
Nutritional Therapy for Critically Ill Patients

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Abstract

Nutrition therapy provided early in the critical care setting has been shown to improve outcome. Appropriate and early nutrition interventions can attenuate the hyperdynamic systemic response and depressed immune reaction to injury, serious illness and major surgery. Controversies limit the uniform application and potential benefits of nutrition, including failure to accurately predict who will 'need' nutritional intervention, lack of consensus on what the optimal enteral formulation is, overreliance on parenteral nutrition, failure to maximize the use of early enteral nutrition (EN), and how much and how best to feed the morbidly obese population. Despite challenges and inconsistencies in today's critical care setting, specialized nutrition has evolved from metabolic 'support' during critical illness to a primary therapeutic intervention designed, individualized and focused to achieve metabolic optimization and mitigation of stress-induced immune and hyperdynamic systemic responses. Nutrition should be considered early and commenced after initial resuscitation has taken place. This is most effectively accomplished with the use of protocols that aggressively promote early EN, and will result in lower mortality and a reduction in major complications. Though the complexity of the heterogeneous critically ill population will always be challenging, we are developing a better understanding of immunity, metabolic needs and catabolism associated with intensive care unit admissions.

Introduction

Nutrition therapy provided early in the critical care setting has been shown to improve outcome [1, 2]. Appropriate intervention can attenuate the hyperdynamic systemic response and depressed immune reaction to injury, serious illness and major surgery. Not all intensive care unit (ICU) patients will derive similar benefits, nor tolerate prolonged periods of starvation or underfeeding. One of the main criticisms of aggressive nutritional interventions in the ICU is that not all ICU patients need it. In fact, previously well-nourished patients with a mild degree of critical illness and a relatively short stay in the ICU may derive little or no benefit from nutritional intervention. Most patients admitted at moderate-to-severe nutritional risk, however, should realize benefits from early enteral nutrition (EN) and could be harmed by ongoing prolonged iatrogenic underfeeding [3].

Controversies limit the uniform application of nutritional interventions, including failure to accurately predict who will 'need' it, lack of consensus of the optimal enteral formulation, overreliance on parenteral nutrition (PN), failure to maximize use of early enteral feeding, and how much and how best to feed the morbidly obese population. Recent studies on trophic feeding have been misinterpreted to imply that nutrition therapy is not important in the first week of hospitalization following ICU admission [4–6]. Across the globe, most ICUs fail to take steps to identify degrees of nutrition risk, determine the need for nutrition therapy or implement protocols to optimize delivery of the nutrition regimen. There are a number of modifiable factors that will determine whether or not benefits are realized, including the route of delivery, dosing, timing, content of nutrient substrate, interruptions in delivery and efforts to promote patient mobility [3]. Nonmodifiable factors include age, gender and genetics.

Despite challenges and inconsistencies in today's critical care setting, specialized nutrition has evolved from metabolic 'support' during critical illness to a primary therapeutic intervention designed, individualized and focused to achieve metabolic optimization and mitigation of stress-induced immune and hyperdynamic systemic responses.

Enteral Nutrition Therapy

Historically, multiple reports have shown the significant physiologic value of EN over PN delivery (table 1) [7]. EN should be started as soon as possible, i.e. following admission to the ICU, to establish its nonnutritional, immunologic benefits and minimize the protein-calorie debt that frequently occurs during the 1st week of critical illness [8]. Nonnutritional benefits are described as the

Table 1. Advantages of EN over PN

Gastrointestinal benefits of EN

Maintains gut integrity
Reduced gut/lung axis of inflammation
Enhances motility/contractility
Improves absorptive capacity
Maintains gut-associated lymphoid tissue
Supports and maintains commensal bacteria
Reduces virulence of endogenous pathogenic organisms
Promotes the production of secretory IgA
Promotes trophic effects on epithelial cells

Immune benefits of EN

Modulates key regulatory cells to enhance systemic immune function
Promotes dominance of anti-inflammatory Th-2 over proinflammatory Th-1 responses
Influences anti-inflammatory nutrient receptors in the gastrointestinal tract (duodenal, vagal and colonic butyrate)
Maintains mucosa-associated lymphoid tissue at all epithelial surfaces (lung, liver, lacrimal, genitourinary and pulmonary)
Modulates adhesion molecules to attenuate transendothelial migration of macrophages and neutrophils

Metabolic benefits of EN

Promotes insulin sensitivity through stimulation of incretins
Reduces hyperglycemia (advanced glycation end products), and muscle and tissue glycosylation
Attenuates stress metabolism to enhance more physiologic fuel utilization

physiologic mechanisms that maintain structural and functional gut epithelial integrity [9], attenuate oxidative stress, maintain humoral immunity and modulate the metabolic response [10–12]. By modulating the metabolic response, EN supports optimal carbohydrate utilization thereby decreasing insulin resistance [3].

