in septic patients is about 100–120:1 rather than the ‘classical’ 150:1. An increase in nitrogen supply does not improve nitrogen balance or decrease net protein breakdown, and leads to a significant increase in energy expenditure, urea accumulation and CO₂ production.

**Micronutrients and the ‘Antioxidant’ Concept**

Iron administration is a matter of debate in septic patients. For some, any attempt at iron replacement could facilitate its availability to microorganisms. For others, severe iron deficiency impairs resistance to infection and should be corrected [14]. Deficiencies in zinc can lead to the persistence, and even the onset, of sepsis due to immune deficiency, and requirements are increased to up to 20–30 mg/day when exogenous amino acids are administered. The clinical value of trace element supplementation was elegantly proven by Berger et al. [15] in burn patients: this supplementation of copper, zinc and selenium led to a significant decrease in the number of bronchopneumonia infections and a shorter hospital stay.
It is clear that oxidative stress is increased in patients with sepsis or at risk of sepsis. Plasma concentrations of potential antioxidants, such as selenium and some vitamins (C, E, and β-carotene) are reduced in critically ill patients. Although results from many animal studies and from one clinical pilot trial [16] are encouraging, trials of early administration of antioxidants have produced uneven results, especially in the settings of reperfusion injury and ARDS after sepsis. Additionally, β-carotene and vitamin C also have pro-oxidant properties [17]. The debate is going on, and meanwhile the only certainty is that septic patients should not be deficient in micronutrients (table 2).

(Early) Enteral Nutrition: A Fashion or a Dogma?

Here I will focus on new (and frequently conflicting) data relevant to the specific field of sepsis and MOF, where definite evidence of the superiority of enteral nutrition (EN) over parenteral nutrition (PN) is still lacking [8, 18].

The Significance of Bacterial Translocation in Septic Patients

Animal studies have shown that loss of the gut-barrier function may result in bacterial (and endotoxin) translocation and, in some instances, in systemic septic complications. In humans, the three main factors promoting bacterial translocation are present in sepsis: increase in intestinal permeability (not synonymous of translocation); decreased host immune defenses, and alterations in gut ecology. However, translocation has been shown to occur in a variety of conditions, such as surgery and intestinal obstruction [19, 20], but excluding sepsis. Thus, there is little evidence in this context that bacterial translocation acts either as a promoter or an initiator of generalized sepsis or MOF, especially when no source of infection is identifiable. This failure cannot be accounted for by inadequate technology, since DNA fragments can now be detected by molecular biology and polymerase chain reaction in the blood of patients [21].

Moreover, there is limited evidence to support the view that bacterial translocation is reduced by the use of EN or increased in patients receiving short-term PN. Thus, the increased incidence of sepsis apparently associated with total parenteral nutrition (TPN) may simply reflect the detrimental effects of overfeeding and hyperglycemia. To summarize, PN is not guilty of mucosal atrophy, altered gut-barrier function, and septic complications. Moreover, EN can cause severe problems in septic patients (see below), so that optimal nutritional care demands the use of both methodologies, often simultaneously [19].

Apart from the use of complex immune-enhancing diets, enrichment in glutamine has been shown to reduce the incidence of endotoxinemia and mortality in various animal models of gut failure, but low-dose glutamine
(20 g/day) does not obviously affect bacterial translocation. The enteral administration of short-chain fatty acids, the preferred fuel for the colonocyte, appears to reduce the atrophy of the colonic mucosa. However, in the future, the optimal therapy to maintain or restore intestinal mucosal structure and function may be a combination of specific enterally administered nutrients and mucosal trophic factors [22].

**Practice and Risks of Enteral Nutrition in Septic Patients**

Good reasons for the increased use of EN in ICU septic patients are numerous. EN is supposed to preserve intestinal-barrier status, to maintain secretory immunoglobulin A and gut-associated lymphoid tissue (which plays a major role as a barrier against intestinal translocation) [23], but also to enhance splanchnic blood flow and mesenteric oxygen utilization in sepsis.

Thus, to institute EN as soon as possible in ICU patients is probably justified, although problems linked to EN and more pronounced in ventilated septic patients, such as gut failure, bacterial overgrowth, and nosocomial pneumonia, cannot be forgotten [24]. Exclusive EN is precluded in unstable patients at the early stage of sepsis, because of the risk of exacerbating intestinal ischemia and of favoring the ischemia-reperfusion phenomenon. However, minimal EN (to preserve the immunologic function of the gut?) could be implemented early, in conjunction with PN, and gradually increased at the expense of intravenous intake [25], underlining that dichotomy between EN and PN is an obsolete controversy.

