

## Which metabolic strategies in the early phase of injury?

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The host's response to tissue injury, commonly called trauma reaction appears to be a spectrum within which one can identify several patterns. With a single uncomplicated injury, the response peaks between day 3 to 5 post injury and decreases within 7-10 days.

Before deciding to start a metabolic support in such patients, we must clarify the possible beneficial or harmful outcomes, these can be categorized by laboratory measures, physiological measurement, clinical events, and economic outcomes. The most important are clinical outcomes: incidence of infectious complications, number of days on high-level of care treatment, incidence of organs failure.

### Aims of artificial feeding

The administration of nutrients to critically ill patients is a supportive measure. Its importance relative to the specific therapy of the underlying disease is often underestimated. The maintenance of physiological balances is, indeed, one of the foundations of

Testo presentato allo SMART.  
Milano, 26-28 maggio 1999.

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intensive care therapy and the outcome of an untreated imbalance is always the same and it is inevitably death.

Thus, nutritional support should be a metabolic therapy able, (by supporting protein synthesis and controlling catabolism, without interfering with other critical equilibria), to maintain the energy equilibrium, at least limiting the reduction of energy body stores and the wasting of lean tissue so that malnutrition may become severe enough to increase the risk of dying.<sup>1-6</sup>

Even if nutritional support is expected to improve the outcome of care, reduce morbidity and length of recovery,<sup>7</sup> it is unrealistic to expect miraculous results in patients with multiple failures and complex and combined therapies.<sup>8</sup>

### Indications of artificial feeding

Patients could be classified according to nutritional (normal or malnourished) and metabolic status (normo or hypercatabolic) (Table I).

TABLE I.—*Definition of malnutrition and catabolism.**Malnutritions*

- loss of >10% of the abitudinal body weight, during three months, in non obese patients
- serum albumin level <3 g/dL

*Catabolism:*

- moderate - 10-15 gN/day
- severe - >15 gN/day

To convert urea to urea nitrogen: multiply by 0.466

To convert urea Nitrogen (mmole/24 h) to g/24 h: multiply by 0.028.

To convert urea Nitrogen (g/24 h) to nmole/24 h: multiply by 35.7.

— Wellnourished & moderately catabolic patients: artificial feeding of a well-nourished patient, able to take enteral nutrition within 4 to 5 days or with a relatively minor injury is overtreatment.

— Wellnourished & severely catabolic patients unable to eat: these are injured or septic patients with an expected prolonged period of intensive treatment complicated by multiple organ failures, in which nutritional depletion, even if not present at the beginning of the illness, will undoubtedly appear during the ICU stay. These patients need early anti-catabolic support.

— Malnourished (>10% weight loss in the last 3 months): in particular, catabolic patients with oral intake impossible for >5 days, need immediate nutritional support.

It is also well clear that in such patients wasting can still occur despite the provision of the nutritional support. Body energy and protein full stores replacement, planned in the acute phase of injury, is dangerous in presence of respiratory and cardiocirculatory failures, is indeed not possible and has to be postponed to the convalescence phase.

Parenteral feeding (PN) should be performed:

— when enteral nutrition support is strictly contraindicated: *i.e.*, gut obstruction, high-output jejunal-ileal fistula (output >0.5 L/h), severe non-hypovolemic gut ischemia, gut failure due to extensive resection or absorption impairment.

It is also ill-advised:

— when enteral nutrition is unable to cope with energy and nutrient requirements (mixed nutrition). Patients with vomiting and upper gastrointestinal bleeding need a differentiated enteral access more than parenteral support.

Enteral feeding needs to be instituted as early as possible to optimize body defenses and to preserve splanchnic blood flow and maintain gut mucosal integrity.<sup>9</sup> Even a small fraction of the overall daily dietary allowance (3-500 kcal) is enough to reach this aim [K.N. Jeejeebhoy, personal communication].

Nasogastric feeding is very simple and it realizes the most complete and high quality goals of nutritional support. We showed that it was possible also in long-term anesthetized and paralyzed patients under extracorporeal respiratory assist for terminal pulmonary failure.

