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Enteral nutrition in intensive care patients: a practical approach

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Abstract Severe protein-calorie malnutrition is a major problem in many intensive care (ICU) patients, due to the increased catabolic state often associated with acute severe illness and the frequent presence of prior chronic wasting conditions. Nutritional support is thus an important part of the management of these patients. Over the years, enteral nutrition (EN) has gained considerable popularity, due to its favorable effects on the digestive tract and its lower cost and rate of complications compared to parenteral nutrition. However, clinicians

caring for ICU patients are often faced with contradictory data and difficult decisions when having to determine the optimal timing and modalities of EN administration, estimation of patient requirements, and choice of formulas. The purpose of this paper is to provide practical guidelines on these various aspects of enteral nutritional support, based on presently available evidence.

Key words Nutrition · Enteral nutrition · Malnutrition · Intensive care · Critical illness

Introduction

The prevalence of malnutrition at the time of hospitalization has increased over the years, as a result of both the steady aging process of the general population and the development of aggressive medical and surgical treatments for various chronic debilitating diseases. Concomitantly, progress in intensive care has allowed prolonged survival of patients suffering from protracted catabolic disease, such as sustained sepsis and multiple organ dysfunction. Hence, severe malnutrition, slowing down recovery and increasing intensive care unit (ICU) and hospital stay, is often present in such patients [1]. This situation has prompted heightened awareness of the importance of optimal nutritional support. A growing body of evidence suggests that, in the presence of a functional gut, nutrition should be administered by the enteral route whenever possible. Indeed, it is becoming increasingly clear that the consequences of ent-

eral nutrition (EN) go beyond the supply of energy and proteins to the body, as there are other beneficial effects, including modulation of the host's immune response and the provision of fuel and protein to maintain gut integrity and possibly prevent bacterial translocation [2]. Hence, even though a favorable impact on patient outcome awaits unequivocal demonstration, improved knowledge on gut physiology has prompted research into optimal delivery methods and products for EN.

The purpose of this review is to focus on practical aspects of EN in critically ill patients, in the light of recent research, and to provide ICU physicians with a simple approach to optimize EN modalities.

Table 1 Advantages of enteral versus parenteral nutrition

Enteral nutrition:

- Favors intestinal villous trophicity
- Promotes gut motility, thus paving the way for oral feeding
- Reduces translocation of bacteria from the gut (?)
- Avoids infectious complications associated with parenteral nutrition
- Is less costly than parenteral nutrition

Table 2 Practical elements of nutritional assessment in critically ill patients

1. Patient history

- Disease states associated with heightened risk of malnutrition (e.g., chronic debilitating disease)
- Recent severe loss of weight ($\geq 5\%$ of usual body weight in 3 weeks or $\geq 10\%$ in 3 months)
- History of chronic low food intake, drug abuse, alcoholism, chronic psychiatric disorders

2. Assessment of present condition

- Diseases associated with hypermetabolism and prolonged catabolic activity (multiple injuries, burns, persistent fever, sepsis, multiple organ failure)
- Signs of malnutrition on physical examination (e.g., cachexia, muscle atrophy, edema)
- Body mass index (body weight in kg/(height in m)²) < 20 kg/m²

Rationale for enteral nutrition

The concept that enteral feeding should be preferred whenever possible is gaining acceptance [2], for the reasons outlined in Table 1. Indeed, complete bypass of the gut leads to adverse structural and functional modifications of the mucosal barrier, which can be reversed by enteral feeding [3]. This favorable effect stems from factors such as the stimulation of epithelial cell metabolism by direct contact with nutrients, increase in mucosal blood flow, and secretion of class A immunoglobulin, as well as enterotrophic gastrointestinal hormones such as gastrin and enteroglucagon [4]. Preventing mucosal atrophy is certainly an important goal, as animal studies indicate that the associated increase in gut permeability can induce translocation of bacteria and toxins from the gut lumen to the circulation [5], although there is no proof of such an occurrence in critically ill patients [4].

Nutritional assessment as the first step of enteral nutrition

The main goals of nutritional assessment are the timely detection of prior malnutrition to prevent or minimize further loss of body weight, in particular of cell mass, composition, and function, and the monitoring of the efficacy of nutritional support [6].

Nutritional state

An ideal clinical marker of nutritional state should be widely available, easily reproducible, highly specific to nutritional state, and sensitive to its modifications. Unfortunately, no such marker is available [6]. Furthermore, biological markers of malnutrition and measurements of bioelectrical impedance suffer from various shortcomings in ICU patients [7].