Once the hemodynamic and respiratory status has stabilized, the two major risks of EN are aspiration pneumonia and diarrhea. In most septic patients, EN intolerance can be controlled by the judicious use of prokinetics [26]. Only when gastroparesis persists, should postpyloric administration of EN be considered, although this does not seem to effectively reduce the incidence of aspiration and pneumonia. Diarrhea can usually be controlled by reducing the flow rate of the mixture, and by providing sufficient intraluminal sodium (above 80 mmol/l of diet), but the danger is to overlook a ‘silent’ gut failure with underlying ischemia with a high risk of entry into a MOF state. Therefore, EN may be considered a ‘stress test’: persistent symptoms of gut failure usually indicate a poor prognosis, and are a formal indication for withholding or withdrawing EN [27] (fig. 1).

**Is Parenteral Nutrition Associated with a Higher Morbidity than Enteral Nutrition?**

There is in fact reasonable evidence that TPN is associated with a higher incidence of septic morbidity in critically ill patients with severe burns and patients with blunt or penetrating trauma [8, 28]. However, there is no consistent evidence that in sepsis EN is associated with improved clinical outcome when compared with TPN.
Does the Timing of Enteral Nutrition Administration Affect Infectious Morbidity and Mortality?

Again this question has never been well studied in septic patients. Based on experimental studies showing that early EN is associated with a decreased cytokine and catabolic response to sepsis, starting EN as soon as possible could be an essential prognostic factor, but results of well-designed studies are somewhat inconsistent, or even worrisome [29]. Clearly, further studies are required before firm conclusions may be made.

To sum up, EN can improve the outcome of (severely?) septic patients when nutrition is initiated at an early stage, within 24–48 h after the initial septic event. After the 2nd or 3rd day, EN and PN appear to give similar results. EN seems to be accompanied by an increased incidence of gastrointestinal side effects and a higher failure rate in achieving targeted nutrition support goals [30], so my experience and my personal recommendation is to institute early partial EN with the goal of exerting beneficial effects on the gut, and to carefully increase the delivery rate to avoid splanchnic hemodynamic impairment.

‘Immunopharmacology’ in Sepsis

During the last decade, new specific substrates now termed ‘immunonutrients’ or ‘nutraceuticals’ have been used with the aim of preserving intestinal
barrier function, maintaining antioxidant defenses, and correcting specific metabolic and/or immunologic disturbances, which are partially dependent on cell activation induced by mediators (fig. 2).

**New Lipids**

Conventional intravenous lipid emulsions and enteral diets are relatively rich in n-6 polyunsaturated fatty acids (PUFAs), and are poor in n-3 PUFAs (fish oil) whose degradation leads to 10- to 100-fold less platelet activation and thrombogenesis compared to n-6 PUFAs. Thus, reducing the n-6/n-3 PUFA ratio makes sense within the setting of severe sepsis and MOF [31]. However, there are some restrictions to this stimulating concept [32]: the suppression of T-cell-mediated immune function has an adverse effect of fish oil supplementation, and the suitable action of fish oils on mediators may depend on the timing of administration, i.e. during the acute sepsis syndrome or later, when ‘chronic sepsis’ is established. Additionally, the metabolic fate of n-3 PUFAs is markedly dependent on the route of administration, either enteral or parenteral. One randomized study was specifically focused on the effect of EN enriched with eicosapentaenoic acid, γ-linolenic acid and antioxidants on the post-injury response in 146 mechanically ventilated patients with ARDS [33]. In the 98 evaluable patients, mainly those in whom a feeding period of 4–7 days could be completed, the specialized diet had beneficial effects on gas exchanges, the need for mechanical ventilation and ICU care, and significantly reduced the onset of new organ failures. However, in the intention-to-treat analysis, there was no difference between the groups.
in terms of infectious morbidity, hospital stay, and mortality. Future studies are now needed to elucidate the molecular mechanisms modified by fish oils to improve dietary strategies in sepsis and MOF.

**Is Qualitative Manipulation of Nitrogen Substrates Useful In Septic States?**

Glutamine becomes an essential amino acid in inflammatory conditions such as injury and sepsis, and is the preferred fuel and precursor of purines and pyrimidines for rapidly dividing cells such as lymphocytes, macrophages and enterocytes. It is involved in inter-organ nitrogen transport and in glutathione synthesis, thus offsetting free radical generation. Moreover, glutamine requirements increase considerably during inflammatory states, and relative tissue glutamine deficiency may thus occur [34]. As with other pharmaconutrients, data gathered from studies carried out in heterogeneous populations of critically ill patients should be carefully extrapolated to septic ICU patients [35]. In addition, dose-effect studies aimed at determining the optimal dosage of glutamine are lacking.

In a randomized, controlled trial of 84 ICU patients, including a large subset of septic patients [36], survival at 6 months was improved in the group of patients receiving glutamine-supplemented (20 g/day) TPN (p = 0.049), owing to late deaths in the control group, which were unlikely related to nutrition. Costs and length of hospitalization were also reduced in the patients receiving glutamine. It is noteworthy that the author himself has indicated that these results ‘seem too good to be true’ and are only applicable ‘to a very small subset of very sick septic ICU patients with gut failure’. This is in agreement with the global negative results of the largest trial of glutamine supplementation (20 g/day) of PN in 170 hospitalized patients [37], although subgroup analyses suggest that supplementation may have advantages in selected populations, such as septic patients, patients with MOF and those with hematologic malignancies.

