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RISKS AND BENEFITS OF NUTRITIONAL SUPPORT DURING CRITICAL ILLNESS

Yves Debaveye and Greet Van den Berghe
Department of Intensive Care Medicine, Catholic University of Leuven, B-3000 Leuven, Belgium; email: greta.vandenberghe@med.kuleuven.be

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■ **Abstract** Critically ill patients who depend on intensive care for more than a few days reveal profound erosion of lean body mass, which is thought to contribute to high morbidity and mortality. Despite a shortfall of evidence that supplemental feeding actually alters clinical outcome of these life-threatening disease states, this observation evoked an almost universal, albeit often inappropriate, use of nutritional support (NS) in the critically ill, administered via the parenteral or the enteral route. Lack of knowledge and overenthusiasm subsequently resulted in complications associated with both parenteral nutrition (PN) and enteral nutrition (EN), which led to the standing controversy over which should be preferred. With time, however, it became clear that EN and PN are not mutually exclusive and that critically ill patients requiring NS should be fed according to the functional status of the gastrointestinal tract. In addition, tight blood glucose control with insulin is advised in fed critically ill patients because overall metabolic control appears to surpass any outcome benefit attributed to the route of feeding. Recently, various special nutritional formulas have been suggested to prevent or treat multiorgan failure in the critically ill, among other pathways via modulation of immune function. Although special nutritional formulas may be promising in a variety of clinical settings, based on currently available data, these cannot be recommended for routine use in critically ill patients.

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INTRODUCTION

Throughout evolution, the human body has developed natural defense mechanisms to face and survive a great diversity of insults, such as disease or trauma. By definition, critical illness is such an insult, but its severity makes support of failing organ functions necessary, either with mechanical aids (such as mechanical ventilation, hemodialysis, or cardiac-assist devices) or with pharmacological agents (such as inotropes or vasopressors), without which death would rapidly ensue. Anorexia and intolerance of oral feeds lead to starvation, which, together with a multifactorial hormonal and immune response to stress, largely independent of the type of underlying disease (51), results in hypercatabolism of the critically ill (30). Because this orchestrated stress response is universal and has been selected throughout evolution, it is considered to be beneficial. Indeed, it liberates necessary fuel substrates for vital organs and systems, such as the brain and the immune system, while it reduces costly anabolism in the, for the time, less vital organ systems such as skeletal muscle (43, 152). However, the development of modern intensive care nowadays allows patients to survive conditions of a magnitude and duration that are beyond the capacity of these natural defense mechanisms. Over the years it became clear that survival mediated by intensive care also has a reverse side (69). By intervening in the natural course of the dying process, intensive care has unmasked previously unknown conditions, such as the "wasting syndrome" of the critically ill characterized by substantial protein losses (29). Development of this wasting syndrome is a major and frustrating clinical problem because it hampers the recovery process, despite adequate and successful treatment of the underlying disease. It contributes to prolonged dependency on intensive care, exposing patients to potentially lethal, often septic, complications and carrying a high risk of death (155). Indeed, almost a quarter of the adult patients requiring intensive care for more than three weeks do not survive the intensive care phase, and up to 50% do not leave the hospital alive (154). Those who do survive often need institutional care for a long time after hospital discharge.

In the era of evidence-based medicine, a medical intervention should be justified, preferably by prospective, randomized, controlled clinical trials. However, studies in the area of nutritional support are difficult to conduct, particularly in the intensive care setting, because of the heterogeneous nature of the patient populations. This explains the dearth of solid trials investigating nutritional support in

intensive care patients and why most nutritional strategies in the intensive care unit (ICU) are deduced from data obtained in noncritically ill, mostly surgical, patients. Furthermore, in most studies on the impact of nutritional support, no attempts were made to achieve overall metabolic control (9, 156). Hence, clinicians are lacking evidence-based guidelines on many important aspects of nutritional support of the critically ill patient, and thus the many standing controversies force them to use a more pragmatic approach to feeding in daily ICU practice.

In this review, we discuss the available scientific evidence for and against the use of enteral, parenteral, and combined nutrition in the ICU, and call attention upon the pivotal role of overall metabolic control during critical illness. In addition, we briefly evaluate the scientific basis for the use of selected specialized nutritional formulas.

