

Nutritional support in critical care

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Ethical issues

Many people believe that having access to an adequate and appropriate diet is a basic human right. The provision of nutritional support to the critically ill, therefore, is an issue that is fraught with ethical implications, particularly in patients who have chronic, but stable, illnesses that necessitate intensive care, but in whom recovery is unlikely. Such circumstances, manifest particularly in patients who have severe brain injuries that led to the persistent vegetative state, clearly mitigate against the conduct of placebo-controlled trials of nutritional support [1]. Moreover, it is an irrefutable fact that prolonged starvation will ultimately lead to death. These arguments may have led the critical care community to subject the questions surrounding the provision of feeding to less rigorous scientific evaluation than has been afforded to other interventions, and an assumption that nutritional support must, by definition, be beneficial.

Malnutrition versus catabolism of critical illness

A substantial body of evidence indicates that medical and elective surgical patients who have evidence of malnutrition suffer greater levels of morbidity and mortality with those who have adequate nutritional reserve [2]. The metabolic status of many critically ill patients is fundamentally different from that detectable in the malnutrition that may tragically be manifest in the community, or in the extreme circumstances that

are seen in famine victims [3–5]. Thus, in the critically ill, basal metabolic rate (BMR) is usually elevated, whereas in malnutrition, it is depressed. The increase in BMR is attributed to a complex catabolic process that teleologically represents an attempt by the body to aid in the healing process. Although initially beneficial, prolonged catabolism ultimately causes severe protein loss and probably contributes to the high mortality and morbidity that are seen in critically ill patients who required a prolonged intensive care unit (ICU) stay.

Identifying the differences between malnutrition and the catabolism of critical illness, therefore, is highly significant in evaluating the efficacy of nutritional support. Malnutrition is reversible, given careful and adequate refeeding, unless a preterminal stage of illness has been reached. By contrast, the catabolic response to critical illness is not reversed by simple nutrition [3–5]. This fact is now well understood, but in the early days of critical care, attempts were made to completely replace the marked nutritional losses that were observed. This led to overfeeding, an inability by the patients to adequately metabolize the nutrient load, and resulted in a variety of metabolic and clinical complications [6]. The naïve view that feeding the critically ill must be beneficial also led to the widespread use of total parenteral nutrition (TPN). Enthusiasm for TPN in the ICU setting has diminished in the last decade, as a result of mounting evidence that it is associated with an increased incidence of infection and immune-related problems in certain patients [7].

The evidence base

Advocates of aggressive nutritional support in the critical care setting have also been repeatedly chal-

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lenged by practitioners of evidence-based medicine (EBM). At one extreme, the proponents of EBM could reasonably suggest that the lack of randomized, controlled trials of nutrition against starvation mitigate against the use of such support [8]. This interpretation of current data may find few supporters, but EBM can provide useful guidance in making choices between enteral and parenteral nutrition [8–12], the cost-benefits that are attributable to immunonutrition [13,14], and the use of specific nutritional additives [13,14] and promotility agents [15].

We aim to provide a concise review of the metabolic changes that are associated with the hypercatabolic critically ill patient, in contrast to those that are found in patients who have malnutrition. An evidence-based approach to identifying the feeding regimen will then be taken, which examines the optimal route of nutrition, feed composition, and the use of prokinetic agents. Recent trials of anticatabolic therapies and tight glucose control will also be reviewed. Because many of the important areas of ICU nutritional support remain controversial, despite clinical trials, we conclude by providing a pragmatic approach to feeding.

The hypercatabolic state of critical illness

Basal metabolic rate

During prolonged starvation, BMR decreases and reduces energy expenditure by approximately 20% to 40% [16]. Following the rapid depletion of glycogen stores, energy is supplied by the metabolism of protein and fat. By replacing glucose oxidation in the brain with ketone body oxidation, protein loss is reduced from about 80 g/day at the beginning of starvation to approximately 20 g/day after several weeks. This adaptive strategy permits survival for up to 60 days, or occasionally beyond, in victims of starvation, if there is access to water.

Metabolic changes in the (acutely) critically ill are different [17]. Resting energy expenditure increases by up to 100% and marked nitrogen losses occur. In normal individuals, a zero nitrogen balance can be achieved with an intake of approximately 5 grams of nitrogen per day. By contrast, patients who have severe burns may lose up to 27 grams of nitrogen per day, which represents approximately 1 kg of body cell mass. This hypercatabolic state is consequent upon the acute phase response to injury and infection [5] and leads to changes in the metabolism of carbohydrates, lipids, amino acids, and proteins and is mediated by alterations in hormones and cytokines.