Nevertheless, in the critically ill gastroparesis could be very frequent. In medical patients, prokinetics agents<sup>2</sup> or endoscopic placement of a nasoenteric tube in duodenum or jejunum is the solution: in surgical patients we ask the surgeon to manually pass a nasoenteric tube or to perform a jejunostomy. Nevertheless, we agree with Frost that intensivists had to be hardly motivated forward being through early enteral nutrition.<sup>2</sup>

## Methods

Planning of nutritional support should start with the definition of energy and nitrogen needs.

### *Energy need*

Energy requirement is considered equal to measured or assessed energy expenditure. By feeding a patient, we try to replace oxidized endogenous substrates by diet-derived substrates. Therefore, it should be more appropriate to consider nutrient balance than energy balance.<sup>10</sup> The energy production rate of a patient under basal conditions (supine subject, thermoneutral environment and after a 12 h fast) can be:

a) determined by indirect calorimetry,<sup>11</sup> by oxygen consumption assessment (l/day times 4.8=kcal/day) utilizing the Fick method<sup>12</sup> and, roughly, by the carbon dioxide production rate;

b) calculated with formulas;

c) estimated.

Measurement is appropriate, at least in more clinically unstable and catabolic patients,<sup>13</sup> particularly those with respiratory failure in the phase of clinical instability, and in patients requiring prolonged intensive treatment.<sup>14</sup>

The basal energy production rate (-kcal/day) is predicted by the Harris-Benedict equations:

Males= $66.473+(13.752 \text{ times weight in kg})+(5.003 \text{ times height in cm})-(6.755 \text{ times age in years})$ .

Females= $655.095+(9.563 \text{ times weight in kg})+(1.850 \text{ times height in cm})-(4.676 \text{ times age in years})$ . These values are corrected only for stress (final value not >1.15-1.25 the calculated except for burned patients). Calculated or measured values, minus the amount of energy derived from protein oxidation (g nitrogen loss times 26.6) are utilized to plan nonprotein calorie intake. In overweight patients we suggest to enter the formula with the ideal body weight to avoid further overstimulation. Rough estimates (20-35 kcal/kg) are reasonably adequate in clinical practice.

### *Nitrogen need*

This is evaluated by measuring daily nitrogen loss corrected for body urea pool variation. The determination of basal nitrogen loss has to be performed during a 24 h fast, owing to the mandatory contribution of protein-amino acid intake to the urea production rate (about 30-40% of the supply).<sup>15 16</sup>

The nitrogen loss value represents the need to maintain the actual lean body mass, *i.e.*, nitrogen balance (reasonable goal for not depleted injured patients in acute stress phase).

In case of malnutrition, nitrogen support could be increased (in addition to loss value) to also obtain replacement of body protein

stores. In depleted injured patients this can only be done in the weaning phase of acute stress (see below).

### *Energy-nitrogen relationship*

Even if nitrogen excretion and retention are affected by calorie amount either in stressed wellnourished or in malnourished no-stressed patients, nitrogen intake is the main determinant of nitrogen balance.<sup>16 17</sup> In both types of patients the effect of calorie intake is comparable and accounts for the retention of about 1 mg/kg/per kcal/per day of nitrogen. Also, the effect of nitrogen intake is comparable and gives rise to the retention of about 60% of nitrogen supply.

It is easier to obtain nitrogen balance in malnutrition, because malnourished patients show nitrogen losses that are consistently less than those of stressed patients. Nitrogen retention cleared of the calorie effect is the net protein utilization. A figure between 50-80% is reported by many authors in different clinical settings and with different nitrogen intake [see above]. The simple replacement of fasting nitrogen losses leads to a negative nitrogen balance due to incomplete utilization of the load. It may be necessary to add a further amount to fasting losses, depending on patient's metabolic environment (stress or malnutrition), on nitrogen clearance ability (renal and hepatic function) and on planned nitrogen balance (replacement or maintenance). Even in the most favorable conditions (nonstressed depleted patient) it is unlikely to obtain a nitrogen balance greater than 2-3 g/day.