Two randomized studies of glutamine-supplemented EN in critically ill patients have also been reported. The first compared a glutamine-enriched (10 g/l) diet with an isonitrogenous glycine-enriched control diet in 78 ICU patients [38], and was unable to show any difference in mortality or the length of ICU and hospital stay between the 2 groups, but showed reduced costs in the glutamine group. The other compared a diet based on strong enrichment in glutamine (30.5 g/100 g of protein) and a large percentage of arginine (8.5 g%), with a control isocaloric, isonitrogenous enteral diet in 72 multiple trauma patients [39]. There was a significantly lower incidence of pneumonia and bacteremia in patients fed glutamine. However, the duration of mechanical ventilation and the length of hospital stay were not different, and the mortality rates (probably low) were not reported.

In sum, although the body of evidence suggesting clinical benefits from the utilization of glutamine is growing, the available data are not sufficient to recommend its routine use, either by the enteral or the parenteral route, in
critically ill septic patients. Further trials are clearly required to establish firm
dose recommendations, to identify whether the enteral route for glutamine
administration should be preferred for patients with mild infection, and to
confirm whether a reduction in mortality is effective in severe sepsis.

The anabolic properties, the anticitobolic properties (stimulation of
 glutamine, arginine and proline synthesis), and the immunomodulatory
capabilities of ornithine η-ketoglutarate (OKG) are well adapted to ICU septic
patients. Moreover, ornithine is a precursor of polyamines, which are essential
for cell multiplication in the intestinal mucosa. Indeed, enteral administration
of OKG in severely burned patients has shown favorable results in terms of both
metabolic parameters and morbidity [40]. However, no study demonstrating the
effect of this nitrogen compound in septic patients is presently available.

Arginine is a conditionally essential amino acid in adults and becomes
essential in hypermetabolic and septic states. Arginine enhances T-lymphocyte
proliferation and activation, and significantly increases hepatic protein
synthesis in various models of gram-negative sepsis [41]. In addition, arginine
may contribute to the complex cellular interactions evoked in septic animals
or patients via increased production of reactive nitric oxide [42]. However,
administration of arginine-enriched enteral diets raises certain conceptual
problems in sepsis, on one hand, because the metabolic interactions between
arginine and glutamine (in diets containing both substrates) are complex and
potentially detrimental, and on the other hand, because its bioavailability is
strongly decreased after enteral administration in severe infection. There is an
urgent need to better define the value and the optimal level of enteral
supplementation in arginine for critically ill septic patients, as certain animal
data suggest that an excessive concentration could be harmful [43].

Do Immune-Enhancing Diets Improve the Outcome of Septic
Patients?

The concept of nutritional immunopharmacology has become the rationale
for the marketing of specific enteral formulas aimed at modulating the
inflammatory and immune response injury in immunocompromised patients.
All the recent systematic reviews confirm that these diets reduce the rate of
infective complications and the length of hospital stay after major surgery
and in trauma patients [44, 45]. But whether they are likely to improve the
clinical outcome of ICU septic patients remains questionable. Well-designed
randomized, controlled studies have been carried out recently in heteroge-
neous populations of ICU patients, some of them being septic, but only one
study specifically addressed the question in septic patients (table 3).