Carbohydrate metabolism

Hyperglycemia commonly occurs in the critically ill, despite an increase in circulating insulin levels [18,19]. This is attributed to tissue-specific changes in glucose production and use. Increased liver gluconeogenesis occurs, using amino acid, lactate, and glycerol substrates. Further, increased glycogenolysis occurs in the liver. In insulin-dependent tissues, including skeletal muscle, adipose tissue, and liver, other metabolic adaptations are observed, including a decrease in insulin-dependent glucose uptake (“insulin resistance”) and increased glycolysis and glycerol synthesis from the hydrolysis of triglycerides. In non-insulin-dependent tissues, including the brain, kidney, and immune system, glucose uptake and oxidation increases. Lactate production from pyruvate is elevated, which is subsequently metabolized by the liver [20]. Lactate production may also be increased by tissue hypoxemia and reduced perfusion.

Lipid metabolism

Lipids are a major endogenous energy source in the critically ill [21]. In adipose tissue, triglycerides are hydrolyzed which increases the release of glycerol and free fatty acids (FFAs). The levels of circulating FFAs tend to increase with the degree of injury. Peripheral tissues use these FFAs to provide energy by oxidation. FFAs are also taken up by the liver to produce ketone bodies and triglycerides.

Protein and amino acid metabolism

Increased skeletal muscle protein breakdown occurs in critical illness and causes severe depletion of intramuscular glutamine [3]. In many organ systems (eg, gut, immune system) protein turnover decreases. In the liver, there is increased synthesis of acute phase proteins, but a decrease in albumin synthesis and amino acid oxidation. In visceral tissues, there is an increased rate of protein synthesis, which compensates only partially for the elevated breakdown in muscle. As a result, the excess of amino acids is oxidized in liver and muscle and the nitrogen is excreted by the kidney.

Metabolic regulation in the critically ill

The catabolic response is regulated by a complex and dynamic interplay of hormones, cytokines, and lipid mediators [22]. In the acute phase of illness, circulating levels of the three principle catabolic hor-

mones, cortisol, glucagon, and catecholamines, increase [23,24]. Insulin release also increases, but there is concomitant insulin and growth hormone resistance. Levels of other anabolic hormones, such as testosterone and insulin-like growth factor 1, decrease [25].

Cytokines play a pluri-potential role in mediating the inflammatory response [26]. Several have significant metabolic effects, either directly or as a result of interactions with the hypothalamic-pituitary axis. Interleukin (IL)-6 regulates the synthesis of acute phase proteins in the liver. IL-1 and tumor necrosis factor- α can reproduce most of the metabolic changes that are reported in the severely ill, including the increased protein breakdown and increased energy expenditure. Proinflammatory lipid mediators, including leukotrienes, prostaglandins, and thromboxane, are also synthesized during critical illness and contribute to the hypercatabolic state [27].

An evidence-based approach to nutritional support

Early versus late nutritional support

No randomized, controlled trial (RCT) of prolonged nutritional support in the critically ill has randomized patients to nutrition versus starvation. It is inconceivable that such a study would ever be conducted and the critical care community would likely be unanimous in agreeing that, at some stage in their illness, all patients require feeding. On the basis of experimental work that showed that early nutrition can prevent atrophy of intestinal villi, many units commence enteral feeding at an stage of illness. Contrary views are expressed occasionally [8] and are supported by some evidence that the intensity of the initial catabolic and inflammatory state prevents the successful metabolism of externally provided nutrients.

Few studies have attempted to address the issue of early versus delayed nutrition in the ICU. Victims of major trauma, who were randomized to either early enteral feeding by jejunostomy or to no early feeding, displayed no significant difference in outcome, although the incidence of infection was marginally lower in the group that was fed enterally [28]. Approximately 30% of the control group was receiving total parenteral nutrition (TPN) by day 5, which could explain the difference in infection rate (see later discussion). In a second study, 28 patients who had undergone liver transplants received either TPN or no nutritional support [29]. Recipients of TPN had shorter ICU stays, but other outcomes were similar. Finally, in patients who underwent elective valve

replacement and had suffered significant preoperative weight loss, the half that was randomized to receive 5 days of postoperative TPN suffered more complications and endured longer ICU stays [30].