RATIONALE FOR NUTRITIONAL SUPPORT DURING CRITICAL ILLNESS

Simple Malnutrition Versus Hypercatabolism of the Critically Ill

Malnutrition is a disorder evoked by inadequate nutritional intake and resulting in reduced body mass, abnormal body composition, reduced organ function, and abnormalities in blood chemistry, which together carry a risk of adverse outcome (31). The notion that malnutrition affects outcome of a superimposed stress or disease was already noted in 1936 by Studley (141), who reported that malnourished patients undergoing ulcer surgery had a tenfold higher risk of death than did well-nourished individuals. Nowadays, there is substantial evidence that patients who suffer from starvation or have signs of malnutrition are exposed to a higher risk of complications, such as nosocomial infections (128, 131), and an increased risk of death in comparison with patients who have an adequate nutritional reserve (52). Malnutrition is common among hospitalized patients (101, 105) and may be particularly deleterious among those who are critically ill (52). The notion of benefit attributable to nutritional support in such patients is based on the premise that nutrient intake can prevent or correct the malnutrition that accompanies the illness. In the discussion on efficacy of nutritional support, however, it is crucial to differentiate simple starvation-induced malnutrition from hypercatabolism of the critically ill. Indeed, critical illness results in changes in substrate metabolism and leads to clinically obvious alterations in body composition (166), but the metabolic status of critically ill patients is fundamentally different from "simple" starvation or malnutrition. Hence, the nutritional requirements of patients who are stressed by sepsis, trauma, or complicated surgery may be entirely different from those who are nonstressed and who need nutritional support only for repletion of energy stores. Although resting energy expenditure (REE) is depressed during simple starvation (26, 30), during critical illness it rises proportionally to the amount of stress (77, 143, 150). In contrast to simple malnutrition evoked by starvation, which is

reversible by careful and adequate refeeding, malnutrition accompanying critical illness is the result of a catabolic response driven by the underlying disease process and is not reversed by nutrition alone (135, 139, 163, 164). In the early days of intensive care, attempts to fully replace the nutritional losses led to overfeeding and resulted in a variety of complications. Since nutrition alone is ineffective to reverse hypercatabolism in critically ill patients, nutritional therapy in the ICU is at best to be considered "supportive."

Nutritional Support Versus Starvation or "Standard Care"

Undernourishment or starvation, if prolonged, ultimately leads to death, an outcome that can undisputedly be prevented by the provision of nutrients (70). However, how long critically ill patients can be starved or undernourished without clinical sequels is an unresolved issue. Although early feeding can change nutritional outcome during critical illness, there are no solid data as to whether nutritional support can modify the clinical course of the critically ill patient. Most of the clinical studies evaluating nutritional support focused on patients recovering from acute and self-limiting insults (e.g., surgery and trauma) instead of those with ongoing or progressive disease (e.g., shock and multiorgan failure). There are no data from randomized, controlled trials investigating the effect of nutritional support versus starvation in such a critically ill population. Also, only a handful of randomized studies, using clinically important endpoints, have compared the impact of parenteral nutrition (PN) with that of "standard care" (i.e., oral diet plus intravenous dextrose; critically ill patients receive glucose infusion because they are unable to eat) in the critically ill (1, 126, 129, 130). A meta-analysis of these studies concluded that PN of the critically ill may increase rather than reduce mortality (73). Furthermore, no randomized study has investigated the impact of enteral nutrition (EN) versus starvation or standard care during critical illness. Because of this lack of evidence and the belief that the intensity of the initial catabolic and inflammatory state hinders successful utilization and metabolism of externally provided nutrients, some authors postulated that nutritional support in critically ill patients is not beneficial (84, 97).

There are, however, several reasons why these conclusions may not be appropriate. Apart from the important methodological biases, most studies included well-nourished patients who arguably have little to gain from nutritional support but are nonetheless exposed to the associated risks of PN (161, 167). This notion is supported by data from the Veteran Affairs Study Group (149), which showed that only severely malnourished patients benefit from nutritional intervention before surgery. Further support came from two meta-analyses that reported that the use of PN in malnourished patients may be able to reduce complication rates (24, 73) and decrease mortality in comparison with standard care (24).

Hence, in this setting of scarcity of solid evidence, and with the rationale that it does not make sense to allow malnutrition to develop in order to treat it subsequently, the current guidelines are largely based on expert opinions and

consider nutritional support in the critically ill as justified when inadequate oral intake for 5–7 or more days is present or suspected (5, 71, 168).

NUTRITIONAL SUPPORT: HOW MUCH AND WHEN?

What Is Sufficient Energy Intake?

The estimation of the energy requirement of critically ill patients remains a difficult, if not impossible, task. Indirect calorimetry to determine energy expenditure is suggested as the gold standard for assessing a patient's individual energy requirement. However, time limitations and financial restraints preclude the use of this method in everyday clinical intensive care practice. Recent work suggests that in sepsis and trauma the total energy expenditure (TEE) of critically ill patients rises from 30 kcal/kg/d in the first week to 50–60 kcal/kg/d in the second week (150). It is likely that the ratio of TEE over REE rises with time in ICU because newer approaches of mechanical ventilatory support allow patients to be more awake and physically active. This high amount of energy expenditure is in strong contrast with the American College of Chest Physicians guidelines recommending 25 kcal/kg/d as caloric content of nutrition for the critically ill (31). Furthermore, this target goal of 25 kcal/kg/d appears to be achieved in only two thirds of patients fed via the enteral route in real-life intensive care (59). Indeed, for years now, survey after survey has continued to show that the real practice in the ICU is to deliver considerably less than prescribed (38, 75). However, there is also no evidence to suggest that failure to match energy intake to energy expenditure adversely affects clinical outcome. Prospective studies in neurological intensive care patients have shown that early EN as compared with early PN is associated with clinical advantages, despite the fact that this mode of feeding failed to reach the preset goals for energy and nitrogen intake that were achieved in the comparative PN group (64, 170). The amount of energy delivered may thus be less critical than previously thought, provided that excessive hypocaloric (or hypercaloric) feeding is avoided. A recent prospective observational study of medical ICU patients even suggested that the classical caloric target of 25 kcal/kg/day may overestimate the needs, since caloric intake exceeding the mid-tertile of 9–18 kcal/kg/day resulted in a poorer hospital survival (87). However, this conclusion should be viewed with considerable caution because patients were not randomly allocated to different levels of caloric intake and the amounts given were highly variable.

