Nutritional Support in ICU Patients: Position of Scientific Societies

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The most prominent metabolic alterations which characterize the systemic inflammatory response syndrome and sepsis include hypermetabolism, hyperglycemia with insulin resistance, accelerated lipolysis and net protein catabolism [1–3]. The combined effect of these metabolic alterations associated with bed rest and lack of nutritional intake can lead to a progressive depletion of lean body mass.

Even if nutritional support in critically ill patients cannot fully prevent or reverse the metabolic alterations and, consequently, the disruption in body composition and the erosion of the body cell mass, it can nevertheless slow the rate of net protein catabolism by providing an exogenous load of energy and nitrogen [2, 4].

Recent publications demonstrate increased non-resting energy expenditure (i.e. activity) after the first week of critical illness [5]. Total energy expenditure in septic patients was in fact 25 ± 5 kcal/kg/day during the first week of critical illness and increased to 47 ± 6 kcal/kg/day during the second week. However, it remains to be determined if administering more than 25–30 kcal/kg/day is beneficial to these patients, and if providing more than 1 g amino acid/kg/day (a quantity sufficient to minimize loss of body protein during the initial 2 weeks of critical illness) carries further benefit [6].


It is worth noting that the guidelines of the ESPEN on this topic have not been properly published and all ESPEN statements refer to the book officially supported by the educational committee of the society [14].

Regarding the AGA, we refer to the medical position statement concerning parenteral nutrition only [15].

For each society statement, we considered the following issues: (1) selection of patients; (2) timing; (3) requirements of macronutrients; (4) composition of the nutritive admixture; (5) special nutrients, and (6) special conditions.

**Selection of Patients**

Even if data from patients recovering from major surgery cannot be fully extrapolated to other critically patients, morbidity and mortality increase significantly after 2 weeks of glucose infusion (250–300 g/day) when compared to nutritionally complete total parenteral nutrition (TPN) [17]. Initiating TPN after 2 weeks of glucose infusion does not improve outcome [17].

The Italian and the American societies have the most strictly defined criteria in the selection of patients requiring nutritional support.

SINPE 1995 [7] recommends nutritional support in all patients with hypercatabolism (>15 g urinary nitrogen/day) or 10–159 urinary nitrogen/day if they are unable to be adequately fed by mouth (<50% of the basal requirements) for 7 days. If patients are already malnourished and have a catabolism exceeding 10 g urinary nitrogen/day, they should receive nutritional support if 5 days of inadequate feeding is anticipated.

ASPEN 2002 [16] recommends ‘that some form of nutritional support be started after 5–10 days of fasting in patients who are likely to remain unable to eat for an additional week or more’.

This statement confirms the previous recommendations of the ASPEN-ASCN 1997 [13] that suggested nutritional support for ‘patients who are unlikely to consume adequate nutrient intake for prolonged period’ (7–10 days).

The other societies have a less strict criterion of patient selection:

- ACCP 1997 [9]: ‘clinical setting requiring at least 4 days of ICU confinement’.
- SFNEP 1998 [8]: malnourished patients (weight loss exceeding 10% of the body weight) and those unable to reassume ‘normal’ nutrition in a week after the acute episode.
Nutrition Support in ICU Patients

- ESICM 1998–1999 [11, 12] recommends nutritional support in patients malnourished or well-nourished but candidates for fasting of more than 3 or 4 days and in severe trauma or burn patients.

With reference to enteral nutrition (EN) only, ESICM 1998–1999 [11, 12] suggests that enteral support is indicated in septic malnourished patients unable to eat, or in well-nourished candidates for prolonged fasting (>7 days).

EN may also be given as a supplement if one expects an insufficient oral intake for >7 days.

AGA 2001 [15] simply concludes that TPN does not affect mortality in trauma patients or length of time on mechanical ventilation. However, it points out that some but not all the randomized clinical trials (RCTs) comparing TPN to EN found less infections in patients receiving EN.

**Timing**

SINPE 1995 [7] and ACCP 1997 [9] recommend starting nutritional support as soon as possible after resuscitation. In fact, in critical states when splanchnic blood flow is compromised, EN can increase blood flow in the proximal part of the bowel (where EN is administered) and decrease blood flow in the distal part with consequent hypoxia, impairment in motility and damage to the intestinal mucosa.

FSNEP 1998 [10] also considers hemodynamic instability as incompatible with the start of nutritional support.

However, it is worth recalling the recent experience of Revelly et al. [18] who showed that enteral delivery of nutrients can be safely performed with good compliance and utilization of substrates also in patients with hemodynamic instability requiring inotropic drugs like catecholamines.


In contrast, ASPEN 2002 [16] seems to propose a policy of wait and see: ‘it appears reasonable to recommend that some form of specialized nutritional support be started after 5–10 days of fasting in patients who are likely to remain unable to eat for an additional week or more’.

With regards to EN, ESICM 1998–1999 [11, 12] suggests that ‘EN should begin as soon as possible, not necessarily with the goal of providing total support, but with that of exerting the beneficial effects on the gut which can be obtained with even small amounts of enteral feeding. In many critically ill patients a 5- to 7-day delay before initiating EN has been considered reasonable, since no deleterious effects of short fasting have been demonstrated in these conditions. However, if prior malnutrition or a simply catabolic condition are present, this delay should be shortened to 1–2 days.’
Requirements of Macronutrients

Energy

SFNEP 1996 [8] recommends for septic patients 34–44 kcal/kg/day, which should correspond to 1.3–1.5 times the estimated resting energy consumption.