In a multicenter double-blind, randomized study involving 326 ICU patients
(mostly young and traumatized), the patients received early EN with either
Impact or an isocaloric nonisonitrogenous diet [46]. The only objective,
paradoxical result of the intention-to-treat (ITT) analysis is that mortality
was higher in the Impact group than in the control group (23/147 vs. 10/132;
Table 3. Prospective randomized controlled trials of immune-enhancing diets in septic and nonseptic ICU patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients (n) Diet(s)</th>
<th>Isocaloric isonitrogenous Diet(s)</th>
<th>Results</th>
<th>Statistical significance</th>
<th>Efficacy? Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bower et al. [46], 1995</td>
<td>ICU (n = 326) Impact vs. Osmolite</td>
<td>No (IED &gt; Std) No (IED &gt; Std)</td>
<td>↑ Mortality with Impact(!!)</td>
<td>No (IED &gt; Std)</td>
<td>No In the 'septic' subgroup</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ Infections (NS)</td>
<td>No (IED &gt; Std)</td>
<td>Complex and questionable</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ LOS (p &lt; 0.05)</td>
<td>No (IED &gt; Std)</td>
<td>post hoc stratification</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>In the 'septic' subgroup</td>
<td>No (IED &gt; Std)</td>
<td>Marginal and partial benefit for septic patients</td>
</tr>
<tr>
<td>Atkinson et al. [47], 1998</td>
<td>ICU (ITT, n = 398; 'successful early nutrition', n = 101) Impact vs. Std</td>
<td>Yes</td>
<td>Identical mortality (48 vs. 44%) in ITT</td>
<td>Yes (48 vs. 44%) in the 'successful early nutrition' subgroup</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ Duration MV, LOS, SIRS (all p &lt; 0.05) in the 'successful early nutrition' subgroup</td>
<td>Yes ?</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Waiting for the medico-economic study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jones et al. [38], 1999</td>
<td>ICU patients (n = 78) Gln-enriched EN vs. Std</td>
<td>Yes</td>
<td>No difference in late (6 months) mortality, ICU and hospital LOS (p = 0.036) in the treated group</td>
<td>No</td>
<td>Per protocol analysis (50 'successful EN' patients)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ICU and hospital costs (p = 0.036) in the treated group</td>
<td>No</td>
<td>Interesting cost-efficacy evaluation</td>
</tr>
<tr>
<td>Gadek et al. [33], 1999</td>
<td>ICU patients with or at risk of ARDS (n = 142) n-3 and vitamin E-enriched diet vs. Std</td>
<td>Yes</td>
<td>↑ PaO₂/FIO₂ (p &lt; 0.05)</td>
<td>Per protocol analysis (n = 98)</td>
<td>± Mortality and hospital LOS not improved</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Duration MV and ICU LOS (p &lt; 0.05) in the treated group</td>
<td>Intrinsic role of antioxidants on lung?</td>
<td></td>
</tr>
<tr>
<td>Galban et al. [48], 2000</td>
<td>ICU, septic patients (n = 176) Impact vs. Precitene HN</td>
<td>Yes</td>
<td>↓ Mortality (19 vs. 32%; p &lt; 0.05)</td>
<td>Yes</td>
<td>No difference in LOS and duration of MV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nosocomial Infections (p = 0.01) and bacteremias (p = 0.01) in the Impact group</td>
<td>No difference in LOS and duration of MV</td>
<td></td>
</tr>
</tbody>
</table>

IED = Immune-enhancing diet; LOS = length of stay; ITT = intention-to-treat; SIRS = systemic inflammatory response syndrome; Gln = glutamine; MV = mechanical ventilation; EN = enteral nutrition.

1Nonblinded study.
p = 0.051 in the \( \chi^2 \) test)! The post hoc allocation of the patients to 4 subgroups according to the food actually received is a flawed use of baseline data, as the statistical power of the study was insufficient, and it is based on the assumption that treatment has no influence on the result. To make a long story short, the incidence of infections was not different between the 2 groups, and the shorter median length of stay in the Impact subgroup of 89 patients with sepsis (18 vs. 28 days; \( p < 0.05 \)) was no doubt explained by the excess deaths!

The study of Atkinson et al. [47] evaluated the clinical effects of Impact and a control diet in 398 mechanically ventilated ICU patients. In the ITT analysis there was no difference between the 2 groups in terms of mortality, infectious morbidity, or the ICU/hospital length of stay. However, in the ‘early effective nutrition’ subgroup (those receiving more than 2.5 liters of EN in the first 72 h), Impact yielded a significant reduction in the duration of mechanical ventilation, the length of ICU stay and hospital stay, as well as the average duration of SIRS (\( p < 0.05 \) for all these markers). These results strongly suggest that immunomodulating diets are clinically effective in those ICU patients who can receive early and complete EN, but the key problem is that we are unable to identify this subpopulation a priori. Are septic patients the best candidates? Is it worthwhile offering this type of nutrition to all ICU patients, and then to select probable responders according to EN tolerance?

The most relevant study by Galban et al. [48] was a multicenter, nonblinded, prospective, controlled trial involving 181 ICU septic patients who were randomly assigned to receive Impact or an isonitrogenous, but not isoenergetic, diet. The most striking result was that mortality was reduced in the Impact group of these ‘true’ septic patients, and in post hoc analysis this reduction was even more significant in the subgroup with less severe illness (APACHE II score between 10 and 15). However, the length of hospital stay and duration of mechanical ventilation (after censoring for the mortality rate) were not different between groups, nor was different the number of nosocomial infections. The more favorable effect in the less severely septic patients suggests that this subset of patients, close in terms of severity to surgical and trauma patients, may be more responsive to nutraceuticals.

**For the Future, Is It Really Alimentary?**

The clear ambition of immunopharmacological (enteral) nutrition in (septic) critically ill patients is to improve the outcome of patients. The counterpart is that proof of clinical efficacy must be shown in trials with the same methodologies as those used for new drugs (e.g. antibiotics).