The inability to deliver a preset amount of calories, particularly when EN is the only source of caloric intake, is often the reason why nutritional intervention trials have failed. In two large randomized studies that investigated early administration of an immunomodulating EN versus standard EN, morbidity benefits were only found in the 27% (6) and 30% (22) of patients who achieved the complete, although modest, feeding target. In other words, 70% to 73% of the included patients were distinctly underfed and had a higher mortality than did those patients who were

better fed (59). Similarly, in an open-label study of an immunonutrient cocktail versus standard EN, the striking benefits associated with the intervention may have been due to the fact that more calories were delivered rather than being related to the type of feeding (50). Similar observations were made in head injury patients. Two prospective randomized controlled trials at the University of Kentucky investigated the influence of early EN versus PN on neurological outcome. In the first study, enterally fed patients had significantly worse neurological outcome than did those receiving PN (123), whereas no difference was observed in a subsequent trial (170). These results, which initially appear to be conflicting, are probably explained by a poor enteral energy intake in the EN group of the first study (123), since the outcome difference was abolished with a more adequate energy delivery in the second study (170). Faster neurological recovery occurred with a higher amount of nutritional support in both trials (123, 170), a finding confirmed by other investigators (64, 148).

Although critically ill patients seem to cope with wide ranges of energy supply, and solid evidence for any amount is actually lacking, it is the opinion of experts that prolonged administration of markedly hypocaloric regimes (i.e., below 50% of metabolic requirements) is likely to promote rapid onset of malnutrition (122).

Is Early Feeding Beneficial?

It has been long known that inadequacy of recent dietary intake rather than the absolute nutritional status determines injury response and healing (165). During critical illness, nitrogen losses are huge, and nitrogen loss due to inadequate nitrogen or energy intake on one day cannot be compensated for by a positive energy balance on the next day. Indeed, the nitrogen-sparing effect of a positive energy balance is limited under these circumstances of critical illness (144). Postoperative insulin resistance appears to be induced by starvation rather than by the concomitant immobilization and can be reduced by preventing caloric restriction (117, 142). Furthermore, inadequate early nutrient intake in head-injured patients has been associated with prolongation of the acute-phase response and an increased incidence of septic morbidity (148). Animal studies also suggest a benefit of early EN versus starvation in protecting against oxidative organ injury through attenuation of lipid peroxidation (20, 146). Although the benefits of early nutritional support have been demonstrated at the cellular and tissue level and in animal studies of critical illness, the effect on patient morbidity and mortality is less clear (96). The reason for this is that clinical studies specifically addressing this question are lacking. Indeed, most studies have considered that early nutritional support is inherently good (88, 112) and have investigated potential benefits deriving from the route of early feeding (enteral versus parenteral) rather than the influence of the time at which feeding is commenced (122). This is unfortunate, because there is only poor evidence that early EN (10, 33, 46, 56, 66, 78, 137, 148) or PN (1, 126) has clinical advantages over brief starvation (i.e., 3–5 days). It is difficult, if not impossible, to ascertain relevance for intensive care practice from the available

data owing to the heterogeneity of the studied patient population, the small sample sizes, the use of different feeding formulations and routes, and inconsistency about the term "early" and the minimal amount of energy delivered.

There is, however, some evidence, albeit indirect, to support early initiation of nutrition in the critically ill. A first bit of evidence comes from a Scandinavian study of 300 patients undergoing major general surgical procedures (129). Patients on glucose treatment (250–300 g) for a period of 14 days had a higher complication and mortality rate than did those receiving PN. A recent randomized multicenter trial that included 499 critically ill patients was actually the first study to provide more solid data to support the suggestion that early initiation of nutritional support can significantly alter patient outcome (98). Use of feeding guidelines reduced overall duration of hospitalization by no less than 10 days (25 versus 35 days), and patients in the intervention group showed a trend toward reduced mortality. A recent meta-analysis of studies on parenteral versus enteral nutrition (136) indirectly suggested that the beneficial effects of early feeding *in se* might even surpass those induced by the feeding route. Indeed, although there was no benefit from the use of PN when EN was initiated early (<24 h), a significant survival benefit from the use of PN was found only in the trials where EN was delayed (136).

Experts in the field have interpreted the scarce data on the issue of early versus late feeding as follows: If we fail to deliver adequate amounts of nutrition, it is not possible to catch up for the lost days of feeding. Or as so elegantly stated by Griffiths (57), "underfeeding is a debt that must eventually be repaid, and like all debts it is worse when it is compounded."