ESICM 1998–1999 [11, 12] differentiates males who should receive 25–30 nonprotein kcal/kg/day from females who should be treated with 20–25 nonprotein kcal/kg/day. This society also specifies the reference body weight in malnourished and obese patients; this should be calculated as the mean between measured and ideal weight in severely malnourished patients, and as a value 20% higher than the ideal weight in obese patients.

SFNEP 1998 [10] suggests that energy intake should be very close to the resting metabolic expenditure. The estimate by the Harris-Benedict equation should be corrected by different factors depending on the nature of the injury: postoperative period 1–1.1; fractures 1.1–1.3; severe infection 1.3–1.6, and burns 1.5–2.1. However, different conditions may affect the metabolic expenditure: hyperthermia increases metabolic expenditure by 10%/1 °C, and infection also by 10%. In contrast, both hypothermia or sedation tend to reverse hypermetabolism to a value close to basal.

ESICM 1998–1999 [12] also specifies that the lower values should be followed in patients >60 years of age.

When body temperature is increased, 10% should be added to energy needs for every degree >37 °C, according to this society.

Glucose

SINPE 1995 [7] suggests that glucose should account for more than 80% of total energy requirements, whereas SFNEP 1996 [8], ACCP 1997 [9], SFNEP 1998 [10] and ESICM 1998–1999 [11, 12] suggest that glucose should cover 60–70% of the energy requirement.

Consequently SINPE 1995 [7] recommends a dosage not exceeding 5.7–7.2 g/kg/day, while ACCP 1997 [3] suggests 2–3 g/kg/day, SFNEP 1998 [10] 3.8–4.5 g/kg/day (15–18 kcal/kg/day) and ESPEN 2000 [14] a value ranging from 3 to 6 g/kg/day.

Fat

There seems to be an agreement that long-chain triglycerides (LCTs) should account for at least 3% of total energy intake [7] and n-3 PUFAs for at least 7% of total calories.

for 20–30% and 30–40% of nonprotein calories, respectively, whereas according to ACCP 1997 [9] fat should represent 15–30% of total energy.

ESPEN’s 2000 [14] indications are more concerned to avoid toxicity (no more than 1.4 g LCTs/kg/day or no more than 1.7 g medium-chain triglycerides (MCTs) as MCT/LCT emulsion/kg/day rather than to suggest the optimal dose of lipids.

SFNEP 1996 [10] recommends that lipid should not exceed 2 g/kg/day in septic patients.

FSNEP 1998 [12] recommends 0.7–0.9 g/kg/day (6–8 kcal/kg/day).

This society also states that there is no evidence of a significant clinical difference among LCTs and mixed emulsions of LCTs and MCTs and emulsions with a prevalent olive oil content (80%).

Amino Acids

ACCP 1997 [9] and ESICM 1998–1999 [11, 12] suggest amino acids be given at 1.2–1.5 g/kg/day. According to ACCP 1997 [9] recommendations for amino acids should account for 15–20% of total calorie intake, while ESICM 1998–1999 [11, 12] suggests that patients should never receive more than 1.8 g/kg/day unless they have exceptional losses (extensive burns, digestive losses, etc.).

This society also suggests that body weight used for this computation should be the mean between ideal and measured weight in severely malnourished patients, and 20% higher than the ideal weight in obese patients.

FSNEP 1998 [10] recommends 1.5–2.1 g/kg/day.

ESPEN 2000 [14] and SINPE 1995 [7] recommend higher quantities, 1.5–2.0 g/kg/day and also 2.5 g/kg/day in severe catabolism [7]. SFNEP 1996 [8] suggests that an amino acid intake of 2.5 g/kg/day is a maximum beyond which further supply is inefficient and even harmful, and an appropriate energy/nitrogen ratio should be in the order of 100–150 kcal/g nitrogen.

Micronutrients

There is no recommendation for an extra supply of micronutrients [10], except if patients are supported enterally with 1,500 ml of enteral formula or less or in the presence of severe conditions combining increased needs and large losses of trace elements.

Route of Administration

According to SINPE 1995 [7], ACCP 1997 [9], ESICM 1998–1999 [11, 12], and ESPEN 2000 [14], the enteral route and a continuous administration are preferred [10].

ASPEN-ASCN 1997 [13] and ASPEN 2002 [16] also prefer the enteral route but ‘it is not clear whether EN provides a specific benefit or whether TPN itself or overfeeding by TPN is associated with an increased risk of infection’.
ESICM 1998–1999 [11, 12] recommends the use of standardized, industrially produced feeding as iso-osmotic (approximately 300 mosm/l) mixtures containing 1–1.5 kcal/ml, 45–60% of which should be in the form of carbohydrates, 20–35% as lipids, and 15–20% as proteins. These mixtures should be gluten- and lactose-free.