Recommendation

Simple parameters should be used and combined in a practical approach such as that summarized in Table 2.

Energy and protein requirements

The next step is to evaluate the patient's energy needs. The reference method is indirect calorimetry, which requires costly equipment and technical skills not widely available and is also time-consuming. A pragmatic estimate of energy requirements is 25–30 and 20–25 nonprotein kcal/kg per day in males and females, respectively, the lower values being used in patients > 60 years of age [8]. It is generally accepted that protein intake should be between 1.2 and 1.5 g/kg per body weight per day and should certainly not exceed 1.8 g/kg body weight per day, except in patients with extreme losses (extensive burns, digestive losses, etc.). The body weight used for this computation should be the mean between ideal and measured weights in severely malnourished patients and 20% higher than ideal weight in obese patients. Body weight should be determined either by weighing the patient, or, if not feasible, by estimation from height and anthropometric tables. Considering the rapid and marked shifts in body water content in ICU patients, caution should be exercised in the interpretation of body weight measurements. When body temperature is increased, 10% should be added to energy needs for every degree $> 37^\circ\text{C}$. The use of more sophisticated equations, such as the Harris–Benedict equation, allows an improved assessment of energy requirements, but is of little use in daily practice because of the various computations and correction factors involved.

Recommendation

Patients should receive 25–30 and 20–25 nonprotein kcal/kg per day for males and females, respectively, the lowest values being used in patients > 60 years old. Protein intake should be between 1.2 and 1.5 g/kg per body weight per day, never exceeding 1.8 g/kg per body weight per day, except in patients with extreme losses.

Micronutrient requirements

Trace elements and vitamins, also known as micronutrients, play an important role in various enzyme-catalyzed key reactions [9], many of which exhibit increased activity during the inflammatory response associated with critical illness [10]. Concomitantly, several critical conditions such as prolonged diarrhea or hemodialysis and extensive burns are accompanied by increased losses of trace elements and higher vitamin requirements [11–13].

Recommendation

Providing added micronutrients to those already contained in enteral feeding formulas to meet minimal daily requirements is not necessary when patients receive ≥ 1500 ml of such formulas. Adding micronutrients is recommended when smaller volumes of EN are administered for several days, or in the presence of severe conditions combining increased needs and large losses of trace elements [10].

Nutrients

Having determined the patient's nutritional state and energy requirements, the next step is to define the type of nutrients to administer. Caloric intake during stress is administered as a mixed fuel system. The ideal relative concentrations of carbohydrates and fat have not been fully determined in critically ill patients. However, current practice is to give carbohydrates and fat in a proportion of 60–70% and 30–40%, respectively, of total nonprotein calories [14].

Carbohydrates

The carbohydrates contained in enteral formulas range from starch to simple sugars; however, polysaccharides are the predominantly used. Polysaccharides are well tolerated but require pancreatic enzymes for digestion. Disaccharides (sucrose, lactose, maltose) require specific disaccharidases in the small bowel mucosa for hydrolysis and absorption. During illness, a decrease in lactase production can result in lactose intolerance. Monosaccharides (glucose, fructose) do not require hydrolysis for digestion, but tolerance may be limited by the absorptive capacity of the small bowel.

Both the sources and amounts of carbohydrates influence the osmolality of enteral diets [15]. In patients with vagotomy, gastrectomy, or intestinal dysfunction, the rapid infusion of large volumes of a high osmolality diet (≥ 350 mOsmol/l) may induce rapid transit, glucose

malabsorption, abdominal discomfort, and diarrhea. Diabetic patients with infection and/or dehydration may develop hyperosmolar nonketotic coma with high carbohydrate formulas [16], and glucose load should thus be reduced and insulin titrated accordingly.

Carbohydrate oxidation yields more carbon dioxide than fat oxidation. Ventilatory insufficiency with hypercapnia can be a complication of excess calories, which can be prevented by the reduction of total calorie administration, through a decrease in carbon dioxide production [17]. The clinical significance of hyperglycemia remains unclear. Moderate hyperglycemia promotes cellular glucose uptake. However, a link between hyperglycemia and risk of infection seems to exist in critically ill patients [18]. A blood glucose level < 225 mg/dl (12.5 mmol/l) is tolerated, and insulin should be added if glycemia rises further

Fibers

Insoluble fibers rich in cellulose and lignin [19–21] can exert beneficial effects by increasing fecal mass through water adsorption, thereby regulating intestinal transit, and decreasing the incidence of diarrhea. Soluble fibers (pectin, gums, mucilages) are degraded by anaerobic colonic microflora forming short-chain fatty acids (SCFA). The SCFAs are the primary fuel source of the colonic mucosa, and exert trophic effects on the mucosa of the large bowel, while preventing atrophy of the ileal mucosa and, finally, by delaying small intestinal glucose absorption, thus improving control of glycemia and decreasing insulin requirements.