Some evidence supports the use of TPN in prolonged starvation. In a study of 300 patients who were randomized after major surgery to either TPN or prolonged glucose infusions [31], the subgroup who was unable to take food for more than 14 days and received glucose suffered significantly more complications and a higher mortality.

Total parenteral nutrition

Most published trials have evaluated the benefits of TPN in patients who underwent major elective surgical procedures, rather than in those who had critical illness. In several studies, the effects of TPN in patients who had preoperative malnutrition was the problem addressed. Those trials with relevance to ICU recently were subjected to meta-analysis and systematic review [10,11]. Using formalized search criteria, 22 trials that compared TPN to intravenous (IV) glucose or oral diet alone were identified; most studies recruited surgical patients, although three included patients who were suffering from major burns, pancreatitis, and liver transplantation. Only one of these investigations considered (following pancreatic resection) the effects of TPN that was administered by a dedicated team (versus IV dextrose) [32], which was shown previously to greatly reduce the complications that are associated with parenteral nutrition. Despite this, significantly greater morbidity was identified in the group that received TPN, although survival at 24 months did not differ. A further study of preoperative and postoperative TPN in patients who needed laparotomy found no difference in either postoperative complications or overall 90-day mortality [33].

When these studies and others that were identified in the search were subjected to meta-analysis, TPN had no effect on mortality (odds ratio [OR] 1.06, 95% confidence interval [CI] 0.83–1.35) [9]. There was a trend toward lower total complication rates in the groups that received TPN, but this was not statistically significant (OR 0.83, 95% CI 0.64–1.06). The meta-analysis also examined the effect of trial quality and year of study on outcome. Earlier studies and those of lower quality showed evidence of improved outcomes with TPN, whereas later studies and those of higher quality were associated with increased mortality and complication rates.

The results from few, if any, of these studies (and, therefore, the meta-analysis) was strictly relevant to the critically ill patient who was in established multi-

organ failure. Many ICUs limit the use of TPN to those patients in whom enteral feeding is either impossible (eg, the short bowel syndrome) or cannot be established after prolonged attempts. The use of TPN as a supplement to enteral feeding has been suggested, but evidence for the efficacy of this approach is lacking.

Enteral nutrition

Over the past decade, enteral nutrition has become much more widely used in the critically ill. It is significantly less expensive than TPN and is generally more straightforward to administer. Despite this trend, evidence that enteral nutrition alters outcome in the critically ill is lacking. Excluding the more recent studies of immunonutrition, no RCTs have studied the effect of enteral feeding on outcome in the critically ill. In a recent review, six randomized studies were identified that examined the benefit of supplemental enteral nutrition on outcome following surgery [11]. Two studies randomized patients who underwent major gastrointestinal surgery to enteral nutrition versus oral and IV dextrose. Neither study showed a mortality benefit, nor a reduction in the incidence of postoperative complications. One [34] reported an increased hospital stay in the control group and the other found an lengthened stay in those who received enteral nutrition [35]. In two small, additional studies on postoperative care, enteral nutrition improved surrogate measures (wound healing, body composition), but conferred no actual outcome benefit [36,37]. A study following liver transplantation found no difference in clinically important outcomes, but was significantly underpowered [38]. Finally, a study of 60 patients following bowel resection found a reduced length of hospital stay in those who received enteral nutrition [39].

Infection risk: total parenteral nutrition versus enteral feeding

Experimental studies suggest that enteral nutrition (EN) is likely to be associated with fewer infectious complications than TPN [40]. At least 12 RCTs have compared EN to TPN using a variety of end points, although most were performed on stable preoperative patients who were undergoing major elective surgery [10]. Several studies found no significant difference in terms of clinically relevant endpoints, although all demonstrated cost savings by using the enteral route.

Some studies that are more relevant to critical care showed a benefit of EN compared with TPN. In trauma victims who needed emergency laparotomy [28], 37% of those who were randomized to receive TPN developed sepsis, compared with 17% of those who re-

ceived EN ($P < 0.05$). A randomized, unblinded study of patients who had abdominal trauma allocated half to EN and half to TPN within 24 hours of injury [41]; infectious complications were higher in those who received TPN (40% versus 15.7% for EN). By contrast, other investigators have demonstrated a higher incidence of aspiration pneumonia with EN administration [42]. Finally, in an analysis of eight studies, some not previously published, there were fewer infectious complications with EN [43]; however, the studies analyzed were heterogeneous in terms of the timing of nutritional support.