The consensus of ACCP 1997 [9] also states the modalities of the EN: ‘Intragastric feeding requires adequate gastric motility. In general, a gastric residual exceeding 150 ml will require a moderation of the infusion rate, consideration for supplemented intravenous nutrition, or the use of small bowel feedings. Small bowel feedings can usually be performed, even in the presence of gastric atony and colonic ileus … and the presence of bowel sounds and passage of flatus or stool are not necessary for the initiation of enteral feeding. … Diarrhea may occur with administration of enteral feedings. It is usually secretory and it is generally not an indication to discontinue enteral feedings. If it exceeds 1 liter/day, an evaluation is required. If a relevant medical or surgical cause is not found, including Clostridium difficile enterocolitis, antidiarrheal agents may be used.’

According to ESICM 1998–1999 [11, 12], EN is absolutely contraindicated in intestinal obstruction, anatomic disruption or severe intestinal ischemia.

EN should be administered with caution in patients with reduced intestinal perfusion due to a state of prolonged or severe shock. Such patients are unable to increase their splanchnic flow in response to enteral feeding, and thus are unable to sustain the process of digestion and nutrient absorption.

Many patients with severe pancreatitis or high output proximal intestinal fistulas are intolerant to EN.

Regarding some practical aspects, this society also recommends that bags containing 500 ml of feeding admixture should be used, due to easier storage, manipulation and convenience at the bedside. The tubing connecting the container to the patient’s feeding catheter should be changed once a day to avoid contamination, even if clear evidence of an association between the latter and an increased risk of clinical infection are still lacking.

**Immunomodulation and Special Nutrients**

The consensus guidelines of the Italian, American, and European societies edited before 2000 mentioned immunonutrients, but did so only to state that their role was still to be defined.


ASPEN 2002 [16] also considers intravenous glutamine as being efficacious in reducing the infection rate [19] and improving survival [20].
Regarding the immune-enhancing enteral formulas, ASPEN 2002 [16] states that they may reduce the incidence of infectious complications but do not alter mortality [21, 22], which in some subgroups may actually increase [23, 24]. This statement mainly relies on the meta-analysis of Heyland et al. [24] which showed that in studies of critically ill patients with a high-quality score, immune-enhancing formulas were associated with an increased mortality rate and a significant reduction in infectious complications, compared with RCTs with a low-quality score.

**Monitoring Nutritional Support**


- Avoid overfeeding (i.e. RQ >1) and reduce calorie intake in patients with respiratory risks.
- Avoid protein overload by checking nitrogen balance every 5–7 days, decrease nitrogen if BUN exceeds 100 mg/dl. If there is no benefit with formulations for acute renal failure, dialysis should be considered.
- Avoid excessive levels of triglycerides (more than 500 mg/dl).
- SFNEP 1998 [10] advises to start at 25 ml/h during the first 24 h and to increase by 25 ml/h every 12–24 h depending on the digestive tolerance and the desired volume to be administered. Tolerance is checked every 6 h by measuring the gastric residue and temporarily withdrawing the infusion should such volume be 200 ml or more.
- With reference to EN, ESICM 1998–1999 [11, 12] recommends obtaining an abdominal X-ray after placement of a nasogastric tube and to monitor tolerance to gastric feeding by, ‘measuring the gastric residue once a day (normal <300 ml) in order to reduce the risk of bronchoaspiration, especially in patients without protection due to tracheal intubation. If gastric residues are >300 ml, the infusion rate should be decreased by 50% for 4–6 h, and then resumed progressively over 24–48 h, during which time gastric residues should be monitored twice daily. Prokinetic agents such as erythromycin should be used in this situation to improve gastric emptying’.
- Diarrhea persisting for more than 3 days after exclusion of other common causes in patients receiving antibiotics should lead to stool culture for *Clostridium difficile* toxin, as well as a decrease in the flow rate of EN administration. If necessary, transient use of TPN should be considered in this situation to ensure adequate nutritional support. Finally, the value of administering antidiarrheal agents or *Saccharomices boulardii* should be considered in individual cases.
Administration of EN and TPN


- Gastric feeding is usually poorly tolerated, especially if volumes >1,000 ml/day are administered.
- Nasoenteric route is preferable for short-intermediate (2–4 weeks) EN.
- Small diameter (6–12 french) silicone or polyurethane tubes are preferable. Depending on the desired location (in stomach, duodenum or jejunum), the appropriate length of the tube (90,110, at least 120 cm) is chosen.
- Proper placement is easier if performed under fluoroscopic guidance or endoscopic assistance using tubes with inner stylets.
- Percutaneous route is advised if EN is extended for ≥4–6 weeks and 9- to 24-french tubes are available.
- SFNEP 1998 [10] does not recommend the use of cyclic TPN to avoid the potential risk of fluid overload if all the solution is infused over a limited period of time, and the possible toxic effects of lipids (increase of intrapulmonary shunts, possible immunosuppression) due to a fast or abundant administration.

Special Conditions

Some societies have differentiated special acute clinical conditions with particular reference to the energy and nitrogen requirements. SFNEP 1998 [10] has considered that there is some specificity in the nutritional approach in patients with severe sepsis, trauma, burns, and organ failure.