This crucial question has been analyzed in several articles on the effects of supplemented enteral nutrition in critically ill patients [44, 45], but not specifically in septic patients. For septic patients in the ICU, the correct mortality and length-of-stay endpoints depend on a variety of factors related to the severity of illness, primary disease, reason for admission to the ICU, the nature of nutritional treatment, etc. Survival analysis techniques should be
used to avoid the influence of practice patterns on the interpretation of mortality, and to censor the effects of death on the length of ICU or hospital stay. To avoid the problem of competing mortality, another solution might be to calculate life-support-free days (e.g. the number of days without mechanical ventilation), a measure that combines mortality and morbidity. In addition, some discrepancies among efficacy analyses of immune nutrition can be explained by the different methodological approaches of the individual studies: ITT analyses, efficacy analyses, and compliance analyses. Despite the progress borne to our practice by evidence-based medicine, we must never forget that truth has variable geometry in medicine, that recommendations are not rules, and that each medical decision relies on outcome trials but should be highly individualized [44].

My personal opinion is that infective morbidity and, presumably, length of hospital stay are reduced by immune EN in multiple trauma patients, and in major surgery. However, such clear-cut evidence is lacking for ICU patients, and especially septic ICU patients, who are too often intolerant to (early) enteral nutrition despite the extensive use of prokinetics. Another subsidiary problem is that we cannot yet determine which nutraceutical(s) is (are) responsible for the improved clinical outcomes, so we have to blindly arbitrate between individual immunonutrients (glutamine, n-3 fatty acids, OKG, etc.), and between the different immune-enhancing diets.

**Hormonal Interventions**

Recombinant human growth hormone (GH) has the strongest anabolic properties, including stimulation of muscle-free glutamine retention, and plays a role in the enhancement of antioxidant defenses and in the control of proinflammatory cytokine production. Unfortunately, in severely stressed patients, such as those with sepsis, added GH may not be biologically active or could even be harmful. Thus, in two well-designed parallel randomized studies involving a total of 532 ICU patients (in which we concede the subset of septic patients was not clearly stated), in-hospital mortality was significantly higher in the GH groups and persisted at the 6-month follow-up, whatever the type of stratification [49]. Among the potential reasons for such an apparently paradoxical result, the unusual underfeeding of the patients and the very high doses of GH that were used in the trial (0.10 mg/kg/ – 1 mg = 3 IU) must be underlined. In summary, the use of GH in ICU septic patients cannot presently be recommended.

A large number of the physiologic actions of GH are mediated at the tissue level by IGF-1 that is released in response to GH. The lack of response to GH could be due to a blunted response of IGF-1 to GH, a consistent finding in sepsis [50]. IGF-1 is a short-acting compound, which reduces protein breakdown, increases protein synthesis, but causes abrupt and severe hypoglycemia.
Preliminary results of recombinant human IGF-1 use in catabolic patients are encouraging, but the effects are transient, so additional studies are needed to determine if this concept is valid in critically ill septic patients.

It has become evident that male and female sex steroids are involved in the regulation of immune responses and in the development of cell and organ dysfunction after acute stress. Knoferl et al. [51] have nicely explored this approach in different animal models with exciting preliminary results. In a recent study [52], 60 multiple trauma patients were randomized to receive either 10 mg oxandrolone twice daily or placebo (thiamine, 50 mg) in addition to the same immune-enhancing diet for 28 days. No differences were seen in body cell mass changes, length of ICU and hospital stay, and incidence of septic events or MOF. Therefore, whether anabolic steroids play a role in selected (septic?) subsets of catabolic ICU patients is yet to be elucidated.

Conclusions

The primary goal in the initial phase of sepsis is to implement aggressive measures to preserve the hemodynamic and respiratory status, while searching for and treating the cause of sepsis. Nutritional support is useless and potentially detrimental, until the patient’s condition has stabilized. When this is achieved, nutrition must begin without any delay in order to prevent severe post-insult malnutrition, but the role of nutrition (enteral or parenteral) as a life-support modality remains controversial in these instances. Some principles are now considered as ‘gold standards’ for conventional nutrition, such as the dangers of overfeeding, the restriction of lipids and to a lesser degree carbohydrates, a careful increase in nitrogen supply, and special attention must be paid to micronutrient supply. However, we have to remain open minded about unsolved debates: the actual benefit of (early) enteral nutrition, the adequate amount and nature of the nitrogen supply, the optimal lipid/carbohydrate ratio in severe sepsis, or the clinical relevance of antioxidant therapy. In these times of cost containment, we have to bring proof of the clinical efficacy of the concept of ‘immunopharmaconutrition’, before the use of nutraceuticals, individually or in combination, enterally or parenterally, can be proposed as a standard of care. The conception, realization and interpretation of well-conducted prospective clinical trials in ICU/septic patients, characterized by the highest risk of development of multiple organ dysfunction, are our challenges for the next years.