Feed composition: Does it matter?

Early work in the field of critical care nutrition concentrated on the effects of changes in gross composition of feeds, in terms of protein, fat, and carbohydrate. More recently, trials have focused on the possible role of specific nutrients (amino acids, fatty acids, nucleotides, antioxidants) in preventing or treating multi-organ failure. Consequently, feeds that contain so-called “immunonutrients” have started to emerge [44–47]. Some feeds contain enhanced amounts of a single nutrient (eg, glutamine), whereas others combine several immunonutrients. Several RCTs have emerged, which, in general, have been larger and of a higher standard than those that compared the benefits of EN and TPN. The rationale for immunonutrition has centered around several supplements.

Glutamine

Glutamine is a nonessential amino acid that is synthesized and released from skeletal muscle [48]. It has a vital role in modulating nitrogen transport and is an important energy source for rapidly-dividing cell types, including enterocytes. Glutamine availability may become limited in catabolic illness [49–51] and mortality in the critically ill is associated with low levels [52]. Glutamine supplementation may augment immune function [53] and reduce intestinal permeability when compared with standard TPN [54]. An early study of glutamine administration [55] in a single-center general ICU population randomized 86 patients to receive standard TPN or TPN supplemented with glutamine. Six-month survival was significantly better in the group that received glutamine supplementation and hospital cost per survivor was reduced by 50%.

In a recent systematic review of 14 studies that met predetermined inclusion criteria, glutamine supplementation reduced mortality in 751 patients with risk ratio (RR) of 0.78, although the 95% CI crossed the no-effect line (0.58–1.04) [56]. In seven studies

(326 patients), a significant reduction in infection rates with glutamine supplements emerged. Glutamine also significantly reduced the length of hospital stay. In a subgroup analysis of trials that involved only the critically ill, a trend toward reduced mortality and fewer infections was confirmed, although no reduction in hospital stay was found. Enteral glutamine had no mortality benefit in the critically ill, whereas parenteral supplements (>0.2 g/kg/day) significantly reduced mortality and hospital length of stay.

This analysis suggests that critically ill patients who require TPN should also receive high-dose parenteral glutamine supplements; however, the number of critically ill patients who receive TPN continues to decrease. Whether patients who are tolerating standard EN should also receive glutamine supplements is unknown and should be addressed in future studies.

Arginine

Arginine is another nonessential amino acid which may become depleted in critical illness [57]. A precursor of nitric oxide, arginine supplementation also upregulates immune function [58] and stimulates the secretion of several hormones, including growth hormone, and may reduce ischemia-reperfusion injury [59].

Nucleotides

Nucleotides are the building blocks of RNA and DNA and are central to the generation of ATP. They are either synthesized from amino acids and ribose or ingested from dietary sources. Experimentally, they were demonstrated to alter immune function by shifting the T-helper 1 (Th1)/T-helper 2 (Th2) balance toward Th1-dominant immunity [60]. IV nucleotides promote recovery from ischemia-reperfusion injury [59] and improve gut mucosal barrier function [61].

Omega fatty acids

n-6 and n-3 polyunsaturated fatty acids (PUFA) are enzymatically converted to eicosanoids [62]. They are essential nutrients and are metabolized by the same enzymes which makes them competitive [63]. The n-6 PUFA are converted to proinflammatory, prothrombotic and prochemotactic mediators, whereas n-3 PUFA tend to have the opposite effect. On this basis, it was suggested that dietary manipulation of the n-6/n-3 balance might be beneficial in the critically ill.

Trials of immunonutrition

The hypothesis that immunonutrition might alter outcome in the critically ill has been explored in several RCTs, other than those related to glutamine supplementation alone. All studies used commercial components that contain a mixture of “immunonutrients” including arginine, glutamine, nucleotides, PUFAs, as well as standard protein/carbohydrate/fat combinations (Table 1).

A multicenter study of enteral immunonutrition versus conventional nutrition in six ICUs in [64] entered 181 patients who had sepsis and an Acute Physiology and Chronic Health Evaluation (APACHE)-II severity of illness score of 10 or greater into the trial. The groups were well-matched in terms of demographics and nitrogen balance. Overall mortality was significantly lower in the treatment group compared with controls (19.1% versus 32.2%). Infection rates were also reduced significantly in the treatment group.