A limit (0.24 g/kg per day nitrogen supply) beyond which there is no further improvement of nitrogen balance has been advocated for stressed patients.<sup>18-21</sup> Other authors state that the optimal nitrogen intake is between 0.28 and 0.35 g/kg per day of nitrogen.<sup>16 18 22-29</sup> This discrepancy could be explained by different nitrogen needs, equal or exceeding 0.24 g/kg. Nevertheless, the studies supporting a lower nitrogen figure were all conducted with a mixed calorie system, all the others with a prevalent or pure glucose system, thus suggesting differential

nitrogen utilization elicited by a different calorie system. In any case protein store accretion is not the main goal in the acute injury phase and it is also unlikely to be reached.

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### Timing

Critically ill patients show daily negative cumulative energy and protein balance (1-2% of body cell mass). The aim of treatment is to provide early support preventing, rather than correcting, later tissue wasting and nutritional deficit. After the start of treatment, cell energetics (sodium pump and calcium kinetics) rapidly recover immediately resulting in improved cell function.<sup>30</sup>

Obviously, it is mandatory to start when hemodynamic, water, electrolyte and acid-base balances reach equilibrium.

### Amount

The approach with respect to the nutrient balance depends either on the amount of nutrients necessary for a particular aim (*i.e.*, to optimize the nitrogen utilization), or the possibility to safely utilize body fat stores to accomplish energy requirement. From a theoretical point of view, a patient with preserved fat stores can tolerate negative nutrient balance, *i.e.*, hypocaloric regimen, (until death, the energy balance is balanced!), while depleted patients require promptly oxidizable nutrients to reach energy balance and a further intake to replace depleted stores (net positive nutrient balance).

Two concepts are key stones to correctly planning the nutritional metabolic treatment in the critically ill:

1. the nutrient intake has to be within a range to avoid over- or underfeeding (the first considerably more dangerous);

2. with in the range, any variation must be performed step-by-step until the therapeutic goal or the range limit is reached.

This programme avoids mean standard supply and enables "personalized" treatment on the basis of routine clinical information. Intake has to be referred to actual body

weight (see above), although the absolute values must also take into account the ideal body weight to avoid over- or underestimation in "outlier" patients.

The calorie figure is difficult to evaluate when a measure of energy production is lacking; 35 kcal/kg is the top limit of the supply (to avoid overfeeding in non burned patients), even if the estimated value is higher. Otherwise, if the estimated value is less than the upper limit, this value had to be considered the maximum calorie intake.

The higher load of nitrogen intake can be planned according to the therapeutic goal: a near nitrogen balance vs a positive one (not more than 3 g/day).

Insulin administration and adjuvant therapies are useful in controlling and avoiding hyperglycemia. When resistance is severe, it is safer to administer insulin, 1-3 UI/h, by a syringe pump. Several anabolic agents are effective in, or should improve the efficacy of conventional nutritional-metabolic approach to protein metabolism in stress conditions.

Particularly promising are hormones like insulin, growth hormone (GH) and insulin-like growth factors.<sup>31</sup>

The recommended dietary allowances for parenteral administration of vitamins and trace elements have been reviewed elsewhere. The optimum dose and frequency of administration has not been defined in detail in critically ill patients. The need to provide increased amount of zinc (large intestinal loss), magnesium and vitamine E to prevent acute deficiencies and to maximize antioxidant potential was emphasized (K.N. Jeejeebhoy, personal communication).<sup>31</sup>

Water supply had to be strictly planned according to the patient's need. Injury increases extracellular water, while intravascular space is reduced. The best way is to freely adjust fluid intake without changing the nutrient program.

## Fuel substrates

Nutrient available as calorie source are carbohydrates (*i.e.*, glucose) and lipids. Also available are emulsions containing medium

chain triglycerides. The choice between glucose and fat is one of the more frequently discussed topic of venous nutrition. We can address the question analysing the key points useful for therapeutical decisions.