Soy polysaccharide (with little fermentable fiber) is the fiber source commonly used in enteral formulas. Until recently, it was technically impossible to produce enteral formulas with pectin and guar gum.

It should be noted that the efficacy of fiber in ICU patients is still not clearly demonstrated. From a physiological point of view, fiber-enriched feeding solutions should be used to mimic normal oral food. Adverse effects have not been reported, even though caution should be exercised in patients with prolonged fluid restriction, due to an increased risk of bezoar formation.

Lipids

Lipids decrease the osmolality of enteral diets, and provide substantial amounts of energy for a small volume administered. Absorption of lipids from the gut is, however, more difficult than that of carbohydrates. Lipids provide a source of essential fatty acids, and are potential candidates in modifying the cell membrane composition and the regulation of mediators through the eicosanoids derived from their polyunsaturated fatty acids

[22]. The lipids used in enteral formulas (corn oil or soy oil) contain large amounts of long-chain triglycerides (LCT). Coconut and palm oil are sources of medium-chain triglycerides (MCT). MCTs do not stimulate pancreatic secretion and are hydrolyzed faster, being rapidly absorbed as free fatty acids and rapidly oxidized in the liver. MCT-containing enteral diets may be beneficial in fat digestion defects, are a readily available source of calories, and have fewer immunosuppressive effects than soy oil LCT, even though a higher incidence of diarrhea with MCT than with LCT has been reported [23]. Fish oil derivatives containing high levels of extra-long omega-3 fatty acids, and additionally enriched with nucleotides and arginine, have been introduced in enteral formulas, with the aim of enhancing the immune response [24, 25], as discussed below.

Proteins

The forms of nitrogenous constituents used in enteral solutions include intact, native proteins (polymeric diets) or “predigested nutrients” in the form of small peptides (semi-elemental or oligomeric diets) or amino acids (elemental diets). The energy content of proteins, small peptides, and amino acids in enteral diets is between 12 and 18 % of total calories. The forms of protein used in enteral solutions include intact protein such as sodium caseinates, soy protein isolate, whey protein, or lactalbumin. The protein quality is assessed by measuring protein quality (biological value) or chemical score. The highest biological value is defined as 100, which implies that 100 g of a protein replaces 100 g of body protein. The protein with the highest biological value is egg protein (100) followed by beef (92), cows milk (88), cheese (84), soy (84), rice (83), rye flour (76–83), and corn (72–76) [26]. Enteral feeding products have a wide range of biological values ranging down to 10 [27].

The nitrogen source used in enteral products determines the absorption of the components. Intact proteins do not have a significant impact on the formula’s osmolality, but they require normal levels of pancreatic enzymes for complete digestion. Peptide-based diets are better absorbed than proteins and even free amino acid solutions by both the healthy and diseased gut [28]. However, controlled studies have revealed that peptides offer no advantages over standard enteral formulas in terms of tolerance or outcome in the acutely injured. Because semi-elemental diets are associated with reduced trophic and immunostimulant action on the gut, their use should be reserved for conditions that clearly warrant predigested products. Hydrolysate formulas are sometimes prescribed for patients with impaired digestion, short-bowel syndrome, chronic intractable diarrhea, and severe inflammatory bowel disease, although this remains largely controversial.

Immunomodulating agents and micronutrients

Despite adequate nutritional support, nosocomial infection still remains a major problem in critically ill patients. Therefore, addition of specialized nutrients to the standard diet has been suggested in order to decrease such patients’ susceptibility to infection by enhancing the immune response [29]. In vitro, addition of some specific compounds amplifies the response of immune cells to stimuli. In animals, enrichment of the diet increases their survival to a septic challenge. In contrast, a decrease in the immune response may sometimes be desirable in critically ill patients, when a severe or prolonged inflammatory response contributes to multiple organ dysfunction [30]. Therefore, the ideal diet should be customized according to the patient’s condition. This approach has been called “immunomodulation.”

