Timing of Nutritional Support

R.L. Chioléro\textsuperscript{a}, L. Tappy\textsuperscript{b} and M.M. Berger\textsuperscript{a}

\textsuperscript{a}Surgical Intensive Care Unit, Department of Surgery and \textsuperscript{b}Department of Physiology, University Hospital – CHUV, Lausanne, Switzerland

Introduction

Extensive progress has been made in techniques of artificial nutrition of critical care patients. Nutritional support has progressively evolved from an adjuvant to a supportive life-saving therapy, like mechanical ventilation, hemodynamic support or dialysis. Malnutrition may develop rapidly in starving critically ill patients due to the presence of acute phase responses, which not only promote catabolism but also alter the response to nutritional support. Once established, malnutrition exerts well-known deleterious effects by altering immunity, favoring nosocomial infection, decreasing wound healing and by altering the function of vital organs and promoting organ failure [1]. The persistence of critical illness is associated with a decreased ability of aggressive nutritional support to reverse established malnutrition, due to the persistence of acute phase responses. There is therefore a negative coupling between critical illness and progressive malnutrition: malnutrition eventually promotes organ failure, while the critical illness not only leads to malnutrition, but also alters the ability of feeding to reverse malnutrition.

Such consideration suggests that the timing of nutritional support may be a key factor in intensive care unit (ICU) patients. This, however, is a highly complex issue since numerous nutritional and non-nutritional factors may confound the effects of timing per se. The pre-illness nutritional status, type, severity and stage of critical illness, type and severity of organ failure, route of feeding, the use of special diets and adjuvant therapies such as insulin and antioxidants, may all play a role and influence the overall effect of nutrition. For example early feeding was combined with the use of special diets in
Timing of Nutritional Support

several studies, increasing the difficulty in delineating the specific effects of each component.

In 1993 the ASPEN recommended not to exceed 7- to 10-day starvation in critically ill patients, but did not propose a clear definition or any additional recommendation concerning the timing of nutritional support. For simplification, we propose the following definitions: (1) early feeding refers to beginning nutrition within the first 24–48 h after an acute event (see below); (2) conventional feeding is nutrition within 3–10 days, and (3) late feeding is nutrition after the 10th day.

Conceptually, four main hypotheses could justify the use of early feeding in critically ill patients: (1) fasting is deleterious in ICU patients, rendering early feeding mandatory; (2) energy supply plays an important role in the promotion of energy metabolism; (3) the delivery of nutrients is important for gut maintenance, and (4) specific nutrients should be provided to support the functions of organs and systems. Actually none of these hypotheses is supported by solid clinical evidence. The mechanisms behind the beneficial effects of early nutrition therefore remain elusive. However, several controlled studies show the clinical benefits of using this type of nutrition in highly stressed surgical patients and provide reasonable arguments for administering early nutrition.

The aim of this review is to provide information on the effects of the timing of nutritional support in critically ill patients requiring intensive care management, focusing on early feeding. It will not consider other categories of patients, particularly noncritically ill patients undergoing major surgery, since their response to nutritional support may differ.

**The Critically Ill Patient**

Different patient categories are treated in the ICU. A large proportion of these patients do not require specific nutritional therapy, since they have no pre-existing malnutrition and suffer from moderate stress and a short-lasting condition, like myocardial infarction or major elective surgery. This contrasts with other patients with major and prolonged critical illness, in which artificial nutrition is a key element of the intensive therapy, although this point is rather difficult to demonstrate [2]. They typically include patients with major burn or trauma, severe infection, severe or multiple organ failure. Such patients usually have marked endocrine, metabolic and immunological changes, the so-called acute phase responses, associated with varying acute organ failure which may influence the response to nutritional support. The resting metabolic rate is increased, fasting and post-absorptive glycemia is increased due to insulin resistance, while protein breakdown exceeds protein synthesis both in fasting and fed conditions. Sophisticated body composition studies in severely traumatized and septic patients have shown that increasing energy
supply over the measured requirements was unable to completely prevent the progressive erosion of the fat-free mass, while favoring fat deposition [3, 4]. Similarly, increased protein supply was unable to maintain total body protein stores during the first 2 weeks after the onset of critical illness [5]. Growth hormone administration was considered a promising therapy to decrease the accelerated tissue catabolism associated with the critical illness, but a recent randomized controlled study demonstrated that growth hormone therapy was associated with a substantial increase in mortality in septic and nonseptic ICU patients [6]. These data clearly show that the response to nutritional and metabolic support is altered in critically ill patients, favoring the development of malnutrition and ultimately the occurrence of progressive organ failure. Such resistance to nutritional support does not occur in critically ill patients with a lower degree of stress in which the acute phase response is short and of lower intensity. The results of the nutritional studies performed in postoperative patients or in other patients with moderate stress illness, may thus not apply to more acutely ill patients requiring prolonged intensive care.