References

Nutrition in Sepsis


Nutrition in Sepsis


**Discussion**

**Dr. Bozetti:** Are you suggesting that side effects from long-chain triglycerides were mainly caused by fast infusion, and if followed as low infusions they can be given cyclically?

**Dr. Nitenberg:** I think it is a complex situation as usual. In terms of hemodynamic status and also in terms of the properties of polymorphonuclears, such as chemotaxis and phagocytosis. We showed 10 years ago that when you administer the usual lipid emulsion, 20% intralipid, over more than 8 h without exceeding 500 ml in 8 h, you do not modify the chemotactic and phagocytic properties of the cell. In the same way we and others have shown that in fact the modification of intrapulmonary shunting and pulmonary circulation is very small, very marginal and over a very short time. One hour after the end of the infusion you have no effect, and when you administer lipids over 24 h you have absolutely no effect. This has been proven, and I remember it was also shown by your group a few years ago.

**Dr. Rosenfeld:** We are now going into a new area with new methods of depuration in the critical illness setting, such as plasma absorption for sepsis and hepatic dialysis. Are there any recommendations or work going on about this subject?

**Dr. Nitenberg:** In the setting of nutritional support I am sure there are none, unless you are aware of any work on this topic. In general about the intensive care unit (ICU) population, there are many studies about blood purification, I don’t like the term blood purification. There are stimulating studies about the idea that when you perform depuration of cytokines at the right moment in the right people, which is very difficult to achieve, you can perhaps modify the course of severe sepsis. But to date, to my knowledge, there is no study at all in the ICU population about this type of intervention. But obviously it is one of the future goals of support to septic patients in the ICU.

**Dr. Déchelotte:** I would like to come back to the first part of your presentation on conventional parenteral nutrition in septic patients. I find it quite interesting that 10 or 30% lipids do not make any difference in the outcome of the patients. But it would be very interesting to know what difference the 10% makes in comparison to 45 or 50%, because many commercially available free-component total parenteral nutrition (TPN) diets do provide about 40 and even 45% lipids, and are routinely used in many ICU units. So I think it would be wise to check whether 10% lipids would be enough for essential fatty acid supply and provide energy with only glucose on the other hand.

**Dr. Nitenberg:** I totally agree with you. Until recently I wasn’t sure that the administration of lipids or standard lipid emulsions in ICU patients was really dangerous. Now my opinion has changed a lot and I do agree. Probably until the threshold of 30 or 40% lipids in the amount of calories you administer to the patients, there is no clear difference in the outcome of these patients. If you go beyond this point to 50 or 60%, as you can see in some bags, it could be dangerous and it could also be metabolically dangerous because you provoke fatty infiltration and you have other problems that have
been demonstrated for example by Tappy and Chioléro in Lausanne. That is the reason why in my unit we don't use these bags in ICU patients. We do not use triple solutions, only glucose protein solution in bags and we add lipids after that at various quantities, not exceeding 25–30% of the amount of calories. Sometimes in very sick patients we only administer lipids two times a week. So I totally agree with your opinion.

Dr. Berger: You were advocating early TPN especially if enteral nutrition was failing, but then we are far away from early TPN because we don't know if enteral nutrition will fail clinically before the 3rd or the 4th day if we have managed to reach the targets. So we are actually talking about medium TPN, my question is, do we know of any evidence that there are early high requirements for energy in sepsis? I am not aware of any trial in that sense.

Dr. Nitenberg: In the beginning of the sepsis, it depends on what sepsis you are talking of. In septic shock nutrition is not a problem so you have to concentrate on other therapeutic measures. In several forms of sepsis during the phase of resuscitation the need for nutrition probably does not exist, and it was suggested in old work by Payen that it could be deleterious, especially on the splanchnic bed. That study was performed in rabbits but it could perhaps be translated to patients, although I am not sure of that. In severe sepsis you really have to wait until the beginning of nutritional support. How long you have to wait, nobody knows.

Dr. Heyland: I feel the need to clarify or respond to the immunonutrition data that were presented and are limited to the sepsis population. But I think there are two other studies that contribute to this debate on the value of immunonutrition in the septic population. They are unpublished studies but they demonstrate an increased mortality in patients with infections and patients with sepsis. One of those was a study by Ross that it is coming to press at least in abstract form at an upcoming meeting. In that study there was a subgroup of patients with pneumonia which explained all the excess mortality. There is another study which compared parenteral nutrition to an immune-enhanced diet and was stratified on the basis of sepsis, similar to the Bauer study, and they found excess mortality in the septic population so they stopped enrolment of patients with sepsis in the study. So there is an emerging signal that immune stimulation in this septic population has a potential for doing considerable harm. Now on the contrary, there is the Golban study which is very challenging to interpret because the definition of sepsis was extremely loose. It certainly would not meet the same criteria as the other studies with severe sepsis, basically in positive culture and treatment with antibiotics to get into the study. All the treatment effect was observed in the least sick patients, patients with an Apache score of 10–15. Our average Apache score for patients on enteral feeding is in the 20s. So I don't know who these patients are but they don't represent severely septic patients. There are a lot of methodological limitations with that study and that leads me to why we differ in our interpretation of the literature. If you look at intention-to-treat analysis and if you look at all the studies on critically ill patients you see different signals. If you combine the experience in elective surgical patients, in obese patients, you are going to see a different picture, but if you look strictly at what is happening in critically ill patients then you look at the intention-to-treat analysis, you see a lack of signal of any benefit, but a signal of harm in the critically ill septic patients.