The target of the so-called “immunonutrients” can be the gastrointestinal tract (i.e., the enterocytes or the immune cells of the intestinal wall) in order to prevent or diminish the translocation of bacteria or bacterial products. Indeed, during critical illness, the amount of fuel for these rapidly renewed cells may become the rate-limiting step of an appropriate immune response. The function of circulating immune cells (mainly lymphocytes and macrophages) may also be influenced by the dietary constituents. However, undebated proof of a beneficial role of immunonutrients in terms of infection incidence, or response to ongoing infection, in critically ill patients is still lacking. Nevertheless, data reported from several studies on small numbers of patients suggest the response of immune cells can be enhanced by immunonutrients [24, 31–37]. However, the size of most of these studies was too small to detect a clear clinical benefit, and they assessed the effects of the addition of several compounds (i.e., glutamine and arginine, ω -3 fatty acids, nucleotides, vitamins, and trace elements) so that the reported effects can hardly be attributed to any of them [38]. Hence, even though recent preliminary data suggest a beneficial effect on infection rate and length of hospital stay for some ICU patients with the use of immunonutrient-containing enteral formulas [39], this topic remains controversial and clearly warrants further research.

Glutamine

Glutamine is essential for cultivating cells in vitro, serves as an energy substrate in rapidly replicating cells (enterocytes and immune cells) and as a glucose precursor (intestine, liver), counteracts acidosis (kidney), and is partly responsible for the regulation of the intracellular water content in skeletal muscle [40, 41].

Several in vitro experiments have revealed that glutamine influences the immune system by stimulating

the proliferation of T-cells, the formation of interleukins, and the phenotype and function of monocytes [42, 43]. Experimental studies have demonstrated that enteral administration of glutamine can maintain normal intestinal integrity by stimulating protein and also DNA and RNA synthesis, resulting in an increase in villus number and height. Moreover glutamine prevents deterioration of gut permeability [44], preserves mucosal structure [45], exerts trophic effects in the ileum and in the proximal and distal colon, and prevents gut translocation of bacteria and endotoxins [46].

Clinical studies demonstrating an effect of glutamine similar to that shown in animal experiments are lacking at this time, possibly because the amount of glutamine in the available commercial EN products is insufficient, and absorption is reduced because of increased utilization of glutamine by the gut [47]. Administration of glutamine in parenteral nutrition in the form of glutamine or glutamine-containing dipeptides has been shown to decrease the incidence of infections in immunosuppressed bone marrow recipient transplantation [48], increase lymphocyte DNA synthesis in postsurgical patients, and exerts a long-term benefit (in terms of 6 months' survival) in critically ill patients [49]. This finding probably requires confirmation by other studies, especially since the mechanism involved is incompletely understood. Possible pathophysiological explanations for the effectiveness of glutamine on intestinal function are that glutamine increases the formation of glutathione, stimulates the expression of heat-shock proteins, acts as a precursor of arginine, and has a positive impact on the intracellular adenosine triphosphate concentration. In fact, the lack of supplemental glutamine in conventional enteral solutions may theoretically per se be detrimental.

Arginine

The relationship between arginine and infectious complications has been more extensively studied. Presently, arginine supplementation has been associated with a better outcome in several animal models, probably reflecting somewhat the anabolic and endocrine effects of this amino acid in addition to its immune properties. Nevertheless, the growth and differentiation of several types of immune cells is increased after addition of arginine in the medium bath. Also, arginine is the substrate for nitric oxide synthesis. Nitric oxide production is activated in inflammatory conditions and has been involved in several immunological mechanisms.

One study in postsurgical patients demonstrated an effect of arginine supplementation on lymphocyte function, but the clinical relevance was not assessed [35]. The other clinical studies performed in critically ill patients assessed the effects of arginine together with other immunonutrients [24, 31–36, 50]. There was usual-

ly an improvement in immune cell function, and an increase in concentrations of circulating immunoglobulins, but little clinical benefit has been documented. This may be related to the small size of these studies, which were designed to assess immunological parameters. The largest study [24] showed a clinical benefit in a subgroup of patients, but the methodology used has been questioned [25].

Nucleotides and ornithine α -ketoglutarate

The rationale for dietary enrichment in nucleotides lies in the immunostimulant properties of these compounds in vitro (i. e., on natural killer cells and T-lymphocytes) and in vivo (increase in survival of rodents challenged with microorganisms). The effect of nucleotide supplementation has only been evaluated in association with arginine and ω -3 fatty acids in critically ill patients [24, 31, 32, 34, 36].

The anabolic properties of ornithine α -ketoglutarate are theoretically adapted to counteract the catabolic state, and administration is easy [51]. Favorable effects on muscle protein synthesis have been observed in trauma and burn patients [51, 52], but the clinical impact of these findings requires confirmation by further controlled studies.