ROUTES OF NUTRITIONAL SUPPORT

Is the Use of Parenteral Nutrition Really Dangerous?

PN has been defined as an intravenous solution containing protein and a source of nonprotein energy with or without lipids (73). Because older studies showed a beneficial effect of infusing both glucose and amino acid on postoperative protein sparing (35), PN was advocated as an effective means to halt protein loss and muscle wasting. Based on the reasoning that if some nutrition is good, more must be better, the term "hyperalimentation" was coined and practiced in the surgical community. However, this enthusiasm revealed that well-nourished patients served no benefit from such an intervention and that the fetterless use of PN is not without inherent risks. These risks include infectious complications and metabolic disturbances, which may lead to adverse outcome.

Because of the frequent misuse of PN and the wealth of experience gained in all its complications in surgical patients, PN is nowadays considered by many to be a dangerous and risky venture in the critically ill (61). A recent editorial equating PN with poison (95) and a meta-analysis suggesting that the use of PN in critically ill patients may result in significantly increased mortality (73) further nourished

this fear. However, the meta-analysis covered 21 studies of surgical patients, of which only 6 included patients in intensive care. In addition, most of the studies had methodological problems: inclusion of noncritically ill patients (129, 130), overfeeding in the PN group (67), combined enteral and parenteral feeding (1, 67), and some reports on strategies that probably do not reflect current practice. This implies that the evidence provided by the meta-analysis against the use of PN is weak (160).

Another major point of controversy is the septic morbidity that is often attributed to PN. The theoretical background of this association is, besides risks related to the vascular access, the view that PN results in an altered gut barrier, prefacing the patient to translocation of enteric bacteria, which then could cause septic morbidity at a distant site. This concept was developed from results of animal studies demonstrating that PN adversely affects villus architecture and intestinal permeability. However, in human studies there is no evidence that PN causes atrophy of the intestinal mucosa (63, 80, 93, 134) or promotes bacterial translocation (92, 133, 134). The results of frequently quoted trials in abdominal trauma patients (88, 112–114) are largely responsible for the conviction that PN predisposes to septic complications. However, the investigated population differs markedly from the majority of patients receiving nutritional support in terms of age, type of disease, and nutritional status (15). Moreover, the relative protein and energy intakes in these studies were often not comparable, usually being much higher in the parenterally fed patients. Whereas most of the data advocating the risks of PN come from older surgical studies, most newer studies (after 1988) and studies with a higher methodological standard show no effect on the rate of complications (73). After careful review of these early studies, it has become apparent that the increased risk associated with the administration of PN could be largely attributed to the overfeeding rather than to the parenteral route itself (104). Clinicians are nowadays well aware that overfeeding can lead to infections and severe metabolic disorders, ranging from hyperglycemia, hypertriglyceridemia, and azotemia to hepatic steatosis, fat-overload syndrome, and hypertonic dehydration (83). With the risks of indiscriminate and inappropriate use of PN now well recognized and demonstrated, they can be prevented by conscientious calculation, monitoring, and titration of the provided nutrients (16, 61, 160). As a result, recent studies demonstrated that use of PN in surgical (23, 119) and critically ill patients (9, 156) is safe and is not associated with an excess morbidity or mortality. A meta-analysis suggested that use of PN may even be associated with a significant survival benefit over EN (136). Another large pragmatic study comparing PN to EN concludes that "when correctly applied, the complications of PN are less likely to result in death compared with those of EN" (168).

It is thus fair to conclude from the available data that PN, when used wisely, can deliver adequate nutrition safely. This is extremely important in view of the large numbers of patients in the ICU that do not tolerate adequate quantity and quality of nutrients via the enteral route for various reasons (121, 168) and the 8%–10% of patients in whom EN is not possible or safe (12).

Potential Advantages of Enteral Nutrition

Over the past 15 years, enteral nutrition has gained considerable popularity and is the currently recommended technique of artificial nutrition in critically ill patients (5, 31, 71). Almost every clinical study on nutritional support in the critically ill starts with the seemingly obligatory introduction that EN is the preferred method of nonvolitional feeding (93). Over the years, several advantages were indeed attributed to enteral feeding. EN is claimed to be more physiological, to promote gastrointestinal tract function and integrity, to prevent bacterial translocation, to reduce nosocomial infections, and to be more cost-effective than PN. However, with the exception of lower costs, the available literature does not support the other advantages so commonly ascribed to EN in critically ill patients (93).

Despite the trend to institute EN early in all intensive care patients, there is actually little evidence for the notion that EN beneficially alters clinical outcome (10, 33, 46, 56, 66, 78, 137, 148). A meta-analysis by Marik & Zaloga (96) suggested that early EN in critically ill patients may be associated with a significantly lower incidence of infections and a reduced hospital stay of two days. However, since there was a significant heterogeneity among the studies and the majority of the studies dealt with patients after elective surgery, it is difficult to draw conclusions from this meta-analysis for the use of early EN in critically ill patients (96).

