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Emerging Concepts in Critical Care Nutrition and the Provision of Enteral Nutrition Support

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Abstract Nutrition support has remained a cornerstone in the management of the critically ill patient despite underemphasis and widespread variation in clinical practice. Although exact definitions vary, pre-existing malnutrition and patients determined to be at high nutrition risk are subjected to increased morbidity and mortality in critical illness. These characteristics remain powerful prognostic indicators in nearly every outcome prediction model. As a result, the provision of nutrition support in the critically ill patient has become accepted practice, but questions remain surrounding the specifics of administration and delivery. There has been a virtual explosion in the publication of large randomized controlled trials addressing areas of nutrition support in critically ill patients over the last 5 years. Many of the results gleaned from recent publications appear to be in direct conflict with the smaller trials and meta-analyses conducted over the preceding 25 years. Controversies now exist pertaining to many of the fundamental tenants of nutrition support including the appropriate timing of initiation of nutrition, dosage (caloric and protein requirements) and which nutrients or additional supplementation, if any, should be provided. Despite a growing body of literature supporting the provision of nutrition support in some capacity, a significant portion of critically ill patients still do not receive nutrition in any form. In this review, we investigate emerging and evolving concepts and existing controversies in the provision of nutrition in the critically ill surgical patient; exploring when, how, and what type of enteral nutrition should be provided.

Keywords Nutrition · Enteral nutrition · Immunonutrition · Critical care · Glutamine · Arginine · Hypocaloric diet

Introduction

Historically, fundamental concepts regarding nutrition support in the critically ill patient can be summarized as suggesting that enteral support delivered as early and as close to goal as possible should be our objectives. Many of these fundamental principles have been called into question over the course of the last several years as a result of recently conducted large randomized controlled trials. Substantial evidence has demonstrated that nutrition provided via the enteral route is preferred to parenteral route in critically ill patients without contraindications and this will be the focus of this review [1, 2]. The intestinal tract supports immune function; after injury or illness, gut immune function is compromised as shown through mucosal atrophy, increased intestinal permeability, and reduction in gut-associated lymphoid tissue (GALT) [3•]. Providing enteral nutrition may preserve gut immune function by maintaining mucosal mass, stimulating epithelial cell proliferation, maintaining tight junctions between epithelial cells as well as the production and release of endogenous agents [4, 5]. In addition, experimental studies on burn animals show a decrease in bacterial

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translocation as well as a decrease in the hyper-metabolic state with enteral feeding [6]. Despite a considerable body of evidence supporting nutrition in the critically ill patient, a significant percentage of patients receive no form of nutrition and those that do, receive much less than the recommended daily calculated intake [7]. Research continues to strive to define the ideal timing to initiate nutrition, the amount of caloric and protein intake required and whether any supplementation is beneficial to these critically ill patients. The goal of this review is to highlight the most recent literature and guidelines regarding enteral nutrition in the critically ill patient and address current controversies in the provision of nutrition support. This review specifically addresses when enteral nutrition should be administered in the critically ill patient, what percentage of daily recommended caloric intake is appropriate and whether an immunomodulating diet is beneficial in this setting.

Early Versus Late Enteral Nutrition

While much of the historical evidence has demonstrated decreased infectious complications with enteral nutrition, the optimal timing for the initiation of enteral nutrition has yet to be established and has not been stringently investigated. Moore demonstrated in 1986 that early enteral nutrition (within 18 h post celiotomy vs. 72 h) was associated with reduced septic complications [8]. Since then, timing of nutrition has continued to be investigated in several small trials. Most recently, guidelines surrounding enhanced recovery after surgery programs have gained attention by demonstrating reduced morbidity and mortality with early enteral feeding as part of a protocolized approach to the care of the elective peri-operative patient [9]. Ascertaining the specific components that contribute to the perceived outcome benefit with this protocolized approach has been difficult. A meta-analysis by Heyland et al. supported early enteral nutrition, defined as within 24–48 h of admission or initiation of ventilation, after demonstrating a trend toward a reduction of mortality and infectious complications [7]. The authors did note variability in design and heterogeneity across studies reviewed in this meta-analysis, which are common confounders prevalent in much of the literature surrounding nutrition support. Doig et al. also supported early enteral nutrition based on a meta-analysis of relevant studies published prior to 2009 [3•]. In this meta-analysis, the authors revealed a statistically significant reduction in mortality and pneumonia attributable to initiating enteral nutrition within 24 h of ICU admission [3•]. Doig proposed that the provision of early enteral nutrition may assist in decreased morbidity and mortality through the preservation of GALT, gut