Another important point is the choice of relevant endpoints of nutritional studies in ICU patients. In acutely ill patients with acute organ failure and an expected high mortality, nutritional support is unlikely to have a measurable effect on survival. Other relevant outcome variables should be preferred to detect the beneficial effects of nutrition, such as inflammatory responses, incidence or duration of infection, duration of mechanical ventilation and level of oxygenation, length of ICU or hospital stay, and total cost.

**Starvation in ICU Patients**

Normal humans tolerate prolonged periods of starvation without apparent harm [7]. Several adaptive behavioral, metabolic and endocrine mechanisms allow the body to slow down the rate of protein and tissue catabolism. When fasting exceeds 3 days, ketogenesis is progressively stimulated and ketone bodies are used as preferential substrates by many organs and tissues including the brain. This will decrease their obligatory requirements in glucose and therefore the rate of gluconeogenesis and protein catabolism. In addition, the resting metabolic rate decreases as well as the physical activity. These mechanisms allow obese patients to tolerate up to 6 weeks of complete fasting.

This adaptation to starvation is blunted in critically ill patients, secondary to the release of cytokines, stress hormones and inflammatory mediators. There is a marked stimulation of gluconeogenesis, which in the most severely ill patients will not be suppressed by the administration of carbohydrate, contrasting with healthy subjects [8]. The increase in plasma ketone bodies is markedly blunted, secondary to an impaired ketogenesis [9, 10]. As a consequence, starvation leads to rapid protein-calorie malnutrition. This constitutes an
argument for the early beginning of nutritional support, although other aspects should be considered, particularly the ability of intravenous nutrients to upregulate the inflammatory and metabolic processes (see below).

The maximal duration of safe starvation has never been systematically assessed in critically ill humans. Although this duration is known to be dependent on the actual nutritional status, it seems likely that it is also influenced by other factors, like the severity of metabolic stress, the level of catabolism and the type of acute illness (trauma, sepsis, etc.).

The Concept of Early Nutrition

The concept of early feeding has mostly been developed in surgical patients. It relies on the hypothesis that artificial nutrition by the enteral route exerts beneficial effects when started early after injury [11, 12]. There is unfortunately no clear definition of what is early feeding, particularly when the enteral route is used for feeding. Such a definition should ideally include two criteria: (1) the delay before beginning the nutritional support, and (2) a threshold for minimal energy delivery. Most authors seem to consider that starting feeding within 24–48 h of injury (or ICU admission) corresponds to early feeding. Others describe patients receiving ‘immediate feeding’, again without any clear definition. The second criterion (i.e. the minimal amount of energy delivered) is ignored in most studies. The consequence in some studies is that patients receiving very low amounts of calories due to failure of enteral nutrition (EN) are compared to other patients receiving full intravenous nutrition [13]. Such studies obviously do not furnish information on the effects of early feeding, but rather on the effects of starvation or semi-starvation. Table 1 summarizes the results of the randomized trials performed in critically ill patients comparing early EN with conventional management.

For practical purpose, we propose to define early feeding as actively starting artificial feeding within the first 24–48 h after an acute insult, aiming at delivering at least 50% of energy requirement on day 3.

Early Nutrition

Animal Studies

Many experimental studies suggest that starvation, even of short duration, is deleterious in stressed animals. Early enteral feeding seems actually to be the simplest means to maintain both the integrity and the functions of the intestinal mucosa. EN improves survival in animals subjected to abdominal infection, hemorrhagic shock or extensive chemotherapy [14]. Compared to fasting or parenteral nutrition, enterally fed stressed animals keep normal intestinal permeability, have decreased translocation of bacteria and toxins as
Table 1. Early enteral nutrition *versus* conventional nutritional care in critically ill patients