Numerous studies have shown that the real-life intensive care practice of enteral nutrition comes down to underfeeding due to inadequate delivery of the nutrients (38, 45, 102, 109, 111, 168). A survey in a Swiss center, which is strongly advocating the use of early EN, documented that the proportion of nutrients adequately delivered was only 75% with EN versus 88% with PN (12). The main causes for not achieving adequate amounts of feeding delivered enterally are gut dysfunction, setting targets that are too low, initiating the feeding too late, elective interruption of the feeding for procedures, not using feeding protocols, and a tendency to stop enteral feeding too readily (59). Indeed, it is unfortunate that diminished or absent bowel sounds are still frequently, but incorrectly, interpreted as an indication of small bowel nonfunction, which results in unnecessary postponing or stopping of EN (31).

Is Enteral Nutrition Without Risks?

Many critically ill patients present with altered gastric emptying and decreased intestinal motility related to the GI consequences of their critical illness and side effects of mechanical ventilation as well as the use of sedatives, opiates, and catecholamines (21, 106). Because of this impaired GI motility, enteral feeds are often poorly tolerated by critically ill patients, resulting in adverse effects such as high gastric residues in turn leading to inadequate nutritional intake, reflux, emesis, and aspiration. Other problems associated with EN in the critically ill are abdominal distention, diarrhea, constipation, and, rarely, mesenteric ischemia.

Mechanical complications include misplacement or dislodgment of the feeding tube or malfunction originating from luminal blockage.

As nasogastric tubes are traditionally used to deliver EN, intolerance to EN is frequently defined by the appearance of high gastric residues, predestining patients for subsequent microaspirations and pneumonia. A carefully controlled study in ventilated patients confirmed that both gastric enteral feeding and feeding in the supine position, as opposed to the semirecumbent position, are independent risk factors for nosocomial pneumonia (41). This important finding firmly associates nasogastric feeding with nosocomial pneumonia independent of the position of the patient. Accordingly, several prospective, randomized trials were set up to evaluate whether there is a clinical difference when delivering enteral formulas into the stomach, the duodenum, or into the jejunum. Although "postpyloric" feeding may result in an improved tolerance of enterally delivered nutrition and concomitant faster achievement of the desired calories (85), no trial was able to reduce the incidence of nosocomial pneumonia compared with nasogastric feeding (37, 72, 81, 85, 109, 111, 115, 140). Contrary to popular belief, however, a study in medical ICU patients suggests that gastric feeding was able to be advanced to caloric goals sooner than jejunal feeding, and this without an increase in aspiration or other adverse effects (115). Because insertion of a feeding tube beyond the gastric pylorus is technically difficult, endoscopic or fluoroscopic guidance are frequently required. Since tube migration or dislodgment remain a major problem (+/−30%) (37), the clinician must always consider whether the effort and expenses are worth the trouble when placing one of these expensive enteral access devices (100). Furthermore, one must also consider that jejunal feeding is associated with a small, but substantial, risk of mesenteric ischemia (99, 132). Because tolerance to enteral feeding can be successfully predicted on clinical assessment alone in up to 92% of patients (168), postpyloric feeding can only be considered as an alternative to PN in patients proven or likely to be intolerant to nasogastric feeding. However, in most stable patients, EN can be safely started via the stomach within the first 12 hours of a patient's arrival in the ICU, eliminating the additional time for placement of postpyloric feeding tubes. This allows the delivery of EN in a time-efficient manner and decreases the costs of tube placement and nutrition delivery. However, it is important to recognize that strict attention to patient positioning as well as vigilant nursing care help to minimize the rates of complications with enteral access and may actually be more important than the location of the enteral access.

There are only limited data regarding the efficacy of motility agents in improving the tolerance of EN. Although metoclopramide was able to postpone nosocomial pneumonia by one day in the only outcome study on prokinetics in the ICU setting, its use was unable to decrease the incidence of pneumonia and mortality (169). A meta-analysis found that although promotility drugs, as a class of drugs, appear to have some beneficial effect on gastrointestinal motility, there is no evidence that they affect any aspect of clinical outcome (19). However, a recent randomized trial demonstrated that intravenously administered erythromycin not only promoted

gastric emptying but also significantly improved the chances for successful early enteral feeding (125).

Diarrhea is recognized as a common complication associated with tube feeding (32, 76, 110, 168). Its consequences can be serious and include infections and skin care problems, loss of electrolytes, and increased costs (118). It is thus of benefit to patients and of great interest to nursing staff that an enteral feed containing soluble partly hydrolyzed guar as a source of fiber successfully proved to reduce the incidence of diarrhea during critical illness (138). In this randomized, controlled trial in mechanically ventilated septic patients, there was a highly significant reduction (from 32% to 9%) in the percentage of days of feeding with diarrhea.