More obvious nutritional benefits are obtained from the delivery of exogenous nutrients that provide sufficient protein and energy substrates and deliver micronutrients and antioxidants, and other specialized nutrients that aid in the attenuation of metabolic responses to stress. Overarching, maintaining lean body mass is the primary goal of successful nutrition intervention (table 1).

Patients receiving early EN versus PN consistently suffer fewer infections and have fewer hospital and ICU days. In some studies, a decrease in mortality has also been reported [13–16]. Randomized controlled trials of early versus delayed EN (e.g. feeding after 72 h) have shown that EN started within the first 24–48 h reduces infection, hospital length of stay (LOS) and mortality [1, 17]. When comparing early EN to ‘standard therapy’ (i.e. no supplemental nutrition) in elective surgical and surgical ICU populations, patients receiving EN initiated

the day after surgery experienced similar results [13–15]. In observational cohort studies, early initiation of feeding prevents an caloric deficit, and improves outcomes in ICU [8, 18]. When a caloric deficit exceeds 4,000–10,000 calories, a rise in complications, including organ failure and infection occur. Other outcomes, including hospital LOS and ICU LOS, also worsen [18–21]. Studies that include protocols to increase the delivery of nutrient and energy to the ICU population improve clinical outcomes, with decreases in infection, shorter hospital LOS and decreased mortality compared to those without an EN protocol [22–26].

Determining patient candidacy for early EN is challenging; not all critically ill patients are appropriate candidates. Patients with minimal metabolic or traumatic stress should not be fed enterally. For example, aggressive, early EN would be inappropriate in patients expected to regain adequate, volitional oral intake within 48–72 h. Additionally, patients with absolute contraindications to EN (e.g. complete bowel obstruction or bowel discontinuity) should not be fed enterally. Nutritionally high-risk patient populations benefit most from early enteral feeds, including those malnourished prior to ICU admission, patients with sepsis, systemic inflammatory response syndrome, persistent inflammatory catabolism syndrome, immunosuppression and catabolism syndrome, and those expected to have a prolonged ICU stay [27–30]. This population should begin enteral feeding as soon as possible after admission. On rare occasions, they may need supplemental PN [31, 32]. If necessary, small bowel feeding should be considered, as well as the use of prokinetic agents to improve tolerance.

While little controversy surrounds the importance of supplemental nutrition for the nutritionally high-risk patient, assessment remains challenging. Nutritional assessment in the ICU population is often inappropriately judged by the use of visceral protein levels, such as albumin and prealbumin [10]. These serum tests are at best surrogate markers and seldom, if ever, of any clinical use in the ICU setting. Alternatively, a number of scoring systems have been developed for nutritional assessment that can be used for more clinically applicable assessment in the ICU population [33]. Nutritional Risk Screening (NRS-2002) [34] and the NUTRIC score [30] are relatively easy to use, and take disease severity and nutritional intake into consideration. The NUTRIC score has been validated in ICU populations [30, 34]. Several other grading systems are useful in hospitalized patients, such as the Mini-Nutritional Assessment, Malnutrition Universal Screening Tool (MUST), Nutritional Risk Index and Subjective Global Assessment, but are much less useful for ICU populations than the NUTRIC score and NRS-2002 [33].