Omega-3 fatty acids (ω -3 FA)

The rationale for the use of ω -3 FA during inflammatory processes lies in their fate once incorporated into a cell membrane. As compared with the conventional ω -6 FA, the synthesis of prostaglandins and leukotrienes is shifted from prostaglandin E_2 and leukotriene B_4 to the less active prostaglandin E_3 and leukotriene B_5 , respectively. Omega-3 dietary supplementation has been associated with alterations in cytokine production (for a detailed review see Blok et al. [53]). In human volunteers, a decrease in tumor necrosis factor- α /interleukin-1 synthesis by human peripheral blood mononuclear cells challenged with endotoxin has been documented [54]. In chronic inflammatory diseases, a diet enriched in ω -3 FA has somewhat improved the symptoms. In critically ill patients, the effects of ω -3 supplementation has been studied together with other immunonutrients [24, 31, 32, 34, 36], so that their influence on outcome or infection rate is still undetermined.

Recommendation

The modulation of gut and systemic immune function by providing substrates with immunomodulating properties is a promising approach in EN. Experimental evidence

and preliminary clinical data point to a beneficial effect on immune function of amino acids such as glutamine, arginine, ornithine α -ketoglutarate, and ω -3 FA. However, conclusive studies, clearly defined indications, and cost-benefit analyses are required before the routine use of immunomodulating agents can be recommended.

Feeding preparations and conditioning

In early days, homemade nutrient mixtures prepared in hospital kitchens were used for enteral feeding. However, this type of tube feeding is often unbalanced, causes feeding tube occlusion, and causes diarrhea secondary to bacterial contamination. Therefore, standardized, industrially produced feeds are recommended, as iso-osmotic (approximately 300 mOsm/l) solutions containing 1–1.5 kcal/ml, 45–60% of which should be in the form of carbohydrates, 20–35% lipids, and 15–20% proteins. Solutions are gluten and lactose-free.

Enteral feeding solutions usually contain homogenized substrates similar to those found in normal feeds and are termed polymeric solutions. Elemental or semi-elemental solutions contain free amino acids or hydrolyzed proteins, glucose, or oligosaccharides and MCTs to facilitate digestion and absorption in patients with altered digestive function. However, most patients can be fed with polymeric solutions, and these should be preferred to elemental formulas, since they are less likely to induce diarrhea and are associated with improved nitrogen retention and improved gut trophicity, while being considerably less costly.

Solutions containing increased proportions of lipids and less carbohydrate to reduce CO_2 production in acute respiratory failure or reduced protein content or increased branched chain amino acids for patients with acute renal or hepatic failure have been developed. However, there are no data supporting the use of such formulas.

Various types of feeding formula conditioning are possible. Most preparations are contained in 500-ml bottles, which, compared to larger bottles or pouches, implies added work, since most ICU patients receive 1500 ml of solution/day, but facilitates storage, manipulation, and organization at the bedside. Furthermore, using 1–2-l containers leads to a waste of feeding solution if it can only be partly administered. There is also an increased risk of bacterial contamination if large containers are left connected to the patient for long periods [55], unless a closed system is used, at an increased cost [56].

Recommendation

Containers containing 500 ml of feeding solution should be preferred, for easier storage, manipulation,

and convenience at the bedside. The tubing connecting the container to the patient's feeding tube should be changed once a day to avoid bacterial contamination [55], even if clear evidence of a direct link between the latter and increased risk of clinical infection is still lacking.

Feeding and organ dysfunction

Liver or kidney deficiencies have in common many metabolic and nutritional disorders. In both cases, malnutrition is frequent and related to the degree of liver failure [57] or to the renal disease. Furthermore, hemodialysis [58] is also an important factor of malnutrition. Liver and kidney share major roles in metabolic homeostasis for carbohydrate (unique organs for glucose production) and amino acid metabolism. These two pathological conditions are also characterized by a state of insulin resistance and by an increase in the ratio of lipid/carbohydrate oxidation. The most striking similarity between these two diseases is the decrease in the yield of utilization of nitrogen from the enteral route due either to liver destruction or to changes in liver metabolism related to chronic acidosis. As with any hydrophilic substrate absorbed by the gut, amino acids must cross the liver and approximately 20–60% of total amino acid uptake by the gut is metabolized by the liver: $\frac{1}{3}$ for protein synthesis and $\frac{2}{3}$ (i. e., half of the total uptake) being just wasted as urea [59]. Amino acids are not equally metabolized by the liver (e. g., branched-chain amino acids are poorly metabolized while aromatic and gluconeogenic amino acids are heavily utilized), hence this misuse of amino acids implies a remodelling of the amino acid mixture finally delivered to peripheral cells. Urea-genesis is decreased by acidosis, which alters this mechanism of amino acid-mixture remodelling [60]. Hence, the needs for nitrogen are higher in patients with liver and kidney failure compared with healthy subjects. In liver and renal failures the first clinical step is always a careful assessment of the nutritional status and of enteral intake limitations.