Sepsis

In these patients maximal care must be made to not exceed the energy requirements especially if hemodynamic conditions are frail. Even if nitrogen balance is negative, there is no particular interest in administering >2 g amino acids/kg/day.

Trauma

The energy requirements may increase to 1.1–1.3 times the basal metabolic expenditure and reach a value of 1.4–1.9 times if a septic state is associated. Fat administration might have a deleterious effect on infectious complications should it be delivered in an excessive quantity. Increasing the glucose level to >9 mmol/l (180 mg/dl) plasma should be avoided in order not to worsen cerebral ischemia.

Organ Failure

In patients with acute respiratory failure the recommendation is to avoid an excessive calorie load which increases CO₂ production and the fast infusion
of lipid because of the drop of the \( \text{PO}_2/\text{FiO}_2 \) ratio. Phosphorus deficiency should be prevented or corrected since it interferes with diaphragmatic function.

In patients with renal failure nitrogen intake should not decrease: in contrast, if patients undergo hemodialysis or hemofiltration, the administration of glucose and amino acid should increase because of their potential loss during the procedure.

Caution must be paid to vitamin C administration because of the risk of oxalose.

In patients with liver failure there should be no restriction in the supply of lipids and proteins if they are not encephalopathic. However, careful surveillance of glucose administration is required.

**Burns**

The energy requirements have to be tailored to the extent and depth of the burn. An approximate estimate is obtained by Curreri’s formula (25 kcal/kg + 40 kcal/% burn surface). However, deep sedation and analgesia reduce the energy expenditure. The administration of glucose and amino acids may reach 7 and 2.1 g/kg/day, respectively. The administration of vitamins and trace elements is recommended to improve the healing process.

The ASPEN Board of Directors [16] has differentiated the chapter on ‘Critical Care for Critical Illness’ from that on ‘Critical Care for Burns’.

Since nutrition is a transverse discipline, a discipline within a discipline, we can expect that future guidelines for ICU patients will differentiate the approach to subjects with prominent organ failure, such as patients with cardiac or respiratory or renal failure. This also is the policy of the new edition of SINPE’s guidelines, which are currently being prepared.

The guidelines of ASPEN 2002 [16] also include those of the American Burn Association Clinical Guidelines [25]. They recommend measuring, if possible, the energy requirement using indirect calorimetry and to increase the measured energy expenditure by 20–30% if physical therapy is performed or wound care is required.

There is also evidence of an increased protein need (20–33% of total calories from protein and a calorie:nitrogen ratio of 110:1 in severely burned children). EN should be used in preference to TPN and should be started as soon as possible. TPN should be reserved for patients who require nutritional support and EN is contraindicated or is unlikely to meet nutritional requirements within 4 or 5 days.

**Areas of Consensus and Discrepancy**

An overall evaluation of the statements of these societies shows a general agreement on the majority of issues we have considered. There is no doubt
that nutritional support, especially via the enteral route, is recommended by all societies. This is not because of a better nutritional effect of EN comparing to TPN but because of greater protection against infections probably due to better preservation of the immune system within the gut. In addition EN is less expensive. TPN as the only nutritional support is reserved for patients who cannot be fed enterally. The selection of patients varies in the recommendations of some societies that modulate the option for nutritional support according to the degree of hypermetabolism or to the prevision of some days of inadequate nutrient intake.

This probably reflects two different positions, a traditional one referring to nutritional support as a tool to maintain an adequate nutritional status of the patients, and a more innovative one which considers nutritional support as a pharmacological tool to control the metabolic response to trauma, regardless of the nutritional status of the patient.

Also the proper time to start nutritional support shows little difference between the societies' recommendations. The authors supporting an early (immediate) start of nutritional support do not rely on the results of RCTs which do not exist, but on experimental data and clinical experience with burn patients or surgical patients receiving immunonutrition.

Perhaps the area of major discrepancy regards the composition of non-protein energy substrates to be administered. A high glucose to lipid ratio may be preferred because glucose is able to improve the nitrogen balance better than fat and represents the preferred fuel for tissue repair and bone marrow, and does not have the immunosuppressive properties of lipids.

In contrast, authors in favor of lipids claim that they are well utilized in injured people who often present a respiratory quotient of <1 and fear the deleterious effects of an excessive CO₂ production on weaning patients from ventilator.

The outstanding study of Van den Berghe et al. [25] is too recent to be considered in the guidelines of these societies. These authors showed that an intensive insulin therapy significantly reduced the mortality of ICU patients, principally through a reduction in the incidence of multiple-organ failure with a proven septic focus in subjects receiving intensive care for more than 5 days.

It is noteworthy that these results were obtained with a glucose:lipid ratio of 60–80:40–20, respectively, and a calorie regimen of 18–19 kcal/kg/day, the clinical benefit was magnified in the weeks–months after admission to the ICU and the mean glucose level was 8.4 and 5.9 mmol/l (153 and 108 mg/dl) in conventional treatment and intensive treatment groups, respectively.

From a speculative point of view, it is noteworthy that neutrophil-impaired phagocytosis has been reported both in laboratory [26] and in postoperative patients [27] when the blood glucose level was 13.3 mmol/l (240 mg/dl) or >12.2 mmol/l (270 mg/dl), respectively. Therefore it would appear that the benefit of intensive treatment was not due to a lack of noxious effects of
blood glucose levels (which were lower than those commonly recognized as capable of badly affecting the host’s defenses), but rather to the positive metabolic effects of insulin and were achieved with administration of 3–4 g glucose/kg/day.