By contrast, a second well-conducted study that used the same commercial immunonutrient preparation (Impact, Novartis Nutrition, Bern, Switzerland) found no difference in mortality. Nearly 400 patients in medical and surgical ICUs were randomized to

Table 1
Composition of some immunonutrition feeds that have undergone clinical trials

Product	Impact	Immun-Aid	Alitraq	Oxepa	Perative
Manufacturer (location)	Novartis Nutrition (Bern, Switzerland)	McGaw (Irvine, CA)	Ross (Columbus, OH)	Ross (Columbus, OH)	Ross (Columbus OH)
Cal/mL	1.0	1.0	1.0	1.5	1.3
% Protein (g/L)	22	32	21	17	20
% CHO (g/L)	53	48	66	28	55
% Fat (g/L)	25	20	13	55	25
Arginine	Yes	Yes	Yes	No	Yes
Glutamine	No	Yes	Yes	No	No
Nucleotides	Yes	Yes	No	No	No
N-3: N-6 ratio	1:2.1	1:2.2	NA	1:1.5	1:4.7
Carnitine & taurine	No	No	Yes	Yes	Yes
Osmolality (mosmol/kg)	375	460	575	493	385

Abbreviations: CHO, carbohydrate; NA, not available.

receive conventional or immunonutrition of isocaloric and isonitrogenous composition [65]. By intention to treat analysis, there was no significant difference in hospital mortality (48% immunonutrition; 46% control) nor in any secondary outcome measures. An a priori subgroup analysis also was performed on 101 patients who achieved successful early nutritional targets. In this group, the duration of mechanical ventilation and length of ICU and hospital stay were significantly reduced in the group that received immunonutrients; however, the move away from a strict intention to treat analysis has been criticized as likely to lead to bias in the interpretation of clinical nutrition trials [13]

Immunonutrition in the critically ill has also been subjected to a systematic review [14] of 22 RCTs which met predefined eligibility criteria. Thirteen studies focused on the critically ill, whereas the remainder examined patients who underwent major elective surgery. When all of the trials were aggregated, immunonutrition was not associated with a decrease in mortality. A similar conclusion was reached when the studies that involved only critically ill patients were analyzed. The aggregated data found fewer complications in those who received immunonutrition. The data were heterogeneous, and, in the critically ill patients alone, immunonutrition did not reduce the incidence of infection, but was associated with a reduced hospital length of stay, albeit of less than 1 day. Mortality was higher in critically ill patients who received lower arginine-containing formulae compared with high arginine feeds.

A summary of evidence-based nutrition

It is easier to criticize clinical trials than to conduct them. Many of the studies of nutrition in the critically ill suffer from several problems, including the use of surrogate endpoints, a lack of power to detect real differences, the heterogeneous populations studied, and the issue of possible bias from industry-sponsored trials. Enteral nutrition using conventional feeds is likely to be superior to, and less expensive than, TPN, whereas the evidence for immunonutrition remains, at best, controversial.

Anticatabolic agents

Nutrition alone cannot prevent the negative nitrogen balance that characterizes the critically ill; the association between a hypercatabolic state and poor

outcome in this patient group prompted several investigations on the use of anticatabolic agents. Several small studies reported that high-dose growth hormone could improve nitrogen balance in the critically ill and in patients who had experienced burns and trauma [66]. On the basis of these, two parallel, prospective, multicenter RCTs of high-dose recombinant growth hormone were performed [67]. A Finnish study recruited 247 patients and a second European investigation enrolled 285 patients. In both cases, a mixture of medical and surgical patients were enrolled who had been in the ICU for at least 5 days and who were expected to require ICU care for at least 10 more days. Recombinant growth hormone was given for either 21 days or until discharge from the ICU. As expected, nitrogen balance was significantly better in the group who was given growth hormone. In the Finnish study, however, mortality was 39% in the group that was given growth hormone compared with 20% in the group that was given placebo; in the second study, comparable figures emerged (44% versus 18% in favor of placebo). Moreover, length of ICU and hospital stay and duration of mechanical ventilation were longer in survivors who received growth hormone. Most of the deaths in the groups that were given growth hormone were attributed to multi-organ failure, although why this occurred is unclear. Several mechanisms have been proposed, including alterations in immune function, hyperglycemia, and insulin resistance and the prevention of glutamine release. It is also possible that the hypercatabolic process is beneficial in terms of survival, despite the nutritional derangements with which it is associated.