Because of the common belief that EN is inherently good, enteral feeding is nowadays increasingly tried in sicker patients with variable gastrointestinal tract function, who in the past either would have been starved or would have received PN (59). In contrast to PN, of which risks and complications were well documented in the literature, complications linked with EN have often gone unreported. Recent publications, however, have clearly demonstrated that gut dysfunction in critical illness, often viewed as upper digestive intolerance to EN (127), is a risk factor for unfavorable outcome. Upper digestive intolerance is associated with pneumonia (106), longer ICU (78, 110) and hospital stays (78, 106), and an increased risk of death that remained significant even after adjustment for severity of illness (106).

Because randomization previously resulted in significant numbers of patients being fed by an inappropriate route, Woodcock et al. (168) have taken a most elegant and pragmatic approach to the question of examining risks, complications, and outcome of feeding. Patients requiring adjuvant nutritional support were fed according to a clinical assessment of the adequacy of gastrointestinal function. Those considered to have inadequate gastrointestinal function were given PN, whereas patients with a functioning gastrointestinal tract received EN. Patients in whom there was reasonable doubt as to adequacy of gut function were randomized to receive PN or EN, thereby providing two truly comparable groups (167). By their pragmatic approach, the investigators overcame the problems of previous comparisons of EN with PN where opinions might differ as to the appropriateness of the particular route of feeding and consequently risk was poorly distributed (59). Patients and diseases of the two nonrandomized groups appeared to be conspicuously different. Similar to other recent feeding trials, there was no difference in the incidence of septic morbidity between the nonrandomized groups of enterally and parenterally fed patients; however, there was a highly significant increase of nonseptic feeding-related complications in the EN group. These complications were not minor since a significant excess in mortality was seen with EN, emphasizing some of the mortality risks associated with the use of EN. Although these survival differences could be seen as a consequence of the different patient populations in these two nonrandomized groups, exactly the same relationship between complications, adverse outcome, and EN was seen in the randomized part of the study.

With randomization, the patients populations were balanced and the effects could be specifically attributed to the different route of nutrition delivery (59). Again, EN was characterized by a lower nutrient intake. The authors concluded that the time has come for the "EN versus PN" debate to be finally laid to rest and that the choice of feeding route should be determined by clinical assessment of the gastrointestinal function (168).

Combined Enteral/Parenteral Nutrition

Although EN is a safe option in the vast majority of patients when applied under close supervision, it is clear that it frequently results in hypocaloric feeding. This finding has prompted several authors to advise a combined parenteral and enteral approach in those patients unable to receive sufficient energy delivery via the enteral route alone (13, 14, 58, 167, 168). With the exception of some older studies suggesting an increased mortality risk probably associated with overfeeding (67, 68), there is actually no evidence that use of supplemental PN in the ICU, when EN fails to reach adequate amounts of energy delivery, holds risks. A recent prospective, double-blind, randomized, placebo-controlled study (9) of 120 critically ill patients demonstrated that 7 days of EN supplemented with PN led to a faster recovery of the nutritional markers retinol-binding protein and prealbumin and reduced hospital stay by 2.5 days. There was, however, no difference in terms of morbidity or day 90 mortality, but this was not surprising considering the relative short duration of feeding and the small number of malnourished patients (9%) included in the study. Contrary to the negative view on PN, this study suggests that supplemental PN does not carry excess morbidity and mortality in the ICU. This was recently confirmed by a posthoc analysis of our intensive insulin therapy study (156, 158). In addition, a meta-analysis including five studies with combined EN and PN also did not document an increased mortality or infectious complication rate in comparison with EN alone (40).

Early EN, supplemented where needed by PN, thus appears to be a safe and effective means of achieving an earlier optimal caloric intake as compared with EN alone. The combined nutritional support may provide a protective window necessary for EN to restore intestinal function. Patients with questionable gastrointestinal function can be fed using a combination of EN and PN. The enteral feed can be increased according to tolerance of EN and PN, with PN decreased to avoid overfeeding (168).

SPECIALIZED NUTRITIONAL SUPPORT

Over the past decade, the field of nutritional support has undergone an enormous transformation. Originally, nutritional support was recommended as a way to provide energy [under the form of carbohydrates (60%–80%) and lipids (20%–40%)], protein (up to 1.5 g/kg/day), and essential micronutrients in order to offset muscle wasting and prevent starvation-induced immune depletion. Subsequently, various

"specialty solutions" have been launched that claim to be tailored to the nutritional requirements of specific disease states. In addition, alternative lipid solutions were developed. Furthermore, various "immune nutrients" have been suggested to prevent or treat multiorgan failure. Below, a brief overview is given of the rationale for the use of these products and of the results from available clinical studies in an intensive care setting.

Alternative Lipid Solutions

The standard fat component in PN is long-chain triglycerides (LCTs). Lipid solutions containing medium-chain triglycerides (MCTs) or structured triglycerides (STs) have been proposed for PN since they are oxidized more readily as compared with LCTs (39). Although short-term administration of an ST emulsion results in an amelioration of nitrogen balance in ICU patients (91), there is no evidence that this results in a better clinical outcome.