**Discussion**

There are some points that deserve consideration. First, there is a great discrepancy between the abundance of data in the literature and the scientific value of their evidence. Only two publications, both from the USA [13, 16], attempted to grade their statements on the basis of the strength of the supporting data, as follows.

- **A** = Supported by RCTs or meta-analyses of RCTs.
- **B** = Supported by well-designed nonrandomized prospective, retrospective or case cohort-controlled studies.
- **C** = Supported by uncontrolled published experiences, case reports, or expert opinion or editorial consensus.

The preference of the scientific community is to rely primarily on RCTs as the basis for establishing practice guidelines, because therapies that are accepted and widely used may subsequently be found lacking when prospective RCTs are performed [28].

However, we fully agree with the opinion of the ASPEN Board of Directors [16] when it states that ‘a major distinction between therapeutic trials of the efficacy of a drug or a procedure and feeding of nutrients known to be essential to maintenance of human health and survival must be made. Withholding a drug or invasive procedure will not produce disease in otherwise healthy humans, whereas essential nutrients must be provided to both healthy and ill people. Patients with advanced malnutrition or who are at risk for becoming severely malnourished must be fed to prevent death by starvation.’

In ICU patients, many of the guideline statements of the different societies were developed on the basis of expert opinion and editorial consensus because of the ethical dilemma of conducting RCTs with patients at risk of starvation who could not be randomized to a control arm without nutritional support.

A further major difficulty in clinical trials on nutritional support in critical illness is the extreme heterogeneity and complexity of critically ill patients. We agree with the conclusions of the Workshop of the American Thoracic Society Critical Care Assembly on Outcomes Research [29] when it states that, ‘... to formulate a research question an investigator must be able to define a disease, treatment, patient population, or provider to study and operationalizing these variables for critical care outcome research is complex. ... Critical care is a challenge to the outcomes researcher precisely because
the key variables of disease, patient population, therapy, and provider are difficult to study.'

Adopting a pragmatic solution that is to define critical care geographically as that taking place in the ICU, by the intensivists working in an ICU, on patients admitted to an ICU, does not solve the problem. In fact ‘… flexible nurse staffing, mobile technology, intermediate care units, and the growth of subacute care for chronically ill patients make the assumption that critical care begins and ends at the ICU door problematic. In addition, some patients, such as those recovering from operative procedures, may receive care in an ICU but not be critically ill…’.

Nutritional therapy, like ventilatory or renal support, is not a disease-specific treatment and the assessment of benefit should be based on correction of nutritional abnormalities.

The outcome of these subjects is primarily affected by organ function impairment and the higher the number of organs and apparatus compromised, the worse the prognosis. As a matter of fact, the common scoring systems of severity of illness as APACHE II and III and SAPS II are composed by multiple items (14 and 12, respectively), thus confirming that nutritional status is only one (and certainly not the most prominent) of the components of the risk of complication/mortality.

Moreover, these scoring systems have recently been criticized because variability in collecting and managing the data could affect an objective determination of risk factors included in the severity of these illness scoring systems.

Finally, the effects of nutritional support are usually measured in many days or weeks whereas the mortality of ICU patients often occurs few days after admission. ICU patients may die just after their admission to the ICU, even if well-nourished or well-supported by artificial nutrition.

Therefore, difficulty in assessing the role of the nutritional status and, consequently of the nutritional support, explains why in the most recent publication [16] the four practice guidelines included in the recommendations for nutritional support in critical illness are classified as B or C and there is no A class.

This finding corresponds with the coding of the ASPEN Practice Guidelines in Nutrition Support as reported by Wolfe and Mathiesen [30]. They found that only 16% of the guidelines were judged to rely on good research-based evidence (class A), 29% on fair research-based evidence, and 55% on expert opinion only.

**Conclusion**

There is a gap between the abundance of data in the literature on nutritional support in ICU patients and the scientific value of their evidence.
This may be due to the extreme complexity of the critically ill patients and to the fact that nutritional support in general is not a disease-specific treatment. Nutritional support aims to treat the metabolic component of the critical illness but this does not necessarily translate into a better outcome for the patient. This chapter reviews the position of some national and international societies with special reference to the role of nutritional support in ICU patients.

There was some agreement on the following points:

- Nutritional support, especially via the enteral route, is recommended by all societies for malnourished patients, patients who are candidates for prolonged fasting or patients who are hypercatabolic or suffering from major injury.
- Nutritional support should start in an early or relatively early phase, as soon as the hemodynamic conditions have stabilized.
- Most societies recommend an energy intake proportional to the energy requirement and, empirically, of about $25 \pm 5\ \text{kcal/kg/day}$.
- The nitrogen intake should range between 1.2 and 2.0 g amino acids/kg/day; on rare occasions 2.5 g amino acids/kg/day should be administered.
- The role of immunonutrition is not scientifically validated.
- There is some discrepancy about the calorie composition of the admixture, since some societies recommended a high glucose:lipid ratio regimen, while others preferred a more balanced regimen.