Simple weight-based equations can be used to predict energy expenditure (for example 20–25 kcal/kg per day) and are appropriate for early, rapid determina-

tions of caloric needs; more accurate methods, however, are available. Indirect calorimetry is more accurate in most cases, but requires specialized equipment, and accuracy of the results may be affected at extremes of weight and height [35, 36]. Despite supporting literature, controversy remains regarding optimal timing, reasonable caloric deficits and when to permit underfeeding or ‘trophic feeding’. Significant recent attention has been paid to ‘trophic’ feeding, following a paper by the Vanderbilt Group in 2011 that described it (approximately 20 ml/h) for 5 days in patients with adult respiratory distress syndrome and acute lung injury, and showed outcomes including hospital stay, ventilator-free days and mortality that were essentially equivalent to full feeds [37]. Subsequently, several other studies have reported similar outcomes in a variety of clinical ICU situations [38], including both surgical and medical ICUs [39]. Conceptually, ‘trophic’ or ‘permissive underfeeding’ in the ICU is attractive, since fewer calories and smaller volumes would lessen the concern for hyperglycemia and aspiration; little data, however, support these findings [40, 41].

Once EN is initiated, nutritional therapy should focus on assuring that resuscitation goals continue to be met, risk for aspiration is minimized, and the rate of delivery is safely and swiftly advanced to goal. It is appropriate and safe to provide EN to patients on pressor agents that have been fully resuscitated and are hemodynamically stable [42]. Jejunal feeding-associated ischemic bowel in the patient on enteral feeding is extremely rarely and occurs unpredictably and often later in hospitalization when the patient is no longer in the ICU [43]. Gastric feeding is successful and usually well tolerated in the vast majority of ICU patients, particularly when feeding is started early within the first 24 h [44]. A specific enteral access device, the location of infusion within the gastrointestinal tract (e.g. gastric, postpyloric or jejunal feeding) and consideration of need for jejunal feeding with simultaneous aspiration of the stomach are all predicated on the degree of tolerance of gastric feeding.

What Is the Optimal Formula for the Intensive Care Unit Setting?

While most patients in the critical care setting will tolerate a standard enteral formula (polymeric at 1.0–1.5 kcal/ml), it is appropriate to consider use of specialty formulas in individual patients in a variety of specific circumstances. Nutrients have traditionally been considered for the delivery of adequate basic energy for cell metabolism and cellular homeostasis. Recently, multiple reports have shown, when selected appropriately, specific nutrients such as eicosapentaenoic (EPA) and docosahexaenoic acid (DHA), arginine, leucine, glutamine and antioxidants given in quantities greater than needed for ‘normal’ cell me-

tabolism as well as protein synthesis have multiple benefits. Benefits include shortening of ICU LOS, fewer days on mechanical ventilation, attenuation of the hyperdynamic metabolic response to stress, earlier resolution of inflammatory states, fewer systemic and blood stream infections, and decreased mortality in some cases. Despite previous speculation regarding the safety of arginine supplementation in ICU patients with sepsis, it has been shown to be safe from a hemodynamic standpoint, and beneficial in the septic and severely diseased patient [45–48]. In trauma patients and patients undergoing major elective surgery, formulas with arginine, fish oil and nucleotides are highly effective in reducing infection and hospital LOS, but have not proven to be consistently beneficial in the medical ICU population [49, 50]. Data support, however, the use of formulas with supplemental antioxidants and an anti-inflammatory lipid profile delivered by continuous infusion in patients with acute lung injury/adult respiratory distress syndrome on mechanical ventilation [51]. Delivery of EPA and DHA by bolus infusion does not appear to achieve the same physiologic effects or outcome benefits [52, 53]. The addition of supplemental enteral glutamine has shown outcome benefits for patients with burns or trauma, but recent studies do not support its widespread use in patients with multiple organ or renal failure, reporting it is harmful to this population [1]. Many specialty formulas, or so-called ‘organ- or disease-specific’ formulations, exist. They include small peptide, medium chain triglyceride formulas to promote more efficient nitrogen absorption in patients with gut dysfunction [54], a high-protein, low-calorie formula for obese patients [55], and organ failure formulas for patients with liver disease or acute kidney injury. While each is designed with the appropriate physiologic rationale for use in a specific patient population for which they were designed, additional study is needed before routine use in the ICU setting can be recommended. Pulmonary and glucose control formulas, however, lack physiologic validity; the use of these specific formulas is not supported by appropriate outcome data in ICU patients.