Specialty Solutions

Liver formulas containing an increased content of branched-chain amino acids (BCAAs) and a reduced amount of the aromatic and sulfur-containing amino acids are deigned for patients with hepatic encephalopathy. Although BCAAs may affect several nutritional parameters in patients with advanced cirrhosis (94), there is no convincing evidence to support the use of BCAAs for patients with hepatic encephalopathy (3, 94). Specialized pulmonary enteral solutions have been conceived for patients with acute pulmonary failure, particularly those with complicating chronic lung disease. These products contain a high fat-to-carbohydrate ratio based on the rationale that providing PN with excessive carbohydrate would increase CO_2 production and respiratory failure (4). Nevertheless, few data exist to support efficacy of this approach, whereas avoiding overfeeding is probably more important in decreasing ventilatory load (145, 151). In addition, although a specialized formulation—which contains eicosapentaenoic acid, γ-linolenic acid, and antioxidants—for acute respiratory distress syndrome appears to be promising (49), there is actually no proof for a survival benefit. Traditionally, critically ill patients with acute renal failure were treated with "renal formulas" characterized by low protein content. However, this dietary approach may be deleterious to the patient's nutritional status and unnecessary, especially if the patient is being treated with continuous renal replacement therapy (CRRT). Since CRRT is able to remove the technical limitations of nitrogen intake and the loss of nutrients through CRRT is limited, critically ill patients with acute renal failure should receive normal diets (11). Diabetic EN solutions with lower carbohydrate and higher monounsaturated fat have a more neutral effect on glycemic control than does a standard formulation in hospitalized patients with type 2 diabetes mellitus (90). However, because strict glycemic control through the use of exogenous insulin should be pursued in critically ill patients (156–158), we doubt whether there is a place for such formulas in the ICU setting.

Immunonutrition

Glutamine is an important fuel for rapidly dividing cells in the gut and the immune system and is substrate for the synthesis of the endogenous antioxidant, glutathione. The possible benefit of glutamine supplementation has been evaluated in several controlled trials, most of which had serious methodological problems or were too small to draw definite conclusions (25). Some randomized studies suggest that glutamine-enriched PN is beneficial for critically ill patients who do not tolerate EN and who are dependent on PN for longer periods, as supplementation of PN with glutamine or L-ananyl-L-glutamine improved six-month survival (53, 62) and lowered hospital costs (62) in this setting. Studies investigating the addition of glutamine to EN in the critically ill, however, failed to affect mortality (34, 65, 79). A recent meta-analysis concluded that the currently available data on glutamine supplementation are merely hypothesis generating, excluding harm but not confirming benefit, and warranting adequately powered studies with relevant clinical endpoints (116). Hence, it is currently not appropriate to recommend glutamine supplementation as routine practice in critically ill patients.

Most of the trials on immunonutrition have used commercially available enteral immunonutrient cocktails, which include supplements of arginine, glutamine, nucleotides, and omega-3 fatty acids. Arginine, a precursor of nitric oxide, is advocated to enhance immune function (8, 36) and wound healing (82). Omega-3 fatty acids, particularly if fed before the pathologic insult, influence cytokine production and target tissue responsiveness (2, 44), and nucleotides are claimed to enhance host immune responses (47, 89).

Multiple randomized studies using enteral immunonutrition cocktails have been undertaken in the setting of critical illness or routine postoperative recovery, but the results remain controversial, as revealed by the most recent meta-analysis on this topic (74). Three large studies in ICU patients have been published (6, 22, 50). The two largest studies addressed hospital mortality (6, 22), and intention-to-treat analysis divulged a significantly increased mortality in the intervention group (60). This disturbing cognition was strengthened by the finding of the meta-analysis that in critically ill patients, studies of higher methodological quality revealed increased mortality (74). Until we understand the causes of these risks, generalized use of immune nutrient cocktails cannot be recommended for the critically ill.

IMPORTANCE OF METABOLIC CONTROL

Hyperglycemia and insulin resistance are common in critically ill patients, even those without a history of diabetes mellitus (104, 108), and initiating feeding may raise blood glucose levels even further. Hyperglycemia has been associated with poor outcome after cardiac surgery, myocardial infarction and stroke (7, 17, 27), and an impaired leukocyte function (124, 162) contributing to an increased nosocomial infection rate (54, 120). Traditionally, hyperglycemia was considered a reflection of severity of illness rather than an indication of harmful effect of

hyperglycemia. Hence, hyperglycemia up to 200–225 mg/dl in fed critically ill patients was tolerated (18, 31) and even considered to be beneficial for those organs and tissues that rely solely on glucose as fuel and that take up glucose independently of insulin.