Hyperglycemia and glucose control

Hyperglycemia and insulin resistance are common in the critically ill and may be independent risk factors for complications. Leukocyte function was impaired during hyperglycemia and infection rates increased [68]. Hyperglycemia is also an adverse risk factor in survival following myocardial infarction [69]. In a landmark study, 1548 patients who were ventilated in the ICU were enrolled in a trial of intensive versus conventional glucose control [70]. Patients received insulin if blood glucose was greater than 6.1 mmol/L (intensive therapy) and doses were adjusted to maintain normoglycemia. The other patients received insulin if the blood glucose level was greater than 11.9 mmol/L (conventional therapy) with the aim of maintaining blood glucose levels between 10.0 and 11.0 mmol/L. Total enteral feeding was attempted as

soon as possible in both groups. The primary end point of all causes of ICU mortality was significantly reduced in the group that received intensive therapy group (5% versus 8%), as were the secondary end points of hospital mortality, duration of ventilatory support, the need for renal replacement therapy, the incidence of bloodstream infection, and critical illness polyneuropathy.

These are important findings, but questions remain concerning the applicability of the study to all critically ill patients. Thus, mortality was low, probably due to the case mix enrolled. Most patients had undergone cardiac surgery; only 6% to 7% had acute abdominal problems. The applicability of these findings to general medical or surgical patients remains unknown.

Delayed gastric emptying and reduced gastrointestinal tract (GIT) motility

It is clear from the work outlined above that the evidence base regarding nutrition in critical care is imperfect. Many decisions about feeding in ICU, therefore, are based more on pragmatism than high-grade evidence. It is our policy to attempt to establish enteral nutrition as soon as possible after admission in most critically ill patients. Absence of bowel sounds and recent surgical anastomoses are not contraindications. Many units have adopted the use of a nurse-driven feeding protocol. In our experience, almost all patients with sufficient functional gut can be successfully established on enteral feeding.

Reduced gut mobility is often a problem in the critically ill. This is caused by a combination of factors, including surgery, sepsis, sedatives, neuromuscular blockers, and the degree of injury. This may result in reduced gastric emptying which leads to large gastric aspirates and poor absorption of enterally-administered feed. In an attempt to improve motility and absorption, promotility agents are often used. Erythromycin, metoclopramide, and, before its withdrawal, cisapride, have all been the subject of small-scale clinical trials in the critically ill [15]. Tolerance to feeding and gastric emptying (as assessed by gastric residual volume) was assessed in a mixed ICU population of 20 patients, half of whom received erythromycin, 200 mg IV [71]. The group that received erythromycin was more likely to be classified as receiving successful enteral nutrition and had lower gastric aspirates.

Three small studies of regular IV metoclopramide (reviewed in [15]) also found a decrease in residual gastric aspirates compared with placebo. A single trial examined the effect of promotility agents on outcome

in critical care, although no difference in mortality or incidence of pneumonia emerged in 305 critically ill patients who were randomized to either regular metoclopramide or placebo [72].

Nasojejunal versus nasogastric feeding

Nasogastric tubes traditionally have been used to deliver enteral nutrition. Gastric motility and emptying are reduced in the critically ill and adequate delivery of nutrition is often impaired by large gastric aspirates. The association of gastric feeding with nosocomial pneumonia has also led some groups to consider alternate enteral access routes.

Nasojejunal feeding tubes can be placed successfully endoscopically, although specially-designed tubes and the use of promotility agents (metoclopramide) can allow successful nonendoscopic placement. The potential advantages of nasojejunal feeding were studied in several clinical trials with results tending to favor the nasojejunal approach.

Davies and coworkers [73] randomized 73 critically ill patients to receive enteral nutrition either by a nasojejunal or nasogastric tube. The group that had a nasojejunal tube had reduced gastric residual volumes at 24 and 48 hours. Tolerance of enteral nutrition (feeding cessation, large gastric aspirates) was also better in this group. Similar findings were reported in a multicenter study of 110 critically ill patients who were randomized to either nasogastric or nasojejunal feeding [74]. Gastrointestinal complication rates were lower in the group that was fed nasojejurally, although total caloric intake and the incidence of nosocomial pneumonia were not reduced. Other studies, however, have found that the nasojejunal route improves caloric intake compared with nasogastric feeding [75,76]

Intermittent versus continuous enteral feeding

In the critically ill, many treatments are given continuously. Delivering enteral nutrition by a continuous drip infusion became a standard practice. There is, however, physiologic and clinical evidence to suggest that this practice may increase the risk of nosocomial pneumonia.