<table>
<thead>
<tr>
<th>Design</th>
<th>Diagnostic category</th>
<th>Patients n</th>
<th>Route of feeding</th>
<th>Time of feeding</th>
<th>Specific nutrients</th>
<th>Effects of early feeding</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>Severe abdominal trauma</td>
<td>75/63</td>
<td>Jejunal</td>
<td>First 24 h vs. oral feeding</td>
<td>No</td>
<td>Decreased infections incidence</td>
<td>33</td>
</tr>
<tr>
<td>RCT</td>
<td>Brain injury</td>
<td>32</td>
<td>Post-pyloric vs. gastric</td>
<td>First 36 h vs. control</td>
<td>No</td>
<td>Decreased infections incidence</td>
<td>43</td>
</tr>
<tr>
<td>RCT</td>
<td>Severe trauma</td>
<td>52/38</td>
<td>Jejunal</td>
<td>31 (13) vs. 82 (11 h)</td>
<td>No</td>
<td>Increased infections incidence</td>
<td>35</td>
</tr>
<tr>
<td>RCT</td>
<td>Liver transplantation</td>
<td>50/31</td>
<td>Jejunal</td>
<td>12 h after surgery</td>
<td>No</td>
<td>Decreased viral infections no clinical effect</td>
<td>34</td>
</tr>
<tr>
<td>RCT</td>
<td>Severe brain injury</td>
<td>30/27</td>
<td>Jejunal vs. gastric</td>
<td>33 (15) vs. 84 (41)</td>
<td>Yes</td>
<td>No clinical effect</td>
<td>36</td>
</tr>
<tr>
<td>PNRT</td>
<td>Severe burns</td>
<td>20</td>
<td>Gastric</td>
<td>4.4 (0.5) vs. 57 (2.6 h)</td>
<td>No</td>
<td>No significant clinical effect</td>
<td>37</td>
</tr>
<tr>
<td>PNRT</td>
<td>Severe trauma</td>
<td>51</td>
<td>Jejunal</td>
<td>1.6 (0.2 day) vs. oral feeding</td>
<td>Yes</td>
<td>Decreased infections</td>
<td>49</td>
</tr>
<tr>
<td>RS</td>
<td>Severe burns</td>
<td>25</td>
<td>Post-pyloric or gastric</td>
<td>3 (2) vs. 7 (2 days)</td>
<td>No</td>
<td>Decreased LOS</td>
<td>38</td>
</tr>
</tbody>
</table>

*RCT = Randomized controlled study; PNRCT = prospective nonrandomized study; RS = retrospective study; LOS = length of stay.*
well as decreased acute phase responses [11, 15], although deleterious effects were also observed in other studies [16]. After a gut ischemic insult, early EN prevents remote organ injury and death [17]. Enteral glucose, peptides and lipids have been shown to improve the mesenteric blood flow in experimental studies of circulatory failure [18].

This contrasts with the delivery of intravenous substrates, particularly carbohydrates, which has been shown to upregulate the inflammatory response, increasing the release of cytokines and mediators, and thus exerting deleterious metabolic and systemic effects [19].

**Human Studies**

Several studies performed in postoperative and critically ill surgical patients suggest that starting enteral feeding directly after injury or ICU admission may be advantageous [11, 12]. Although some experts advocate considering early EN in most critically ill patients, the level of evidence is not high and such a position is controversial. Even if it is clearly established that prolonged fasting should be avoided in ICU patients, the safe duration of starvation in the ICU is yet unknown, as well as the time at which artificial nutrition should be begun to avoid malnutrition-related complications [20]. There is presently no evidence that a short period of fasting (1–5 days) is deleterious in critically ill patients without pre-illness malnutrition. Here again, it should be underlined that the results obtained in postoperative patients may not apply to more severely ill patients.

Unfortunately, there is only a limited number of randomized controlled trials (RCT) comparing early feeding with conventional artificial nutrition, because it was assumed that early feeding is good, focusing only on the effect of the route of feeding. Practically, it has resulted in many studies comparing the effects of total parenteral nutrition (TPN) and EN, but very few assessing the effect of timing *per se*.

**Early Parenteral Feeding**

To our knowledge, there are only 2 randomized controlled studies comparing the administration of TPN to conventional care without artificial nutrition during the first 5–10 days after injury and 2 RCT assessing the effects of intravenous supplemental feeding [21–24]. In one study, early TPN had no beneficial clinical effects in patients with acute pancreatitis, but catheter sepsis was significantly increased [23]. In a small RCT, 28 hypoalbuminemic patients with liver transplantation were randomized to 3 nutritional regimens: no nutrition *vs.* 2 different TPN solutions (with or without branched-chain amino acids). Patients without nutritional support had a longer ICU stay and a tendency for longer respiratory dependency, suggesting a beneficial effect of early feeding [24]. In another controlled study performed in 39 severely
burned children, supplemental intravenous feeding was associated with an increased mortality and lower enteral intakes, in comparison with children receiving EN only [21]. It should be underlined that the supplemented groups were overfed according to actual standards. In a recent RCT performed in 120 adult medico-surgical patients, supplemental intravenous feeding had no demonstrable beneficial effects on ICU variables, but was associated with a significant reduction in the length of hospital stay [22]. A meta-analysis was recently performed to assess the effects of TPN compared to conventional care in postoperative and ICU patients: there was no beneficial effect of TPN on mortality; a trend toward a reduced incidence of complications was observed in patients receiving parenteral feeding.

There are experimental data suggesting that the intravenous delivery of nutrients in animals with life-threatening conditions may dangerously upregulate the inflammatory and metabolic processes [19]. Administration of 7-day parenteral nutrition before endotoxin administration in healthy humans was shown to enhance the metabolic and inflammatory responses, compared to enteral feeding [25]. In agreement with these results, studies performed in critically ill trauma patients also suggest that parenteral nutrition may enhance the acute phase response to injury [26]. In addition, several randomized studies comparing early EN and TPN in patients with severe trauma suggest that EN may be superior to TPN. Septic complications were reduced in some studies, although there was no effect on mortality [27–30]. Altogether, these data suggest that there is no place for the use of early TPN in critically ill patients without pre-existent malnutrition.