Alterations in pancreatic enzyme levels are common in ICU patients, without any demonstration of acute pancreatitis on ultrasound or computed tomographic (CT) examination. If acute pancreatitis is indeed present, EN can worsen it through its stimulatory effect on pancreatic secretions. Therefore, it is usually very difficult for the clinician to adopt the appropriate nutritional strategy if pancreatitis is suspected. Finally, it should be noted that even in the presence of proven acute pancreatitis, EN has been shown to be possible by the administration of a semi-elemental formula into the jejunum [61].

Recommendation

Liver failure

Enteral support in chronic liver disease has been reported to improve the mortality when given for longer than 3 weeks in patients with low spontaneous intakes: 25–35 kcal/kg per day as nonprotein caloric intakes and 1–1.5 g/kg per day of protein are recommended except in the case of severe encephalopathy clearly due to liver failure, where protein intake should be transiently decreased to 0.5 g/kg per day [62].

Renal failure

In the presence of renal failure severe enough to warrant treatment with intermittent or continuous hemofiltration or hemodialysis, protein intake restrictions are not necessary and should not be applied to avoid giving protein-poor solutions in the presence of an increased catabolic state. However, if dialysis is not instituted, protein restrictions such as those applied to nondialyzed endstage renal disease patients (0.6–0.7 g/kg per day if glomerular filtration rate is between 25 and 70 ml/min and 0.3 g/kg per day for a glomerular filtration rate < 25 ml/min) [63] should be used during the first few days of ICU stay, until renal function improves or extra-renal support is instituted.

Pancreatitis

In the presence of signs suggesting severe pancreatitis (abdominal tenderness and distention, increased gastric residues, steadily rising amylase/lipase levels, CT showing necrotic damage), enteral feeding should be transiently discontinued, and replaced by parenteral nutrition until clinical and biological signs of improvement appear. In the absence of signs of severity, EN should be continued, noting any clinical or biological signs suggesting worsening pancreatitis. To reduce the stimulatory effect of gastric feeding on pancreatic secretion, jejunal feeding should be considered except in isolated, moderate, and stable alterations in pancreatic enzymes [61].

Indications, contraindications and timing

Indications

Artificial nutrition is indicated in any critically ill patient unable to eat for a long period or who suffers from malnutrition. The main indications and contraindications to EN are summarized in Table 3. As in other conditions where artificial feeding is required, the enter-

al route must always be preferred to the intravenous route, except in patients with gastrointestinal pathology contraindicating EN (Table 3). Numerous studies demonstrate the superiority of EN over parenteral nutrition: maintenance of gastrointestinal mucosa and functional integrity, improved utilization of nutrients, safety of administration, reduced hospital infection rate in severely traumatized patients, and lower costs [64, 65].

EN is absolutely contraindicated in intestinal obstruction, anatomic disruption, or severe intestinal ischemia [65]. In patients with reduced intestinal perfusion due to prolonged or severe shock states, EN should be administered with caution. Such patients are unable to increase their splanchnic blood 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.

Timing

In critically ill patients, the institution of EN is frequently and erroneously delayed because of prolonged gastric emptying and regurgitation of enteral feeds [66]. Decreased gastroduodenal motility is a frequent finding in ICU patients, whose etiology is multifactorial [67]. As a result of the delay in enteral feeding, a worsening negative nitrogen balance and further weight loss can occur [68]. Consequently, enteral feeding should begin as early as possible, not necessarily with the goal of providing total support, but with that of exerting the beneficial effects on the gut outlined above, which can be attained with even small amounts of enteral feeding [69]. In many critically ill patients a 5–7 day delay before initiating EN has been considered reasonable, since no deleterious effects of a short fast have been demonstrated under these conditions [64, 65]. However, if prior malnutrition or a highly catabolic condition are present, this delay should be shortened to 1–2 days (Table 3). There are no clear data showing a clinical benefit of early EN compared to fast. By contrast, a significant advantage of early EN compared to parenteral nutrition has been repeatedly observed in patients with major trauma, consisting mainly in a reduction of hospital infection rate [64, 70]. Moreover, in such patients, there is accumulating evidence suggesting that early EN may decrease the development of hospital infection – a highly favorable effect. By contrast, no clear effect on mortality and hospital length of stay has yet been clearly demonstrated. Thus early EN may be beneficial in severely traumatized patients, but the evidence is not yet sufficient to make a strong recommendation.