### *Anabolic action*

The aim of nutritional support in catabolic patients is to pursue the best anabolic drive. This is reached: a) administering an adequate protein supply (the most efficient tool);<sup>16 32 b)</sup> optimising the hormonal control of body metabolism that is deranged by stress or injury (*i.e.*, reaching an "optimal" plasma insulin level, spontaneously or with planned insulin supply to overcome resistance). There is an increasing evidence that the best anabolic drive action is reached by vein, giving a prevalent glucose system.<sup>33-35</sup>

### *Gas exchange modifications and diet induced thermogenesis (DIT)*

When planning the calorie load we had to remember that: a) DIT depends primarily on overall energy intake as well as the nutrient used (30-40% of intake for protein, 6-8% for glucose, 3% for fat); b) continuous infusion of nutrients at a rate balancing the energy expenditure seems to abolish DIT (for reviews, see.<sup>14 36 37</sup>

Gas exchange largely reflects the composition of the oxidized fuels. In particular, carbon dioxide production per kcal is maximal with glucose (100%) and decreases with protein (93%) and with fat oxidation (76). Oxygen consumption per kcal is maximal with lipid and decreases with glucose (92%). A mixture of medium and long chain triglycerides increases minute ventilation (+12%), carbon dioxide production (+15%) and oxygen consumption (+20%) compared to long chain triglycerides.<sup>38 39</sup>

Moreover, the supply of any substrate at a rate exceeding the energy need results in storage as fat. Liposynthesis from glucose has high energy cost (12% of stoked energy) and yields a large amount of carbon dioxide. This supports the use of lipid *vs* glucose. Nevertheless, close monitoring of calorie supply will reestablish this problem. Infact sup-

plying energy (even as iv glucose) at a rate not exceeding measured energy demand, stops net liposynthesis and decreases oxygen consumption (with less cardiovascular demand) with respect to the fasting state characterized by endogenous fat oxidation. However, it increases slowly carbon dioxide production (by 17%: paralleled by an increase of minute ventilation) but this leads to a minimal impact on respiratory function in injured intermittent mandatory pressure support ventilated patients.<sup>37</sup> In conclusion, the effect of a substrate load given at a rate not exceeding the energy demand, will be scarcely relevant.<sup>7 14 37 40</sup>

### *Substrate oxidation*

A claimed reason for a preferential use of fatty emulsions in critically ill patients is the belief that fatty emulsions, are easily used for energy, (*i.e.*, promptly oxidated)<sup>41</sup> and as a consequence they could spare the energy drawn during fast by endogenous fat fuels.

In hypermetabolic fasting patients, endogenous fats are extensively oxidated as in fasting volunteers. Moreover, in normal and in stressed patients, the rate of oxidation of exogenous glucose (given without fat) increases with the load<sup>42</sup> and with length of infusion.<sup>43</sup>

At the same time the oxidation of endogenous lipid is progressively reduced even if endogenous fat continues to be burnt, also when glucose intake meets energy needs (RQ np <1) (Respiratory Quotient).<sup>37</sup>

When glucose intake overcomes expenditure, the patient has more energy, reaching 100% (RQ np >1) from the glucose. By contrast, when both carbohydrates and lipids (long chain fatty triglycerides) are given, the RQ np (*i.e.*, the proportion of glucose and fat oxidized) seems determined by the carbohydrate load. The energy not drawn by the carbohydrate load to reach the energy balance, derives from fat. Indirect calorimetry does not distinguish between exogenous or endogenous fat.