On the whole, few recommendations relied on good research-based evidence and the majority on studies of lower quality or on expert opinion.

References

Discussion

Dr. Zazzo: Before we start the discussions, for more information I want to repeat that Dr. Bozzetti has no responsibility except for the last two slides.

Dr. Bozzetti: I think there are some French doctors here who are also responsible for the statement of the French-Speaking Francophone Society.

Dr. Déchelotte: All of us have some responsibility in this situation because we either performed studies in the last years or participated in round tables or conferences. I think it is quite disappointing that over the last 5 years experts in many countries have spent so much time working almost in parallel and we are not even able to draw the same conclusions from the same literature. I think it is quite a pity that so much scientific energy has been misused. I suggest that we take this into account when we plan new consensus round tables, to try to work more together and to obtain some good evidence for everybody, because it should not be so different from one part of the Alps to the other.

Dr. Bozzetti: I think that some discrepancies are untrue but only depend on the fact that we are considering different kinds of patients. For instance if we look at the result of immunonutrition in surgical patients and in critically ill patients, the results are quite different. So perhaps the first thing is that it is better to define which patients we are considering.

Dr. Déchelotte: And the second point is more optimistic. The literature, the good literature, I mean well-performed, high-scale, prospective studies, has probably increased in the last 5–10 years. So we can expect that our next discussion of guidelines will be more roughly based on good literature.

Dr. Labadarios: On the point of the cost-ineffectiveness of all these efforts, it might be an idea that one recommendation of this workshop should be for the International Council of Nutritional Support Organizations, in which all the relevant societies are represented, to be given a mandate to issue unified guidelines which would be a little bit more helpful than the ones we have at present.

Dr. Berger: We all agree that nutrition is perhaps the field where the biggest beliefs have been added. We all agree that we should improve world science and our studies. But aren’t you fed up with this evidence-based trend, absence of evidence is not evidence of absence, and maybe we should start rethinking a few things.

Dr. Bozzetti: I completely agree with you. I would like also to stress that one major limitation of the study, and this in complete agreement with what you said, is that you can study in the proper way, that means a randomized way, patients undergoing a short period of starvation, comparing different types of nutritional support, but when you consider a long period of artificial nutrition as a life-saving treatment, you can’t have a control group and, I agree with you, this lack of evidence does not mean that there is no evidence.

Dr. Carlson: I don’t think it is reasonable to expect massive international agreement between different groups, especially when there is an absence of very clear evidence-based studies and what you end up with is philosophy. It has often been said that you can expect to get agreement between clocks more frequently than between philosophers. The second point is that I am not at all despondent that there are differences in opinions between different expert groups and the lack of clear categorical evidence, because in fact if you look at most of other areas of medical practice and really ask where is the evidence to support this or that course of action, there often isn’t very good categorical evidence from randomized control trials for many things, particularly surgical issues. Lastly, perhaps we are expecting too much of nutritional support if we are expecting to see big differences in outcome in critically ill patients when there are so many other variables. Most people I think don’t die of nutrition-related complications.
these days, or at least easily identifiable nutrition-related complications. On a pragmatic level if you look at differences in outcome between different surgeons, they are several fold greater than any potential benefit that you might expect to see with different strategies for nutritional support. So I think that is the problem we face.

_Dr. Allison:_ If we are allowing philosophical thoughts and I guess it is a bit late in the day for science, penicillin was introduced without any data to support its use. When Alexander Fleming applied to the Medical Research Council for a grant to develop his work, he was turned down on the grounds that it was unlikely to be of any practical use.

_Dr. Herndon:_ I would like to respond to your personal reflection. Point number 3, I think it is very difficult to look at short-term outcomes and perhaps that is the reason for the lack of consensus as alluded to in the previous discussions. But I think as people interested in metabolic support we may have harped too much on short-term outcomes and not looked at long-term outcomes about patient populations, strength, longitudinal growth in children, and that type-1 evidence-based data can be obtained by looking at interventions that we perform in the intensive care units (ICUs) that may affect the long-term outcomes, particularly if we carry through with our therapies and follow our patients as we should. I think the area here is really our own, and not following patients to the outcome and defining the outcomes that we should. Perhaps we should ask the international or national societies to help design studies that look at outcomes that can be achieved.

_Dr. Berger:_ Those guidelines, many of us have given much time to them, and I think they are better than nothing. We all lack education and training in all our countries for nutritional support. These are just meant to be as you said, and I fully agree with you, the minimal standard we are supposed to go for. So having them repeated, having them improved over time is perhaps a limited way to just try to overcome the lack of training and perhaps we can do it better through implementing training in all our countries on this topic. That will produce better studies, better things, and I go also in your direction, I fully agree with you on long-term outcomes.

_Dr. Zazzo:_ In the same way I agree with your proposition. We don't know the gap between the literature and academic recommendations and practice in clinical units, and I think this has to be evaluated first of all. How can we give credibility to the concept of nutrition in postoperative patients or in the ICU and improve diffusion of this recommendation and expert reports? I think this is probably the future and the name of the session is 'from now to the future'. It is probably a challenge for the future, an educational challenge. I think this is a very important point.