**Early Enteral Nutrition**

The claimed advantages of EN are well known, although they are more based on experimental data than on solid clinical evidence. In animals, it has been shown that EN maintains the gut mucosa and preserves important gut functions, like the immune and barrier functions [31]. The results of clinical studies suggest that EN also has beneficial effects in humans. In acutely ill patients, there is some evidence that enteral feeding improves immunity, increases the splanchnic blood flow and may decrease nosocomial infection. This explains why EN is usually considered as the most appropriate form of artificial feeding in ICU patients [31]. Interestingly, enteral feeding is often considered an important means to maintain the gastrointestinal tract in such patients [32], although there is little clinical evidence to support this affirmation.

There are only a few RCT comparing the effects of early feeding with the effects of conventional therapy with no supplemental nutrition during the first 3–7 days of ICU stay. Table 1 summarizes the results of the most relevant studies performed in the ICU settings, excluding the studies performed.
Timing of Nutritional Support

in patients requiring major elective surgery. Most of these studies were performed in severely traumatized patients. Moore and Jones [33] randomized 75 patients with severe abdominal trauma requiring surgical treatment, to receive early jejunal feeding (12–18 h postoperatively) or conventional therapy. Control group patients received dextrose-saline solutions. TPN was administered after day 5 in patients unable to resume sufficient oral feeding or in patients intolerant to EN. Nitrogen balance was significantly improved by early EN, but there was no effect on survival. A significant decrease in overall septic complications was observed in patients receiving early EN, although the total number of complications was not affected. It should be mentioned that the occurrence of complications was not based on predefined criteria. In 50 patients after liver transplantation randomized to receive early EN or conventional therapy, Hasse et al. [34] found that early jejunal feeding was well-tolerated. The patients receiving early nutrition had a better nitrogen balance on day 4 and decreased incidence of viral infections (0 vs. 18%, \( p = 0.05 \)), but there was no significant effect on bacterial infections. Early EN was not superior to conventional EN (after days 3–5) in 2 other studies including patients with severe trauma or severe head injury, but these were clearly underpowered: of 52 patients enrolled, 38 were evaluated in the study by Eyer et al. [35] and of 31 patients enrolled, 28 were evaluated in the study by Minard et al. [36].

The effects of immediate feeding (\( i.e. \ 4.4 \pm 0.5 \) h after hospital admission) were compared to the effects of artificial feeding started 48 h after admission in a prospective nonrandomized study in 20 severely burned patients (burned body surface area 25–60%) [37]. Early intragastric feeding was well tolerated leading to an improved nitrogen balance. No clear clinical benefit could be demonstrated although the study was underpowered for this purpose. Urinary catecholamine excretion and plasma glucagon levels were decreased in patients receiving early nutrition, but there was no effect on the cortisol plasma level. This study was unfortunately not followed by larger controlled trials to determine the clinical relevance of these results. In a retrospective study, Garrel et al. [38] compared 2 groups of 25 severely burned patients receiving enteral feeding starting at 3 ± 2 days or later at 7 ± 2 days. Length of care was markedly increased in the patients receiving late enteral feeding (39 ± 20 vs. 76 ± 49 days, \( p < 0.05 \)).

These data suggest that early enteral feeding may improve the clinical outcome of critically ill patients suffering from severe trauma or burn injury, but the level of evidence is not very high. Several RCT in patients requiring major surgery (not reported here) also suggest that early EN may improve wound healing and some nutritional variables [39]. Altogether, it seems reasonable to recommend early EN in critically ill patients with severe trauma or burns or following liver transplantation. In the other ICU patients the level of evidence is not yet sufficient to recommend such therapy.

158
Timing of Nutritional Support

Feasibility and Tolerance of Early Enteral Feeding

One of the theoretical advantages of parenteral feeding is the ease of administration of the nutrient solutions. This contrasts with enteral feeding, where there is quite commonly a substantial difference between the prescribed and delivered energy due to difficulties of enteral delivery of nutrients (pylorus closure, vomiting, etc.) [40]. Numerous studies have shown that starting EN early at low rate is possible in most ICU patients, although increasing calorie delivery is often more difficult. This is the case in patients with severe trauma with or without abdominal injuries, major burns, liver transplantation, major elective abdominal and nonabdominal surgery, acute respiratory distress syndrome [27, 41, 42] (Table 2). However, the sicker the patient is, the more difficult enteral feeding, due to the effects of critical illness on the gastrointestinal functions. This was assessed in 106 consecutive patients with burns involving more than 20% of their body surface area, receiving early gastric feeding beginning less than 6 hrs after injury [41]. Overall, the clinical tolerance to feeding was excellent, vomiting being the most common complication. The delivered energy was progressively increased, reaching 99 ± 7% of the resting energy expenditure on day 3. Calorie supply was, however, lower in the patients with burns exceeding 60% of the body surface area, as well as in patients with a high predicted mortality, over 50%, i.e. in the most severely burned patients.