Moreover, the exogenous lipid load does not induce further lipid oxidation and does not result in a decrease of carbohydrate oxidation (lower RQ np) compared to that oxi-

dized during the supply of the same amount of carbohydrate without lipid.<sup>10 40 44-47</sup>

In addition, it was recently well documented that exogenous long chain fatty triglycerides are poorly oxidized also when administered by oral feeding in volunteers<sup>48</sup> or by vein in patients with variable degree of stress.<sup>49-51</sup>

Medium chain triglycerides have a faster disposal and relatively independent from carriers like carnitine compared to long chain triglycerides.<sup>52</sup> They result in a much higher oxygen consumption (see above), probably a consequence, beside their oxidation, of the metabolic cost for elongation. This suggests that, after a meal or during continuous *i.v.* nutrition, oxidized lipid is largely derived from endogenous stores and dietary fat is mainly stored and probably oxidated later.

#### *Lipid vs lung function*

Intravenous fat emulsion induces changes in the pulmonary functions generally consisting of a decrease of PaO<sub>2</sub> and the pulmonary diffusion capacity for carbon monoxide. In volunteers<sup>53</sup> this change does not reach clinical importance. In critically ill ventilated patients with normal lung conditions,<sup>53-55</sup> only an increase of pulmonary vascular resistance<sup>53 55</sup> or a minor increase in venous admixture (that decreased to pre-infusion values after lipemia resolved)<sup>55</sup> was detected. The same happened in ventilated patients with an infectious pulmonary disease or chronic obstructive pulmonary disease (-COPD).<sup>54</sup>

The magnitude of the related impairment of gas exchange may be greater, reaching clinical relevance in the presence of acute lung injury (ARDS criteria) with or without sepsis syndrome.<sup>54-57</sup> The adverse effects consist of a decrease in the PaO<sub>2</sub>/FiO<sub>2</sub> ratio, an increase in mean pulmonary pressure, venous admixture, and pulmonary resistences. They are significantly higher when sepsis adds to ARDS.<sup>57</sup> Nevertheless, even in this setting, the pulmonary impairment progressively recovers, after a variable time, span from infusion withdrawal. Reports on critically ill septic patients with ARDS<sup>54-57</sup> state that 20%

fatty emulsions (n-6) infused over 8-10 h may have deleterious effects, especially when hypoxic pulmonary vasoconstriction is working to improve oxygenation. Some authors do not suggest abandoning infusion,<sup>55 57</sup> and some describe that adverse effects can be reduced by slowing the infusion (10-16 h), but do not offer further indications for clinical practice.<sup>54 56</sup>

Fatty emulsions composed also by medium chain triglycerides reduce the -6 polyunsaturated fatty acid load, and seem to be safe also in septic patients.<sup>58</sup>

#### *Lipids vs body inflammatory response*

In animal injury models, standard lipid emulsions may induce enhanced inflammatory reactions and have an adverse effect on immunological function with increased susceptibility to infection.<sup>59</sup>

Currently, under investigation are intravenous emulsions enriched with -3 fatty acids (fish oil), whose metabolic products (eicosanoids) have less biological effect on cell membrane composition and the response to inflammatory stimuli. The modulation of the immune response in patients with persistent hypermetabolism and organ failures following trauma, burns, surgery or sepsis<sup>23</sup> remains a fascinating field of research.

## **Conclusions**

It is perfectly true that fatty emulsions have a high calorie density (but not more than a very concentrated glucose solution) and are isotonic, hence suitable for peripheral vein administration. But, critically ill patients are not treated only by peripheral vein and there is no real difficulty today in controlling pump-driven glucose and/or insulin infusion in an ICU.

The minimal lipid requirement has been estimated at 5-20 g/day of the essential linoleic acid. This amount can be safely given one to three times per week. As a result, (with respect to either metabolic setting/anabolic drive and protein metabolism or substrate oxidation and gas-exchange), the widely sug-

gested mixed calorie system (50% glucose, 50% fat), with intake adjusted to the energy production rate, does not differ from an hypocaloric glucose treatment. In fact, the protein sparing property of glucose is not fully elicited, about 50% of calorie expenditure is covered by glucose (both endo- and exogenous) while the remaining energy is derived from lipids (mainly endogenous, being fatty emulsions being substantially stored), establishing controlled "semi-starvation". This leads to the maintenance of body fat stores in non-fat-depleted patients in a very critical phase of their illness, adding the risk the pro-inflammatory properties of fatty emulsions.