Recently, this idea was disproved by the results of a large randomized, controlled, clinical study of early fed patients in a surgical ICU, further referred to as the "Leuven study" (156). The effect of strict maintenance of normoglycemia (blood glucose between 80 and 110 mg/dl) by intensive insulin therapy during intensive care was compared with the conventional regimen, which recommended insulin only when glycemia exceeded 215 mg/dl (156). Although conventionally treated patients revealed only mild hyperglycemia (mean blood glucose of 150–160 mg/dl), insulin titration to blood glucose levels below 110 mg/dl reduced hospital mortality by 34% (156). The duration of mechanical ventilation and ICU stay, the incidence of bacteremia, excessive inflammation, organ failure, and critical illness polyneuropathy were also significantly reduced (156). The benefit of intensive insulin therapy was particularly pronounced among patients with prolonged critical illness requiring intensive care for more than five days, with ICU mortality reduced from 20.2% to 10.6%. The study showed that controlling blood glucose below 110 mg/dl is crucial in order to obtain a maximum benefit (158), disproving the notion that a threshold level of 144 mg/dl would suffice (48).

In the Leuven study (156), best-evidence nutrition protocols were applied: EN was attempted as early as possible and, in order to achieve a preset target of total caloric intake, PN supplements were given when needed, resulting in patients being fed equally in both study groups. Energy intake was increased from an average of 7 nonprotein kcal/kg/d on day 1 to 23 kcal/kg/d on day 7, resulting in a mean intake of 19 kcal/kg/d. The average nitrogen intake ranged from 0.15 to 0.19 mg/kg/d. The improvements in outcome were entirely attributed to the tight glycemic control with insulin, and the intervention was equally effective regardless of the amount and route of feeding (158). This is in agreement with the knowledge that underfeeding by omitting lipids or by delivering hypocaloric parenteral nutrition prevents neither hyperglycemia nor its infectious complications (103). Exclusively parenterally fed patients required substantially more insulin in order to achieve normoglycemia than did those receiving EN (158). This is explained by the effects of enteral nutrition on incretin-mediated endogenous insulin release and may indicate that some of the potential risks of PN are due to its higher hyperglycemic potential. When insulin is titrated to achieve normoglycemia, this risk of PN disappears (158).

Apart from blood glucose control, insulin also exerts other metabolic effects. As in patients with diabetes mellitus (147), abnormal lipid profiles are observed in critically ill patients (28, 55). Most characteristically, circulating triglyceride levels are elevated, whereas the levels of high-density lipoprotein and low-density lipoprotein cholesterol are low (55). This dyslipidemia is partially restored by intensive insulin therapy, with almost complete reversal of hypertriglyceridemia and substantial increase in serum high-density lipoprotein and low-density lipoprotein

(107). Multivariate logistic regression analysis demonstrated that the improvement of dyslipidemia with insulin explains a significant part of the beneficial effect on mortality and organ failure and, surprisingly, may even surpass those of glycemic control (107). When controlling for all metabolic effects of insulin, including the lipid effect, the risk associated with a high dose of exogenously administered insulin (42, 48) disappears (107). These data provide a strong argument in favor of titrating insulin to doses required to achieve all metabolic effects (153). Clearly, blood glucose level is the marker that is most easily measured, and when insulin is titrated to normoglycemia, the other beneficial metabolic effects occur concomitantly.

Because it was unclear whether the benefits of tight glycemic control could be extrapolated to nonsurgical ICU patients, strict maintenance of normoglycemia with exogenous insulin in all critically ill patients remained controversial. Indeed, apart from observational data obtained in a mixed medical-surgical ICU population (86), scientific evidence for the overall practice of intensive insulin therapy on ICU was lacking. Recently, a large randomized, controlled, clinical study (157) confirmed that implementing tight glucose control with insulin, when continued for at least a few days, improves outcome of medical ICU patients to a similar extent as previously reported for surgical ICU patients.

Thus, both in the surgical and medical ICU population, titrating blood glucose levels below 110 mg/dl with insulin can be recommended as a relatively simple and inexpensive strategy to improve outcome. This strategy was also recently shown to reduce costs of intensive care via prevention of complications which require expensive therapies (159).

GENERAL CONCLUSIONS

As with most intensive care interventions, artificial nutrition carries risks that must be balanced against potential advantages. Artificial feeding should be restricted to those intensive care patients in whom malnutrition is present or expected. Avoiding too few as well as too many calories appears wise in the current state of the art, but evidence is not available as to the exact energy requirements. Making use of a functional gut is always preferable, but PN can be used for those patients with gastrointestinal failure. Early adequate feeding is to be encouraged whenever possible, preferably via the enteral route, but overzealous or inappropriate promotion of enteral feeding may blind one to its potential risks. The adequacy of the gastrointestinal function should determine the clinician's choice of route, but unlike for respiratory or renal function, there is at present no reliable measure available to assess this. Those patients in whom there is no clinical doubt as to whether the gut is or is not functioning should receive exclusively EN or PN, respectively. However, where doubt exists, as is often the case in critically ill patients, optimal nutritional support should be provided by using a patient-tailored combination of the two. Maintenance of normoglycemia with exogenous insulin in fed critically ill

patients improves outcome and, since overall metabolic control seems to surpass the outcome benefit attributed to the route of feeding, this intervention may render the controversy regarding feeding route less relevant. Although special nutritional formulas may be promising in a variety of clinical settings, based on currently available data, it is not appropriate to recommend them for routine use in critically ill patients.

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