Difficult or impossible early gastric feeding has also been described in patients suffering from severe head injury [13], while jejunal feeding was feasible and safe [43]. In one RCT performed in well-nourished patients undergoing esophagectomy or duodenopancreatectomy, immediate enteral feeding was compared with no enteral feeding during the first 6 postoperative days [44]. Enteral feeding was associated with respiratory difficulties like decreased postoperative vital capacity and forced expiratory vital capacity, as well as with reduced physical activity and did not influence muscle strength or fatigue. These results were attributed to the abdominal distension related to feeding. Other studies have reported severe intestinal complications related to early enteral feeding in acutely ill surgical patients, like perforation, worsening of ischemia [45]. Thus, early enteral feeding is safe and well tolerated in most ICU patients, but not in all (Table 3). Early EN, like any other therapy, should not be used without clear indications, a basic medical principle.

Another important point concerns the ability of the gut to absorb the nutrients during the early post-injury period, since several mechanisms may concur to alter the gastrointestinal functions [46]. They often have delayed gastric emptying due to pylorus closure and depressed intestinal motility. Clinical studies performed in surgical ICU patients receiving early EN suggest that nutrient absorption is maintained in many critically ill patients, including those with circulatory failure. There is, however, no simple validated test
### Table 2. Early enteral *versus* early parenteral nutrition in critically patients

<table>
<thead>
<tr>
<th>Design</th>
<th>Diagnostic category</th>
<th>Patients n</th>
<th>Route of feeding</th>
<th>Time of feeding</th>
<th>Specific nutrients</th>
<th>Effects of EN <em>vs.</em> TPN</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>Severe abdominal trauma</td>
<td>46/46</td>
<td>Jejunostomy <em>vs.</em> TPN</td>
<td>First 24 h</td>
<td>No</td>
<td>No demonstrable clinical difference</td>
<td>29</td>
</tr>
<tr>
<td>RCT</td>
<td>Severe abdominal trauma</td>
<td>75/59</td>
<td>Jejunostomy <em>vs.</em> TPN</td>
<td>First 12 h</td>
<td>No</td>
<td>Decreased pulmonary and abdominal infections</td>
<td>30</td>
</tr>
<tr>
<td>RCT</td>
<td>Severe abdominal trauma</td>
<td>98/96</td>
<td>Jejunostomy <em>vs.</em> TPN</td>
<td>24 (1.7) <em>vs.</em> 22.9 (1.6 h)</td>
<td>No</td>
<td>Decreased pulmonary, abdominal and intravenous line infections</td>
<td>27</td>
</tr>
<tr>
<td>RCT</td>
<td>Liver transplantation</td>
<td>24/24</td>
<td>Jejunal tube <em>vs.</em> TPN</td>
<td>18 <em>vs.</em> 24–60 h</td>
<td>No</td>
<td>No demonstrable clinical difference</td>
<td>28</td>
</tr>
</tbody>
</table>

*RCT = Randomized controlled study.*
Table 3. Clinical use of early enteral feeding in critically ill patients

<table>
<thead>
<tr>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Severe trauma</td>
</tr>
<tr>
<td>• Major burns</td>
</tr>
<tr>
<td>• Liver transplantation</td>
</tr>
<tr>
<td>• Acute respiratory distress syndrome (ARDS)</td>
</tr>
<tr>
<td>• Major abdominal cancer surgery</td>
</tr>
<tr>
<td>• Actual malnutrition</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Absolute contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Loss of bowel anatomical integrity</td>
</tr>
<tr>
<td>• Mechanical ileus</td>
</tr>
<tr>
<td>• Severe splanchnic ischaemia</td>
</tr>
<tr>
<td>• Shock (any origin)</td>
</tr>
<tr>
<td>• Severe pancreatitis (gastric feeding)</td>
</tr>
<tr>
<td>• Generalized peritonitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relative contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Short bowel</td>
</tr>
<tr>
<td>• Paralytic ileus</td>
</tr>
<tr>
<td>• Acute circulatory failure</td>
</tr>
<tr>
<td>• Electrical burns (high energy current)</td>
</tr>
<tr>
<td>• Localized peritonitis</td>
</tr>
</tbody>
</table>