The general opinion that aggressively *i.v.* supported, injured, and septic critically ill patients are not protected from consistent protein loss, is mainly based on studies conducted with a <50% mixed system.<sup>33</sup> Otherwise, even if not malnourished and in the early days of injury (2-3 days for elective surgery to weeks or months for severe sepsis or burn), the net nitrogen loss of injured patients can be reduced to a minimum (5 g/day). This is done by a nitrogen supply titrated on fasting nitrogen loss, coupled with a glucose system that allows the spontaneous or supply mediated achievement of an "optimal" plasma insulin level to overcome resistance.

Nevertheless, for the implications of calorie supply on gas exchange, assessment of the minimum energy supply that allows maximum anabolic drive is particularly important.

This amount, that roughly corresponds to the energy requirement in volunteers as well as in stable malnourished and in stressed patients, is one that attains the plasma "optimal" anabolic insulin level and a plateau nitrogen loss.<sup>33 34</sup> Hence, amino acid supply and a prevalent glucose system (>70%), yielding the overall measured or expected energy requirement, perhaps coupled with insulin supply to maintain normoglycemia, seems to be an efficient tool to optimize protein metabolism in critically ill patients.<sup>31</sup>

The intake of -6 could be furtherly decreased by adding -3 fatty acids (3/1 ratio with -3 fatty acids calorie load limited to 4-6% of the supply).<sup>60</sup> This *i.v.* approach is very

similar in composition to a balanced enteral diet (the administration of which must, anyway, be pursued as soon as possible).

### Amino acid

Bearing in mind the amounts necessary to obtain nitrogen balance in stressed and in malnourished patients, the amino acid composition should also consider several other factors.

First arginine, a conditionally dispensable amino acid, has received new attention because of its potential role in immunomodulation, as well as its positive influence on posttraumatic nitrogen metabolism and, by enhancing collagen deposition, on the wound-healing process. Arginine has been shown to be a unique substrate in the production of the biological effector molecule nitric oxide. Nevertheless, there is no evidence that exogenous arginine, even in large doses, modulates the rate of synthesis of nitric oxide.<sup>61</sup> Second, the recent availability of peptides suitable for *i.v.* use allowed the study of glutamine dipeptide infusion in critically ill patients. Glutamine represents an important metabolic fuel for the cells of the gut and the immune system. It is also involved in the regulation of muscle and liver protein balance, probably mediated by increased cellular hydration, a triggering signal or protein anabolism.<sup>62</sup> Third, the oxidation of the administered amino acid increases oxygen consumption and carbon dioxide production rate.<sup>14 40</sup> However, this effect is less relevant because overall protein oxidation rarely exceeds 25% of the energy production rate.

### Special problems and requirements: ARDS

Nutritional metabolic treatment in ARDS patients has to be supplied enterally route as soon as possible.<sup>36</sup> This approach will reduce the -6 polyunsaturated fatty acid supply and substitute oleic and medium chain triglycerides (better avoided, see above) and

-3 polyunsaturated fatty acid. Furthermore, they have a minimal pro-inflammatory and immunodepressive action and are the most quickly oxidized among the fatty acids. Hence, the glucose-lipid controversy becomes almost completely irrelevant. This is another good reason to force an enteral approach feasible even in terminal ARDS patients.<sup>63</sup>

If an *i.v.* approach has to be pursued, one should not use procedures that increase oxygen consumption (cardiovascular demand), carbon dioxide production, ventilation, or ventilation/perfusion maldistribution (ventilatory demand), or impair body temperature control or favor inflammatory reaction or immunodepression.<sup>7 14</sup>

However, to satisfy energy needs with rapidly available calories and to curtail protein loss, i.e., to maintain vital physiologic balance in critically ill patients, administering 1000-1300 kcal, preferentially as glucose, for the short-term or 90-80% glucose and 10-20 % fat for more than 5-6 days treatment, coupled with amino acids and insulin, may be advisable.

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