Colonization and stomach overgrowth with pathogenic bacteria has been associated with loss of stomach acidity. The use of rest periods during feeding may allow natural stomach acidity to recover and prevent bacterial overgrowth [77]. One small clinical trial of continuous versus intermittent enteral feeding found that 80% of patients in each study group had stomach bacterial colonization by day 7 of the study [78]. No differences in nosocomial pneumonia incidence were

observed, although the study, with 60 patients, was probably not sufficiently powerful to exclude clinically significant differences

Feeding and ventilation-associated pneumonia

Ventilator-associated pneumonia, or nosocomial pneumonia, occurs in 9% to 70% of patients who have longer stays in critical care units. Factors that are associated with its occurrence include initial severity of illness, initial level of consciousness, degree of sedation, duration of invasive ventilation, and pre-morbid respiratory disability [79]. Abnormal oropharyngeal colonization and subsequent aspiration are the likely causes of nosocomial pneumonia. In addition, microaspiration of colonized gastric contents may be an important mechanism.

These observations suggest that the gastric route of feeding and the position of the patient during feeding could contribute to the development of nosocomial pneumonia in patients who are ventilated. The importance of patient position is also supported by observational studies of risk factors for the development of nosocomial pneumonia [80]. Drakulovic and colleagues [81] performed an RCT of semirecumbent against supine position in ventilated patients who were enterally-fed. Eighty-six patients who were ventilated were randomized to a supine or semirecumbent position. Feeding was enteral or parenteral, based on the physician's decision. The incidence of clinically-suspected and bacteriologically-proven pneumonia was significantly reduced in the group that was semirecumbent (8% versus 34% for clinical infection; 5% versus 23% for bacteria confirmation). A multi-variable analysis of risk factors for nosocomial pneumonia was also performed. Supine position and enteral feeding were independent risk factors, in addition to prolonged mechanical ventilation and coma on admission. Neither length of stay nor mortality was significantly different in the two groups, although the study was not designed with these end points as the main analysis.

In summary, considerable indirect evidence and one randomized trial support the use of semirecumbent patient positioning during enteral feeding to reduce the risk of nosocomial pneumonia in the ventilated patient.

Energy requirements in the critically ill

The estimation of total energy requirements in the critically ill remains difficult. Needs can be estimated

using bedside measures of energy expenditure that are calculated using formulae and nomograms or by empirical means [82]. None of these methods has been demonstrated to be superior to the others. Stand-alone metabolic carts can measure oxygen consumption in mechanically-ventilated patients, provided the FIO_2 is not higher than 70% to 80%, from which energy requirements can be derived. In those patients who have a pulmonary artery catheter in situ, O_2 consumption can be calculated following the measurement of cardiac output and O_2 content in arterial and mixed venous blood. Formulae can also be used for energy estimation:

$$\text{For men } EE = 66.5 + 13.7W + 5.00H - 6.78A$$

$$\text{For women } EE = 66.5 + 9.56W + 1.85H - 4.68A$$

where EE is basal energy expenditure (kcal); W is weight (kg), H is height (cm), and A is age (years). Modification factors for activity for these equations include multiplying by 1.2 for patients who are confined to bed and multiplying by 1.3 for patients who are out of bed. Modification factors for injury include 1.2 for minor surgery, 1.3 for trauma, 1.6 for sepsis, and 2.1 for burns. Most formulae incorporate a stress factor addition that is subjective and requires the accurate determination of the patient's weight and height, which is often difficult to determine in the ICU.

In view of these problems, many units adopt a pragmatic approach to the estimate of energy needs in the critically ill. In the septic patient, for example, energy needs are on the order of 25 to 35 kcal/kg/day [83]. Higher energy diets are no longer in favor because of the evidence that overfeeding leads to excessive CO_2 production, hyperglycemia and increased energy expenditure. Attempts to fully replace nitrogen losses in the catabolic, critically ill patient also were abandoned because this can lead to an increase in metabolic rate and increased CO_2 production [84]. Current recommended protein intake in sepsis, for example, is in the range of 1.2 to 1.8 g/kg/day.