Not indicated

• Short starvation in moderately stressed patient

enabling an accurate detection of nutrient absorption in such ill patients. $D$-Xylose absorption is mainly used to detect malabsorption in patients with intestinal disease but there is little experience of its use in the ICU [47]. The paracetamol test is a simple means to assess gastric emptying and intestinal absorption [48]. It consists in measuring serum paracetamol levels after the administration of a single dose of paracetamol through the gastric tube. Several studies report its use in critically ill patients, mainly to assess gastric emptying. We recently assessed intestinal absorption in cardiac surgery patients with severe postoperative cardiac failure, requiring aggressive cardiac supportive therapy by means of the paracetamol test [48]. Early gastric or jejunal feeding was initiated on the 2nd postoperative day and was well tolerated in all these patients; energy delivery on day 4 amounted to 50% of the energy requirements. On day 1 paracetamol absorption was markedly reduced in all patients after gastric administration, but normal after jejunal delivery, suggesting pylorus closure but maintained intestinal absorption. In another study we compared the $D$-xylose absorption test with the absorption of $^{13}$C-labeled acetate in 24 critically ill surgical patients (unpublished data). Acetate absorption was very rapid, while $D$-xylose absorption was delayed, despite a good tolerance to enteral feeding. These data suggest that $D$-xylose
Timing of Nutritional Support

absorption is not appropriate to assess intestinal absorption in ICU patients, while labeled nutrients seem promising.

Conclusion

Extensive research was devoted to the artificial nutrition of critically ill patients during the last decade. Several studies assessed the effects of the timing of nutritional support. Encouraging clinical results were found using early enteral feeding in surgical ICU patients with major stress. At this stage, the following sound conclusions can be proposed.

1) There is no evidence that short starvation up to 5–7 days is deleterious in most critical care patients without pre-existent malnutrition.
2) There is reasonable evidence that early enteral nutrition is beneficial in patients with severe trauma, particularly abdominal, major burns and after liver transplantation.
3) In the recent literature, it is difficult to identify the proper effect of early feeding from that of specific nutrients, like glutamine and others.
4) Early parenteral nutrition has no place in the ICU in patients without pre-existent malnutrition.

References

Timing of Nutritional Support


Discussion

*Dr. Becker:* Can I ask you about enteral access? What routes do you prefer and what are your views on the whole concept of post-pyloric feeding?

*Dr. Chioléro:* This is a very important point, as organizing nutrition from the office and doing it practically are very different things. Enteral access is a problem in the intensive care unit (ICU), but there are various possibilities. In our practice we start with simple things: we try to give gastric nutrition when possible, and in fact we find that it is possible in more patients than we thought previously. If we start early, the pylorus tends to stay open and we are successful by this route in at least half the patients. If that doesn’t work, we then use jejunal access, either with a self-propelled tube, where the success rate is about 60%, or by active insertion with the help of a gastroenterologist or a radiologist. Finally, when we need to provide prolonged enteral support, we often use a percutaneous gastroenterostomy, which is very convenient.
Dr. Meguid: We have now started to give patients 100 g glucose as a complex drink 2 hrs before surgery in elective abdominal cases in order to get away from the ‘nil per mouth’ situation that used to prevail. Our initial subjective impression is that we are seeing fewer complications. I’m not sure whether that concept has crossed the Atlantic yet, but we are planning to do randomized studies. Have you come across this practice?

Dr. Chioléro: What is in the drink?

Dr. Meguid: It is a complex fiber-carbohydrate drink that was developed by NASA for astronauts.

Dr. Chioléro: Well, the first thing you are doing is to put nutrients in the gut, which can exert beneficial effects; the second thing you are doing by giving carbohydrates is to modulate insulin sensitivity. Whether this is a good thing or not nobody knows exactly at present. So this approach is a way to influence the gut and the metabolic response to surgery, and one could envisage giving other nutrients like antioxidants, n-3 fatty acids and so on. However, we shouldn’t use such drinks without adequate clinical studies. Obviously this will be a new commercial avenue and I’m sure the industry will soon be producing all sorts of preoperative drinks.

Dr. Becker: I think prospective blind studies have started on the east side of the Atlantic, examining preloading of patients who are to be operated on. One of the end points will be gastric emptying. The claim is that gastric emptying after the operation will be improved.

Dr. Docrat: A good surgeon prepares for his patients’ postoperative course, either before or during the operation. Our routine for major surgery is to insert a nasojejunal tube. There is no great problem in doing this, and if the patients start feeding quickly it can be removed and nothing is lost. So I would not go the route of starting jejunal feeding after the operation, if I already know before the operation that the patient may need it.

Dr. Chioléro: I agree. I would like to have surgeons like you in my hospital!

Dr. Docrat: My second point is in relation to your concept of nonocclusive bowel necrosis. In a trauma patient that means a missed injury to me – nonocclusive bowel necrosis means a kinetic energy injury with delayed presentation.