_Dr. Ribeiro:_ We try to make guidelines in Brazil, the Brazilian Society, and our worry is about guidelines. They all decide who makes good or bad medicine based on rules, and I think medicine is based in experience and evidence is just a little part of medicine. This is my first concern that the guidelines can decide who makes good or bad medicine. My second concern is that this is also the case in the Health Medicine Organization, to decide what you are going to do and what you are not going to do. I don't know if you have these worries in Europe or in United States, but it is some worry we have in Brazil right now with guidelines.

_Dr. Endres:_ I would not be afraid of this I think because it is only our guidelines or recommendations, and all this is based on consensus conferences, and we all know that the reason for organizing consensus conferences is the lack of data.

_Dr. Nitenberg:_ Perhaps we have to stay modest about the impact of guidelines. I remind you about an exploration of that field recently. There was recently an article, I think in the American Journal of Medicine, on why doctors are so reluctant to apply guidelines. I remember well that there was a consensus conference on the utilization of albumin in ICUs a few years ago. There was an inquiry in ICUs and the
first question was: Do you know that there was a consensus conference on the utilization of albumin? About 50% of the doctors said yes. Do you know the conclusions of this conference? 20% of the doctors said yes. Do you apply the conclusions? Less than 4% of the doctors said yes. So I think we spend an incredible time making consensus conferences and guidelines, but in fact we have to think about other measures to implement what we call guidelines and good recommendations for the utilization of nutritional support or any type of support in our patients.

**Dr. Heyland:** Just to follow up on some of the previous comments about the value of evidence-based medicine and practice guidelines. I want to make people aware that a study has been completed in Canada in which evidence-based guidelines were developed, in a randomized design, randomized hospitals, for different implementation strategies. So rather than passively disseminating a piece of paper we employed academic detailing, feedback as strategies to actively disseminate the guidelines. Then we demonstrated significant differences in the practice of nutritional support that was associated with a reduction in hospital mortality with the implementation of those guidelines. So I think there is a potential for guidelines to have an impact in optimizing the best practice with nutritional support. I think there is tremendous potential for the misapplication of nutritional support. We have the potential to do harm with our nutritional support and so there is a need to try and raise the level of practice, optimize care and you can influence patient outcomes. So I see the way for it is to generate more evidence that contributes to the scientific body of what best practice is, and then look further at aggressive strategies to implement those guidelines across the various societies.

**Concluding Remarks**

This morning we decided that I would make some summary statements and let Dr. Cynober talk about the manuscripts. I was trying to figure out how to approach this. I thought I should first give you a background of where I come from. About 18 years ago when I was a surgery resident, I made the observation that feeding patients into the gut improves their outcome. I was in an environment that was very heavily weighted toward research and I was promoted to work on that. In the mid 1980s, like most surgeons, I became very interested in nutritional support, and we actually ran two nutritional support teams in two hospitals. I became quite interested in total parenteral nutrition (TPN), and then somewhere around the 1990s I became more interested in just what the role of the gut was in MOF. When interest in nutrition slowly waned, I shifted my research in that direction. So I don’t really consider myself to be at the cutting edge of nutritional support. When I was approached by Nestlé to co-chair a symposium on nutrition in the intensive care unit (ICU), I thought it would be a wonderful opportunity to be able to invite the leaders of the nutrition to come and lecture me and test my knowledge against what should be the gold standard. So I thought a very quick review of what I have got from the conference would be a nice summary.

The first session was the metabolic response to stress. The physiologic consequence of the stress response is fairly well characterized. It is hard to relate to individual patients. What trajectory a patient is going to go on isn’t very clear. I thought the concept of nutritional stress was valid. I am not quite sure how to characterize it but that is probably something I haven’t thought of. Genomics and proteonomics are going to enable us to better characterize this physiologic response, and I think it is going to give us the ability to pharmacologically manipulate that
response to improve outcome, and in fact in burn patients it appears to work. How that relates to my patients, I am not sure. I think for somebody who is not septic, who is persistently hypermetabolic that perhaps anabolic agents would work, and this whole concept of intensive insulin therapy needs to be better implemented. While we think it is glucose control perhaps it really has some metabolic response to protein metabolism that we just don’t understand.