Dr. Nitenberg: I took that from your recent work and I put the question to the audience and to you: what is deleterious, what could be deleterious in the early phase of sepsis for these patients? Is it glutamine, is it arginine, is it n-3 fatty acids or is it only enteral nutrition by itself perhaps? I think this is a key point because we can't respond to this problem using your analysis.

Dr. Heyland: That is true. You are not going to answer that question looking at a meta-analysis, there are not sufficient details there. I don't think it is enteral nutrition
by itself because both groups got enteral nutrition, so it has to be the additives in the immune-enhancing diet. Which one, I don't know. It is plausible, and I still believe that it is arginine as a precursor of nitric oxide synthetase in this population. But that is just a postulate, I don't know.

**Dr. Cynober:** I come back to a detail which in my opinion is not a detail. I was puzzled by your statement that, and I refer to the study of Griffiths et al. [1], there was a slightly significant difference. What is the difference between 'a slightly significant difference' and an 'interesting trend'. I think you are misusing the statistics because the principle of the statistics is the fact that you accept to be wrong at a certain risk, no more, no less, but once you have accepted this risk the things become significant or not. I think that it is very important to comply with this simple rule, otherwise we are in the situation of a recent meta-analysis discussing interesting trends [2], whereas other trends are considered as not interesting. Finally nobody understands what the final conclusion of the whole statistics together is.

**Dr. Nitenberg:** You can use statistics anyway you want to use them, that is the problem. Evidence-based medicine, which is sometimes called evidence-biased medicine, is a hard part of our work. I really think it helps you to understand how it is in our patients. But we have to think about statistics and we have to see what is clinically relevant and what is statistically significant. Sometimes it is statistically significant but not clinically relevant, and sometimes on the contrary it is not statistically significant but it is clinically relevant. We have to mix what is our experience and what is statistics. To come back to the interpretation of the 0.049 result of Griffiths et al. [1]. Of course this is the result and this is statistically significant. I said yesterday I don't know how 5 days of glutamine administration could influence the occurrence 4 months later of 1 myocardial infarction and 1 pulmonary embolism, which is the difference. In fact the outcome of only 1 patient could lead to nonstatistically significant results. So I think we have to think about that, not to say that the study is incorrect, this is a remarkable study. I won't say anything else. To come back to what you said about tendency, what is tendency? If I follow you it is significant or not. There is no tendency, there is only tendentious interpretation of the results.

**Dr. Carlson:** Just a comment and a question. The comment really relates to what Dr. Heyland just said about the difficulties in interpreting some of the studies of immune-enhanced diets. The problem is that you are not even comparing apples with oranges, you are potentially comparing apples with oranges at different stages of the development of the fruit on the tree, if I can use that analogy. One of the concerns relates to the effect of arginine on nitric oxide production. There is also quite old, I think from the late 1970s, animal data suggesting that if you load animals with arginine before you give them endotoxin you produce a much bigger TNF response than that of endotoxin alone. So I guess one of the concerns that I have is that you may get different effects according to the time frame in the systemic inflammatory response syndrome (SIRS), compensatory anti-inflammatory response syndrome response, and perhaps if you treat people after the acute inflammatory episodes started to subside you may get beneficial effects. Certainly a lot of early deaths are actually from treatment very early in the SIRS episodes with immune-enhanced diets. That is the comment. The question I have is that you showed data which suggest that there are no adverse effects on infection rates using long chain triglyceride-based TPN. The concern I have is that bone marrow transplant patients have a fairly naked immune system, and therefore it could be argued that they are not a particularly useful group in which to compare the effect of lipid emulsion. If you look at the data from Okada et al. [3] on neonates, they found a significantly higher incidence of bacteremia in neonates fed intravenous fat compared with intravenous glucose, and in the TPN group there was impaired monocyte tumor necrosis factor (TNF) production and

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in vitro bacterial killing was found in the intravenous lipid-fed group. So the question I have is do you really believe that in the real world as opposed to in a test tube, giving large doses of intravenous fat is safe in an immuno-compromised septic patient?