Dr. Chioléro: I think you are right in many cases, but not all. There are well-described cases of non-occlusive bowel necrosis in burns patients without any other injury. We had one such case in Lausanne, where we pushed enteral feeding and the patient developed gut distension and eventually necrosis. But I agree that the first differential diagnosis is missed trauma to the intestine.

Dr. Waitzberg: I would like your comments about some recent data published by a Spanish intensive care group. These investigators found that 60% of the complications of enteral nutrition in their ICU were related to gastric tubes. Another paper in the same journal stated that a high gastric residual volume – over 200 ml – was correlated with a high mortality. Do you think that taken together these data mean that we should provide postpyloric enteral nutrition in all ICU patients?

Dr. Chioléro: I think those studies are interesting, but although I accept that there are numerous complications of enteral feeding, most of them are minor. The main difficulty is teaching nurses and other staff how to do it properly. Of course there will be contraindications, it is not a good idea to push enteral feeding in a patient who will not tolerate it. Finally, and this point has been underlined in many papers, the sicker the patient the more difficult it is going to be to feed him enteraly, but in such patients you should probably use both enteral and parenteral routes of nutrition. So it is important to be able to use all routes and to combine them as necessary.

Dr. Waitzberg: But don’t you have doubts about enteral nutrition in these circumstances? I mean, you have to teach the nurse, there are many complications, you may
not be able to give enough energy, the results may not be good, and so on. I just want you to expand your thoughts on this.

Dr. Chioléro: This isn’t any more complicated or difficult than any other technique in the ICU. It is no more difficult for a nurse to learn to do proper enteral feeding, than to ventilate a patient or to use aseptic techniques when dealing with intravenous catheters. It is a matter of basic education. But where the team works nicely, you have impressive results even with difficult cases. You may have read Gadek’s study in acute respiratory distress syndrome (ARDS) patients, an American study, where they gave n-3 fatty acids and antioxidants to patients with ARDS [1]. These are difficult cases to feed enterally – they are sedated and mechanically ventilated – but in fact more than half the patients had gastric nutrition, and after 3 days they were receiving nearly all of their energy requirements by that route. So it was quite feasible, and the nurses were all ICU nurses.

Dr. Pretorius: Do you have specific recommendations for protein intake in trauma or ICU patients, and is there benefit in giving increased amounts of protein or nitrogen to trauma or ICU patients?

Dr. Chioléro: I’m afraid you may be disappointed by the literature. It appears that it is not useful to go over 1.5 g/kg/day of protein in such patients. Increasing the nitrogen supply will simply increase protein oxidation; that has been well established. I’m afraid it’s not the way to improve body composition.

Ms. McMahon: I would like to emphasize the problem of the obese patient. Medical and nursing staff often see such people as being overnourished, and there is a reluctance to start early feeding, whereas in fact, if you look at their percentage of lean body mass, they are perhaps even more at risk of malnutrition than thin people, and they have the insulin resistance that goes with adiposity. Such patients deserve more attention.

Dr. Chioléro: I agree that it is important to start early nutrition in such patients, when they are in the ICU. I expect our North American friends have plenty of experience of that problem!

Dr. Atherstone: Don’t you think we should give early parenteral nutrition in the category of patients who are already malnourished before surgery?

Dr. Chioléro: In that case I agree, but that is probably the only indication for going straight to parenteral nutrition. However, I would start with a different mixture from that used in stabilized patients – for example, I wouldn’t give a lot of lipids.

Dr. Segal: We are often called to the ICU to advise on gastrointestinal tract complications, and one that concerns us particularly is esophagitis due to the passage of the nasal gastric tube. This is sometimes quite severe. Another common problem is stress ulceration. We are not sure what prophylaxis we can give to avoid this, but I am impressed by the damage to the upper gastrointestinal tract in patients in the ICU.

Dr. Chioléro: You are quite right, these are very annoying and disturbing complications. This is also our experience. We have an additional problem in Lausanne, because our anesthetists like inserting large tubes, which increase the trauma. For prolonged nutritional support this could be a reason for using percutaneous endoscopic gastrostomy.

Ms. Marino: You made a comment about the use of inotropic agents in microvascular ischemia. Is there a maximum amount of inotrope support above which the use of enteral feeding would be contraindicated?

Dr. Chioléro: That’s an important question. In the textbooks it is stated that you shouldn’t feed patients enterally who are receiving high doses of inotropes. We were interested in the use of agents like paracetamol to assess pylorus opening and intestinal absorption in such conditions [2]. We feed these patients very carefully, always looking for abdominal distension and we never give their total intake enterally – we give up to
half the theoretical energy supply by that route. As there are many such cases, we need controlled studies to show that enteral feeding is safe and that hasn’t been done yet.

Dr. Gopalan: In your unstable cardiovascular patients given paracetamol, do you see a further depression of cardiac function?