Table 3 Indications, contraindications, and timing of enteral nutrition (EN) in critically ill patients

<p>General statement: Whenever artificial nutrition is indicated, the enteral route is preferred to parenteral nutrition</p> <p>Practical indications</p> <ul style="list-style-type: none"> • Present malnutrition, whatever the etiology, in a patient unable to eat • Prolonged fasting (more than 3–4 days)* in a well-nourished patient unable to resume oral nutrition • Supplementation of insufficient oral intake for > 3–4 days* • Severe trauma and burns: there is accumulating evidence that early EN is beneficial • Maintenance of gut mucosa, prevention of atrophy, stimulation of compensatory hypertrophy after small bowel resection • Opening of digestive tract and preparation of oral feeding <p>Contraindications</p> <p><i>Absolute</i></p> <ul style="list-style-type: none"> • Nonfunctional gut: anatomic disruption, obstruction, gut ischemia • Generalized peritonitis • Severe shock states <p><i>Relative</i></p> <ul style="list-style-type: none"> • Expected short period of fast, except in severely injured patients • Abdominal distension during EN • Localized peritonitis, intra-abdominal abscess, severe pancreatitis • Patients with terminal disease • Comatose patients at risk of aspiration (especially gastric feeding) • Extremely short bowel (less than 30 cm) <p>Timing</p> <ul style="list-style-type: none"> • Early EN (within 24–48 h): severe trauma, burns, highly catabolic state • Standard EN (after 2–3 days): moderate stress in a patient unable to eat
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* Evidence-based elements demonstrate clinical efficacy after delay as long as 7 days. However, clinical practice and experimental evidence strongly suggest that earlier onset of administration is warranted

Route of feeding

Enteral feeding can be provided via transnasal, transoral, or percutaneous transgastric routes or by surgically placed jejunostomy.

Nasoenteric route

Gastric feeding provides the most normal route for enteral polymeric nutrition, but poor tolerance in the critically ill patient due to gastroparesis is common [66]. Tolerance limitation is essentially related to the infusion rate, if higher than 1000 ml/24 h, and the global energy load. On this basis, some advocate aiming for subphysiologic intake (70% of calculated energy needs), if the duration of EN does not exceed 2 weeks and if no pre-existing malnutrition is observed, to improve tolerance to EN and avoid parenteral nutrition.

EN into the duodenum or even the jejunum has not been shown to decrease the risk of aspiration. The nasoenteric route is used for short- (< 2 weeks) and intermediate-term (< 4 weeks) EN. It is much more comfortable if a small-diameter (6–12 Fr.) silicone or polyurethane tube is inserted, and its length is determined by the desired location of feeding (stomach 90 cm, duodenum 110 cm, jejunum at least 120 cm). This type of tube should be preferred, as long as no aspiration of gastric contents is necessary (e.g. before intubation). The majority of tubes for enteral feeding are visible on X-

rays. Spontaneous transpyloric passage of enteral tubes in critically ill patients is commonly unsuccessful even when gut prokinetics are intravenously administered (metoclopramide, cisapride, erythromycin). Nasoenteral tubes with inner stylets are therefore recommended for use in the critically ill and the placement has to be performed either under fluoroscopic guidance or endoscopic assistance. Endoscopic placement of the nasoenteral tube can be performed at the bedside using portable equipment, aiming to achieve a final position distal to the ligament of Treitz. Endoscopic placement of tubes is highly successful and enteral feeding can start immediately following the procedure [71–73]. However, this procedure is more costly and requires that a physician trained in endoscopy be available.

Percutaneous route

Percutaneous endoscopic gastrostomy tube placement has become the procedure of choice for patients requiring prolonged EN support (≥ 4 –6 weeks) when oral intake is impossible or insufficient. Tubes in a range from 9 to 24 Fr. are available. This procedure can be considered in patients who have normal gastric emptying and can be performed at the bedside in the ICU. Relative contraindication are: ascites, gastric cancer, gastric ulcer, previous laparotomy, and hemocoagulation disorders. If postpyloric feeding is necessary (high risk of aspiration), percutaneous endoscopic jejunostomy (PEJ) may be per-

formed. The PEJ tube enables concomitant duodenal/jejunal feeding and gastric decompression [74].