Numerous trials have shown a benefit from the provision of antioxidant cocktails to ICU patients on continuous feeding. A recent meta-analysis, including 21 randomized clinical trials, showed a reduction in mortality in patients treated with antioxidant supplements in the ICU [56]. The most effective ‘cocktails’ appear to contain selenium at higher doses, although the optimal dosing regimen, combination of antioxidants and method of administration (bolus vs. continuous infusion) are not clear. Excessive antioxidants can be detrimental, however, so caution with dosing must be taken [57].

The use of probiotics in the ICU setting has shown promise in limiting ventilator-associated pneumonia, antibiotic-associated diarrhea and *Clostridium difficile* infections. To obtain these benefits, the probiotic product should be ad-

ministered per nasogastric tube and swabbed throughout the oropharynx. Used in this fashion, probiotics can reduce ventilator-associated pneumonia and decrease the likelihood of acquiring antibiotic-associated diarrhea, pseudomembranous colitis and overall infections [58–62]. Probiotic benefits appear to be relatively species specific, which should be considered when deciding which product to use or recommend [63].

A number of metabolically active ancillary agents have been proposed for the use in the critically ill patient based on their appropriate physiologic and/or pharmacologic effects [64]. β -Blockers attenuate the hyperdynamic response, and statins have a general pleiotropic effect and several areas of potential benefit, including antioxidant and immune stimulation. Anabolic agents, such as insulin, human recombinant growth hormone and glucagon-like peptide (GLP-2), have been shown to be beneficial in a very select setting to enhance protein synthesis in the muscles and gut. Anabolic steroids have been shown to support lean body mass in highly selective burn populations, but are not consistently helpful in a wide range of ICU patients. Leucine stimulates protein synthesis, citrulline serves as a substrate for arginine synthesis in the kidney and subsequent nitric oxide production, and carnitine may be beneficial in transporting long-chain fatty acids into the mitochondria for β -oxidation. Rigorous, well-designed studies demonstrating a beneficial effect on clinical outcomes with any of these metabolically active ancillary agents, however, are lacking. The use of these agents in the ICU is considered experimental, and should neither be used outside a research protocol setting nor extrapolated for the use in the general heterogeneous ICU patient population [64].

Impediments to Early Enteral Feeding

In the ICU setting, patients routinely receive only approximately 50% of the calories and proteins required or recommended [65–67]. Multiple factors impair adequate delivery of EN in the ICU. Frequently, feeds are not initiated early due to difficulty in defining full resuscitation and stabilization. In addition, patients can remain nil per os for diagnostic tests or surgical procedures, or nurses hold feeds for routine care like bathing, line changes, transport to radiologic tests and dislodging of tubes. EN is often withheld or stopped inappropriately for perceived intolerance as assessed by gastric residual volumes. These barriers lead to iatrogenic underfeeding. For these reasons, cessation of delivery of EN is estimated to be inappropriate in up to 66% of the time [66]. Gut dysfunction in critical illness typically involves segmental or diffuse dysmotility, reduced villous height and loss of absorptive surface at the villus tips in addition

to significant alterations in gut microbiota [68]. Typically, patients can be and should be fed through these periods of gut dysfunction, since EN itself can lead to restored gut integrity, enhanced contractility, increases in brush border and glycocalyx enzymes, and restoration of the commensal bacteria [12, 68]. While ileus is a frequent problem in critically ill patients, intensivists should be comfortable with more aggressive feeding strategies [68].

A common misconception in the ICU is that patients with high gastric residual volumes [69], patients with stable hemodynamics on vasopressor therapy [42], patients that are hypoactive or those with absence of bowel sounds with evidence of ileus should not be fed [68]. In prospective trials comparing the assessment of gastric residual volumes versus no assessment, the patients that were not assessed had increased EN delivery without any adverse sequelae while delivering more nutrients [70].

Challenging traditional ICU dogmas is one way to overcome barriers that can prevent positive changes in practice [71, 72]. Approaches to early EN designed to reduce barriers will likely improve abilities to provide optimal nutrition to critically ill medical and surgical patients.