Dr. Chioléro: We measured the cardiovascular response to enteral feeding in another series published in *Intensive Care Medicine* this year [3]. Again these were very sick cardiac surgery patients given inotropes. The hypothesis was that such patients might have increased mesenteric blood flow at the expense of the heart when given nutrients into the gut. In fact, on very careful feeding, these patients increased their total cardiac output and there were no signs of steal to the gut from other vascular beds. We monitored the patients for cardiac ischemia and found absolutely no evidence of that, though it was only a small series. More work is needed in this field.

Dr. Gopalan: The reason I brought up that point is that such patients are the ones who may very well have the most need of nutrition.

Dr. Docrat: In patients with microvascular ischemia, there will obviously be limb ischemia as well as mesenteric ischemia on high doses of inotropes. What I have done – and this is purely anecdotal – is to give intermittent infusions of rheomacrodex in the right kind of patient (that is, ones who are not renally impaired). This improves the microvascular circulation, though there may be coagulation problems because of alterations to the viscosity of the blood, so you have to be careful, when you use it. However, it has been very successful in people with peripheral limb ischemia, and I wonder whether you could transfer that effect to your patients with bowel ischemia.

Dr. Chioléro: That might be a solution, but we have no experience with this approach.

Mrs. van Schalkwyk: In many instances the patients arrive in our hospital without nasojejunal access. What criteria do you use to determine whether you can feed your patients by the enteral route? You spoke about bowel sounds, gastric emptying, and gastric aspirate.

Dr. Chioléro: We use very simple clinical criteria. If there is no gastric aspirate, we will use the gastric route; if there is no tube we put one in; if gastric feeding is not possible we will try to insert a jejunal tube. It is a step-by-step clinical approach.

Mrs. van Schalkwyk: What volume of gastric aspirate would be a contraindication to gastric feeding?

Dr. Chioléro: The books say you should not feed gastrically if the residuum is over 150 ml, but this is unnecessarily low. We now continue feeding with aspirates as high as 300 ml, and we discard the aspirate. Where aspirates exceed 300 ml, we assume the pylorus is closed.

Dr. Griffiths: You have identified that it is the type of patient that is the real problem, because we are dealing with such a complex range. This makes looking at the evidence very difficult. You come from a surgical background, and I have noted the sensible comments that you and others in the audience have made, but the spread of intensive care encompasses medical patients as well, and they also present delivery problems. One of the great challenges in this field is that the risk of death is so high. This makes it impossible to do an intention-to-treat analysis, because one is always failing, for whatever reason. So all the results obtained in comparisons between, say, enteral and parenteral feeding are derived from looking only at those patients whom you have been successful in actually feeding. That is one of the great problems of interpreting these comparative data.

Dr. Chioléro: That’s an important point.

Dr. Griffiths: A continuation of that is that you have to look at the overall risk of what you are doing. The trouble is that, as we get sicker and sicker patients, the risks of parenteral nutrition start to diminish, because some of the complications are inherent
Timing of Nutritional Support

in the type of care given. On the other hand, enteral nutrition may increase the risk of mortality, because we know, for example, that supine posture and enteral feeding are both independent risk factors for aspiration pneumonia, which is the single most important complication leading to death. That’s the challenge we have to sort out in our decision making. We mustn’t lose sight of the fact that we can’t get at the true risk of what we are doing.

Dr. Pichard: You stated that in ICU patients without pre-existing malnutrition you would wait for up to a week or 10 days before initiating nutritional support. Might you reconsider that intention in cases where the patient is over 70 years of age or in individuals of any age who are very lean?

Dr. Chioléro: Our patients all receive oral supplements as soon as possible, and some of them will eat if encouraged. But I agree with you in general. We should take account of the level of stress and the patient’s age. The problem is that if we are trying to apply evidence-based nutrition we have no studies that can identify which patient should be fed on the 3rd day or the 7th, and so on. This is at present entirely a clinical approach.

Dr. Leverve: Recent evidence from a Belgian group suggests that tight control of glycemia improves mortality markedly. Can you comment on that in the light of what you have been saying about early enteral nutrition?

Dr. Chioléro: That’s difficult as the paper was published very recently and I have only read the abstract. Basically what was shown was that if you have tight control of glycemia – blood glucose between 5 and 6 mmol/l *vs.* around 10 mmol/l – you will decrease mortality twofold in a general ICU population. I like the phenomenological approach, so my first conclusion is that we should have a better approach to controlling glycemia, but this would apply to patients who are enterally fed or parenterally fed. There is a natural control of glycemia, when we use enteral feeding, which is an obvious advantage. We have data in press on a large population of patients receiving enteral or parenteral feeding, where we assessed glucose turnover, insulin sensitivity, and so on, and in fact there was not much difference between the two types of feeding, when given an isocaloric intake.

References