The ideal combination of carbohydrate and fat is unknown in the critically ill patient. Most commercial enteral feeds supply nonprotein calories as 60% to 70% carbohydrates and 30% to 40% fat (Table 2). Polysaccharides are the predominant carbohydrate in enteral feeds and are usually well tolerated. The lipids that are used in most enteral feeds (corn oil or soy oil) contain large amounts of long-chain triglycerides. Alternate sources of lipid-containing medium-chain triglycerides (MCTs) are coconut oil and palm oil. Fish oil derivatives contain omega-3 fatty acids. Claims for the superiority of these alternate fat sources have been made, but remain unproven in clinical trials.

Table 2
Composition (per 100 mL) of some commercial enteral feeds

Product	Manufacturer	Kcals					Na ⁺⁺ (mmol)	Ca ⁺⁺ (mmol)	PO ₄ (mmol)
		(100 mL)	Protein (g)	Fat (g)	CHO (g)	K (mmol)			
Ensure Plus	A	150	6.27	4.9	20.4	4.13	6.1	2.5	3.2
Jevity Plus	A	120	5.55	3.9	16.1	4.63	4.7	2	2.58
Osmolite Plus	A	121	5.55	3.9	15.8	4.64	5.8	2.07	2.58
NEPRO	A	200	7	9.6	20.6	2.72	3.67	3.4	2.22
Jevity	A	105	4	3.5	14.8	4	4.04	2.3	2.32
Osmolite	A	101	4	3.4	13.6	3.6	3.83	1.7	2.19
Pulmocare	A	150	6.25	9.3	10.6	4.9	5.63	2.5	3.22
Oxepa	A	152	6.25	9.4	10.6	5	5.7	2.6	3.22
Two Cal HN	A	200	8.4	8.9	21.6	6.3	6.35	2.6	3.62
Peptisorb	N	100	4	1.7	17.6	3.8	4.3	2	2.3
Nutrison MCT	N	100	5	3.3	12.6	3.8	4.3	2	2.3
Nutrison Conc	N	200	7.5	10	20.1	4.6	4.3	2	2.4
Nutrison Conc 40	N	200	4.1	10	23.6	3.8	4.3	2.2	1.5
Nutrison Energy	N	150	6	5.8	18.5	5.1	5.8	2.7	3.5
Nutrison Soya	N	100	4	3.9	12.3	3.8	4.3	2	2.3
Ensure Plus	A	150	6.25	5	20	4.66	5.1	2.9	3
Ensure Plus Yoghurt Style	A	150	6.25	4.92	20	5.13	5.2	2.9	3
Enrich Plus	A	153	6.25	4.92	21.5	3.46	3.7	1.75	2.2
Enlive	A	125	4	0	27.3	0.33	0.39	0.67	0.3
Prosure	A	125	6.65	2.56	19.4	5.13	6.52	3.7	3.4
Fortisip	N	150	6	5.8	18.4	5.1	4.6	2.7	3.5
Fortimel	N	100	10	2.1	10.3	5.1	2.2	7	6.5
Fortifresh	N	150	6	5.8	18.7	5.1	4.6	2.7	3.5
Fortijuce	N	150	4	0	33.5	0.5	0.7	1	0.4

Abbreviations: A, Abbott Laboratories, Columbus, Ohio; N, Nutricia Clinical, Trowbridge, UK.

In addition to protein, carbohydrate, and fat, feeds need to contain sufficient electrolytes, vitamins, trace elements, and water. In pyrexial patients, a free water deficit is common which leads to hypernatremia. This requires correction with additional free water, either mixed with the feed or given during “rest periods.”

Critical care units increasingly adopt a “one size fits all” approach to nutrition; feeding regimes that are tailored to specific conditions mostly have been abandoned. For example, before the introduction of modern renal replacement therapy in the ICU, patients who had renal failure were placed on reduced protein diets. Continuous renal replacement therapies (CRRT) are now commonly used for the treatment of acute renal failure and successfully control uremia in critically ill patients who are given normal protein diets. Loss of nutrients through CRRT is also minimal; therefore, patients who are in acute renal failure should receive normal diets [85].

Summary

Despite the key role of nutrition in health and the almost universal use of supplemental feeding in the

ICU, there is a lack of high-quality evidence to guide clinical practice. Enteral nutrition is superior to TPN in almost all circumstances and most patients in the ICU can be fed successfully by this route. There is little evidence to support the use of special feeds and the role of immunonutrients remains unproven. Nutritional support cannot completely prevent the adverse effects of catabolic illness and overfeeding should be avoided.

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