The second session was on specific nutrients that might be used in critically ill patients. Clearly critically ill patients require high proteins, but the optimal amino acid composition of these solutions is not known. I already gave Dr. Cynober a little bit of hard time about this. It seems to be something we were quite interested in the past. What I came away with was perhaps glutamine, possibly alanine, could have some favorable impact. It appears that most of you are all fairly nervous about arginine, a lot more nervous than I am. Clearly similar to the amino acids, lipids were really designed to prevent essential fatty acid deficiencies and not to be used in high doses in septic patients. There appears to be a lot of concern about the use of lipids in high doses in septic patients and I concur with that. While we seem to know a lot about the n-3 fatty acid story, the real proof that it helps patients is lacking. Several people talked about the Gadek study, and while I reviewed that study I can’t believe that anybody would give the control diet to septic patients. It is probably the worst thing to give. Vitamins, antioxidants, what a great idea, it certainly fits with my understanding of acute inflammation. As I told Dr. Berger I take a handful antioxidants every morning, I have yet to prescribe them to my patients. I am anxiously awaiting the results of Dr. Berger’s trials. Most ICU practitioners do not even think about trace elements. In the era of when we were interested in TPN, people talked about it but I think we all need to go home and review these data and make sure we are adequately addressing this issue in our patients. About the route and goal of administration, I really appreciated the observation that we should not be in there, pushing really hard at the beginning. I certainly thought that positive nitrogen and positive caloric balance really should not be an early goal, but it should be a goal sometime later. In regards to the enteral versus parenteral nutrition debate some mechanisms to explain this have now emerged. The gut is a very important immunological organ and we need to promote its function. Now if we accept this to be true, which it appears everybody does, then the major impediment is just how do we achieve this. There is a great variety of gut dysfunctions that occur in ICU patients which are not very well characterized, and the monitoring tools are very crude. With dedicated effort you can achieve surprisingly high tolerance. There appears to be a lot of variability in opinions on how aggressive we should be in getting jejunal access. I think that we should get away from enteral nutrition and talk about enteral therapy. Get in there early and doing something to the gut to make it work, and then think about providing adequate nutrition.

Now the next session was about specific nutritional diseases, and I certainly don’t know too much about neonates but I did find the correlation with adults to be surprisingly similar. The concept of minimal enteral therapy in the sphere of necrotizing enterocolitis, the high protein needs that must be acutely replaced. This is consistent with elderly patients coming to the ICU with no muscle or fat stores. They are not going to do well if we don’t get in there. Similar to the adult population, the first studies on the potential use of glutamine were very favorable. The concept of a mandatory enteral circuit shows that the gut is an important antigen processor. Similar to adults, the role of lipids has not been very well studied. In regards to obesity, this major health care issue which clearly adversely affects the impact of long-term outcome, but the impact on ICU outcome is not as clear. A hypocaloric, high nitrogen strategy is a valid concept, and this is an area where a lot of prospective studies could be done. In pancreatitis, enteral nutrition challenges the traditional wisdom. The small
studies are very impressive, at least to me, but this clearly is not the standard of care across the United States. I think the use of clinical markers to identify severe pancreatitis will be the way to identify these patients, I am still not so clear about the role of CT scan. Jejunal feeding is optimal, and this was a major obstacle to people during the discussion, but as long as there is no gastroenterologist to place the tube, the stomach will still be fed. With multiple organ failure and sepsis, we are talking about a very heterogeneous group of patients and therefore it is difficult for studies to show any difference in outcome. There were the comments that these people have a very bad outcome and the things that are probably going to save them are resuscitation, optimal antibiotics and a draining pus, and to think that enteral nutrition or parenteral nutrition is going to really change their outcome is probably a bit naïve. I agree with the idea that, once the patients survive this and we are trying to get them back into society, they need to have muscle mass and this should be an important part of their rehabilitation. We certainly don’t want to hurt these patients by aggressively pushing enteral nutrition on them. I think enteral nutrition is feasible but again it should be taken carefully. The role of lipids is again an area of confusion. Now for the immune-enhancing diets, we have had a huge amount of discussion about this. I don’t want to get into it other than to say that if you just look at the way the studies were done you can’t expect that going into a heterogeneous ICU and enrolling a lot of patients that you are going to see a difference in outcome. The only way this is going to work is that homogeneous groups of patients are studied. They have to be patients for whom risk can be quantitated, trauma and burns, and postoperative major surgical patients. How this is to be translated into other patient populations, I don’t know. One should be very cautious about saying that because it works on a trauma patient it should be used in a pneumonia patient. Until those studies are done I would not advise it. The other thing that becomes clear in those studies is that we are using the gastric route because it is clinically practical, but from a prospective study it is not very good because you don’t know what you are giving the patients. So if you really want to do the study, put the tube in the right place. I think we can all get over the fact that there is one product that has been widely tested and pushed by a pharmaceutical company. There is one product that works but I would not get all excited about how we want to use that product in all the patients that we might encounter.

I think this has been a great meeting, I hope that it could be repeated in 5 years; it would be nice to see if we have made any advances. Thank you for your attention and participation.

Frederick A. Moore

I have some additional comments. I feel really that we had a very good combination of good science, practice, recommendations, and I am convinced that it is important to have such multidisciplinary meetings to try to have a continuum from high-tech molecular biology to the care of the patients at the bedside. I personally believe that in a few years physicians will ask for a genetic map, and this will work very quickly with an automatic R-PCR machine. From the results and the apparent risk to the patients the physician will be able to select or not select specific diets, and this will probably be very helpful in the discussion of overexpression of nitric oxide and arginine utilization, for example. Perhaps at this moment we will realize that the simple C-reactive protein measurement provides exactly the same information, and we will have to discuss the cost-effectiveness of different approaches. I really enjoyed all the talk and the discussions, the concept of the 40 min of discussion is excellent. I am also especially grateful to have had the pleasure of meeting Dr. Ross internal
file’ because we had the privilege to get some data and I understand that this paper will now be published. It is very important to have direct access to this up to now phantasmagoric study because, from these results, we can achieve quite different conclusions the about arginine story.

Thank you very much, I feel that we have had 3 exceptional days.

Luc Cynober