Surgical placement of enteral feeding tubes is usually performed as the last phase of a laparotomy performed for another indication. Occasionally, surgical placement of the tube is indicated when the nasoenteral or percutaneous approach is contraindicated or unsuccessful. Selection of gastrostomy, needle-catheter jejunostomy, or transgastric jejunostomy depends on the primary diagnosis and status of the patient (e.g., gastrostomy is most common in esophageal cancer and needle-catheter jejunostomy in the critically ill).

Complications and adverse effects

EN generates complications related either to mechanical or to metabolic effects. The latter having been discussed earlier, we will focus on practical recommendations regarding the former. Dramatic complications may occur if nutrients are infused outside the gastrointestinal tract, particularly into the airways. Bronchial aspiration may occur when swallowing disturbances are prominent or in patients with altered consciousness. Abdominal pain, nausea, vomiting, and diarrhea following infusion of enteral feeds may occur, especially when the infusion rate is greater than 50 ml/h.

Recommendation

Abdominal X-rays should be obtained after the placement of a nasogastric tube because malpositioning frequently occurs (e.g., intracranial introduction in the case of cranial fracture, loops in the oral cavity or in the lower esophagus, or intratracheal introduction [75–77]).

Tolerance to gastric feeding should be monitored by measuring the gastric residues once a day (normal up to 300 ml) in order to reduce the risk of bronchoaspiration, especially in patients without protection due to tracheal intubation. If the gastric residues are greater than 300 ml, the infusion rate of the nutrient solution should be decreased by 50% for 4 to 6 h, and then resumed progressively over 24–48 h, during which time gastric residues should be monitored twice daily. Prokinetic agents such as cisapride [78] or erythromycin should be used in this situation to improve gastric emptying [79].

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 parenteral nutrition should be considered in this situation to ensure adequate nutritional support. Finally, the value of administering antidiarrheal agents or *Saccharomyces boulardii* [80] should be considered in individual cases.

Cost-effectiveness

There are not many well-designed placebo-controlled, randomized trials specifically involving critically ill patients, and in none has a complete cost-effectiveness analysis been carried out. Only about five studies investigated, in a prospective randomized fashion, the effects of nutritional support versus no support [81]. These studies could not detect a statistically significant effect of nutritional support on survival, overall cost, or duration of hospitalization, which may be related partly to the fact that all of them were limited by their small sample size, and/or lack of a true, untreated control group.

Somewhat more data are available comparing EN with parenteral nutrition. Because none of these studies contained an untreated control group, the available reports could not assess the efficacy of nutritional support itself. Main outcome parameters included mortality, hospital costs, and complications. It can be concluded from these studies that if either EN or parenteral nutrition is going to be provided, it would appear preferable to use the enteral route, especially if the problem of aspiration can be reduced or eliminated. There is no reason to believe that parenteral nutrition will be superior to EN in terms of clinical outcome, and it is well recognized that it is more expensive. Although meta-analyses of perioperative parenteral nutrition trials have suggested that preoperative parenteral nutrition may reduce the absolute incidence of overall postoperative morbidity by 5%, the cost of preventing one complication will be in the order of US \$ 100 000 [82].

Initially, nutritional support was advocated because it could “beef up” a patient. Later, it was clearly demonstrated that overfeeding could result in increased carbon dioxide production and respiratory failure. Then research focused on the beneficial effects in certain conditions of the relative amount of (macro) nutrients such as high fat nutrition in patients with respiratory failure, essential amino acids in patients with renal failure, and branched chain amino acids in patients with liver disease. Now nutritional supplements are altered to contain disease-specific nutrients, which may functionally be drugs including glutamine as an intestinal growth factor and arginine and omega-3 fatty acids to improve immunologic function. The randomized placebo-controlled trials that have been reported to date have suggested that some promising substances may exist, but the findings are too preliminary to draw definitive therapeutic conclusions.

Conclusion

Present evidence strongly suggests that, in ICU patients, EN should be preferred to parenteral nutrition whenever possible, due to its favorable trophic effects on the

intestinal mucosa, lower rate of complications, and lower costs. Simple guidelines can be set up for assessing the patient's nutritional state, the timing of nutritional support, choice of feeding route and formula, and protein-calorie requirements. Data are slowly accumulating that in some patients a reduced rate of complications and length of hospital stay can result from the use of immunomodulating enteral formulas, but further studies into this promising development should be performed before their widespread use can be recommended.

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