Strategies to Promote Optimal Nutrition Delivery

Adopting one or many of the multiple specific strategies available to improve nutrient delivery will improve clinical outcome [73]. ‘Top-down’ or ‘de-escalation’ therapy is a concept widely used in other areas of medicine to manage complex disorders, such as rheumatoid arthritis, hypertension and surgical infection. Overall, this approach may allow more calories to be delivered. In the ICU nutrition arena, a ‘top-down’ protocol represents aggressive therapy with multiple strategies initiated at the start of ICU admission and beginning of enteral feeding, followed by de-escalation of therapy (as was demonstrated in the ‘PEPuP’ protocol) [74]. These assertive EN protocols are based on the principle that most critically ill patients will show a variety of stages of intolerance at the time of initiation of feeds. Rather than wait for patients to demonstrate intolerance (a reactive approach), a number of strategies are initiated simultaneously at the start of feeds to promote tolerance (a proactive approach) [74, 75]. These strategies include starting at goal rate with prokinetic therapy, monitoring the caloric deficit and changing infusion rates accordingly, elevating the head of the bed, not checking gastric residual volumes, and, in selective cases, use of specialty formulations and adding supplemental protein during the first few days of feeding [74]. Development and implementation of a nurse-driven enteral feeding protocol have been shown to increase

EN delivery [76]. In order to enhance utilization, such protocols should be modified by the individual institution depending on local expertise, culture of the ICU and nursing practice [77].

What Is the Current Role of Parenteral Nutrition in the Intensive Care Unit Setting?

PN has a more limited risk/benefit ratio than EN in the critically ill population, and the selection of who of the patients will benefit requires consideration. Although recently the use of PN has been reported to be essentially equivalent in the ICU setting, in general, PN should only be considered when EN is not practical or possible [78]. If a nutritionally 'low-risk' patient is admitted to the ICU, then PN should neither be started as an initial procedure nor considered as first-line therapy. If a malnourished or nutritionally 'high-risk' patient is admitted, then PN should be started if EN is not feasible or possible [2].

Future Trends

A significant and relatively recent interest in combining early EN with aggressive early resistance exercise of axial skeletal muscle and early mobility in the ICU has been shown to promote the uptake and utilization of amino acids with maintenance of muscle mass and enhancement of function [79]. Prospective randomized trials on the effect of exercise in the ICU have shown reduced ICU LOS, duration of mechanical ventilation and total hospital LOS [80, 81]. The use of probiotics is likely on the rise, as manipulation of intestinal microbiota has already been shown to reduce ventilator-associated pneumonia, the likelihood of acquiring antibiotic-associated diarrhea or *C. difficile* infections, and the risk of colonization with vancomycin-resistant enterococci [58–60, 81, 82]. A newly described persistent inflammatory catabolism syndrome exemplifies the long-term adverse metabolic and immune sequelae from prolonged ICU LOS, where a patient continues a pattern of chronic inflammation, catabolism, degradation of lean body mass and a shift from a normal immune response to ineffective production of immature myeloid-derived suppressor cells [83]. These patients are often transferred from the ICU to long-term acute care facilities and cycle between them, never returning to baseline function [83]. Whether aggressive early nutrition therapy attenuates the persistent inflammatory catabolism syndrome, restores bone marrow function and improves long-term outcome has only been postulated and not yet proven.

Conclusions

The concept of nutrition ‘support’ in the ICU is now shifting toward nutrition ‘therapy’. The concept of providing EN and selective PN to attenuate the hyperdynamic response, maintain gut-associated lymphoid tissue and improve systemic immunity is well supported. Pharmaconutrition, or immune- and metabolic-modulating nutrition, including specific agents such as EPA and DHA, arginine and antioxidants, should be considered in surgical and select medical ICU populations. Nutrition intervention should be considered early and commenced as soon as initial resuscitation has taken place. This is most effectively accomplished with the use of protocols that aggressively promote early EN, and will result in lower mortality and a reduction in major complications. The evidence to support nutrition therapy as a mainstay in the ICUs has matured as data from cellular models have been translated to human trials. Despite this fact, many questions remain unanswered regarding the optimal dosing and timing, how best to combine EN with supplemental PN and which specialized therapies will improve outcome in the critically ill patient. We are, however, developing a better understanding of immunity, metabolic needs and catabolism associated with ICU admissions. The complexity of the heterogeneous critically ill population will always be challenging. As care in the modern ICU progresses to improve outcome, future nutrition studies will also guide us to answer these questions.

Disclosure Statement

Robert G. Martindale is a member of the advisory board for Nestle Nutrition and Metagenics. There is nothing to disclose for Malissa Warren, Sarah Diamond and Laszlo Kiraly.

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