*Dr. Nitenberg:* No, I did not say that. I think when I responded to the question from Dr. Déchelotte, I said that it could be hazardous to go over 30% of the energy amount in terms of lipids because we have some concern about the immunosuppressive risk of intravenous feeding with large amounts of lipid emulsion. However, if you look carefully at the literature, we have no clear proof of that. We have many suggestive data but we have no study proving that clearly, not only in septic patients but even in ICU patients. We have not yet done these experiments. We have to do that. I turn to Dr. Neu, is it true that lipid emulsions are really dangerous? When you showed your data you said that finally nobody knows clearly and you are increasing the amount of lipids you are giving.

*Dr. Neu:* That is the only study that I am aware of that really suggests this. I think in that particular population we really have to weigh the risks against the benefits. If you need a certain amount of calories to maintain these babies and also to provide for growth and to keep them from having denutrition during a very critical period of time, the balance still weighs toward giving the lipids.

*Dr. Chioléro:* I would like to make a comment on hemodynamically unstable septic patients since we all agree that during the septic shock phase is not the time to administer nutritional support. But during the subsequent phase when the patients have had noradrenaline but are unstable, we have collected some experience in Lausanne on enteral feeding giving them at least half or two thirds of the nutritional requirement by the enteral route. At the last ESPEN meeting Dr. Berger provided information on 70 cardiac surgery patients, a third of them had aortic counter pulsation, most received catecholamines. We were able to feed them enterally quite successfully. So in hemodynamically unstable patients, we believe there is no reason that enteral feeding should not be given.

*Dr. Nitenberg:* Really I don't know. I was surprised by the publication by Moore et al. about small bowel absorption, and finally I found two other examples in the literature. In my experience, in the very severe patients we have in our unit, I did not have this problem. So as you said, I think it is a late complication of enteral feeding in fact, not an early complication of enteral feeding. It is very interesting that when patients are hemodynamically unstable we have in fact not observed this type of necrotizing enteritis, unless we missed it. It is possible in very critically ill patients. There is one study from Russell et al., I think in 1995, in septic rats under mechanical ventilation showing that even when the hemodynamic status of the rats was restored, there was an incredible decrease in splanchnic perfusion and splanchnic extraction of oxygen, and when they added some amount of enteral feeding in these very severely septic rats they completely restored the oxygen extraction and the hemodynamic perfusion. Maybe small amounts of enteral nutrition in this critical period could be more beneficial than harmful, but we have to test this hypothesis.

*Dr. Chioléro:* We have tested giving enteral feeding with arginine and it was recently published in *Intensive Care Medicine.* The formula was Impact® which was administered over 6 h in cardiac surgery patients receiving high doses of catecholamine. Cardiac output increased, intramucosal pH was stable and the extraction of cardiogreen increased, so there was no sign of gut ischemia in these patients.

*Dr. Moore:* Nonocclusive bowel necrosis is a late event. In most patients it is due to enteral diets. One notable example was a patient who had recovered from multiple organ failure, and was on continuous hemofiltration. He was switched to intermittent dialysis. At the same time, he developed a septic event. Due to too much volume being removed during dialysis, the blood pressure dropped. Vasopressor agents were started.
The second notable case was a man who had a massive facial fracture and nearly exsanguinated. He survived but developed multiple organ failure. He was ultimately advanced to full dose jejunal feeding. After 12 days he was taken to the OR for a 10 hour reconstruction of his face. This was complicated by some excessive bleeding and his blood pressure dropped. The operating room staff didn’t know that they should stop the feeding, and a day and half later he died. Critically ill patients are at risk for recurrent episodes of ischemia reperfusion, and we just have to be cautious to turn off the feeding when they get sick or something bad happens to them.

Dr. Kudsk: I want to compliment you on your brilliant presentation. There are not many studies in which patients with sepsis are generally randomized. I clearly remember that in both Dr. Moore’s and my studies we showed a benefit. My study was in a group of very highly injured patients, Dr. Moore’s was in a broader group. We did show a reduction in intra-abdominal abscess and septic complications and multiple organ failure. The second point is the Ross study (unpublished data) and I think that the population at risk was elderly septic patients with pneumonia. If one focuses on elderly septic pneumonia patients, I think it should be tested in another study whether there really is going to be an increase in mortality in this patient population. If it can be confirmed in a second study, I would clearly agree that in elderly septic pneumonia patients you should not use immuno-enhancing diets.

Dr. Nitenberg: I know your work and the work of Dr. Moore about trauma patients. The studies are very interesting but they only refer to multiple trauma patients in the States. We do not have that type of patient, they are very severely ill patients. If I remember correctly in the discussion of your paper you stated that your experience in fact concerns only 7% of your trauma patients included in the study. So I think the generality of this result is not obvious. That is my only comment.

Dr. Kudsk: Again it is only 7%, but with 4,500 admissions, many were people who came with isolated femoral fractures and we did not feed them enterally. Some of the patients, who we also did not feed, came in with gun shot wounds to the calf. So that is the whole population, but there was a much higher use in people who were admitted to the ICU.

References