barrier function and the ability to detoxify lipopolysaccharide (LPS) [3•]. Artinian et al. performed a retrospective analysis of a large multi-institutional ICU database with >4000 patients and found decreased overall ICU and hospital mortality in the early feeding group, as defined as within 48 h of mechanical ventilation onset [6]. However, the authors did find an association in the early enteral group with an increased risk of VAP although this did not result in an overall decrease in ventilator-free days [6]. Retrospective studies have been criticized as demonstrating simply that patients tolerant of early enteral nutrition support are thereby less sick and therefore do better. The most recent American Society for Parenteral and Enteral Nutrition (ASPEN) and Society of Critical Care Medicine (SCCM) guidelines from 2009 support early enteral nutrition, defined as within 24–48 h following admission, and this recommendation will likely remain intact in the upcoming revisions [1]. The authors define a "window of opportunity" within the first 24–72 h after insult for starting enteral nutrition that is associated with less gut permeability and diminished activation and release of inflammatory cytokines [1]. In addition, most recent European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines from 2006 also recommended starting enteral nutrition within 24 h of injury. The guidelines graded this recommendation as a Level C recommendation, detailing that no one trial met the standard for a prospective, randomized, double-blind controlled trial [10]. Despite these guidelines, 40–60 % of patients eligible to receive enteral nutrition still fail to receive it within 48 h of ICU admission [11]. Despite concerns for study quality, this growing body of evidence suggests that early enteral nutrition, as defined as within 48 h of ICU admission or injury likely improves outcomes and should remain the goal.

Caloric and Protein Targets: Eucaloric Versus Hypocaloric

Malnutrition is associated with poor outcomes demonstrated by increased infectious complications, prolonged ventilatory requirements, increased length of stay, and increased morbidity and mortality [7]. Multiple equations have been developed to estimate the appropriate caloric intake, including separate equations for patients with BMI < 30 and >30 (Penn State equation and Ireton-Jones equation, respectively) [12]. Current guidelines of 25–30 total kcal/kgBW/day are generally accepted, however there are no studies validating this accepted target, and these targets are increasingly controversial given the findings of recent studies. In addition, ability to reach target caloric intake may be difficult to achieve in critically ill patients

due to interruptions in enteral nutrition for repeated or frequent invasive procedures, placement and/or confirmation of enteral access as well as intolerance of goal intake [2]. The literature regarding what percentage of goal needs to be provided is conflicting; some studies suggest less is better however these studies have significant design flaws [13, 14]. Other well-designed trials question the need to reach goal as smaller half-goal feeding or even trophic feeding over the first week of ICU admission results in similar outcomes [2, 15, 16]. Multiple studies have documented worse outcomes in patients with markedly hypocaloric intake; however, interestingly, in patients where daily caloric intake was near goal, increases in adverse events have also been documented [17, 18]. Patients with near target caloric intake (as defined as >65 %) had increased morbidity and mortality, including ICU acquired infections, VAP, duration of mechanical ventilation, and ICU and hospital LOS [15]. Krishnan et al found that medical ICU patients that received >66 % of targeted caloric intake had a reduced likelihood of being discharged alive or breathing spontaneously at discharge compared to patients that received <33 % of target intake [13]. Therefore, optimal caloric intake goals have yet to be established and there is a growing sentiment that aggressive feeding strategies approaching 100 % of historical goals may produce limited outcome benefit.

Despite multiple guidelines supporting early enteral nutrition within 24–48 h of ICU admission, 40 % of patients are still without feeding after 48 h [19]. ASPEN guidelines 2009 commented briefly on target doses of enteral nutrition, and included in the guidelines was one study that demonstrated patients with head injuries that received more calories and protein had fewer infectious complications with no difference in mortality [1, 20]. ESPEN guidelines 2006 state that, in the acute period, providing nutrition in excess of 25 kcal/kg/day may result in less favorable outcomes [10]. However, multiple studies have since investigated whether restricting caloric intake in critically ill patients resulted in improved outcomes. The EDEN trial randomized patients with acute lung injury requiring mechanical ventilation to trophic feeding versus full feeding for 6 days. The trophic feeding group received 400 versus 1300 kcal/day in the full feeding group. Rice's group did not find that restrictive caloric intake demonstrated improvements in morbidity or mortality, however, also did not find any differences in ventilator-free days, infectious complications or mortality between the two groups [21]. Charles et al randomized surgical ICU patients to hypocaloric (50 % standard calculated daily caloric intake) or eucaloric intake, both with a standard protein goal of 1.5 g/kg/day [16]. The authors failed to show any difference in outcomes between the hypocaloric and eucaloric arms. The authors do note that the targeted

eucaloric goal of 25–30 kcal/kg/day was difficult to achieve secondary to issues including interruptions secondary to procedures and titration to goal. In a very recent trial, Arabi et al randomized 894 critically ill patients to permissive underfeeding (40–60 % calculated caloric requirements) or standard enteral feeding (70–100 %) for up to 14 days, while maintaining similar protein intake across the two groups [12]. The authors failed to find a difference in mortality, infectious complication, ICU or hospital LOS difference between the hypocaloric and eucaloric groups.

Multiple studies demonstrate caloric restriction resulting in prolonged life span across many different species, including mammals; however hypocaloric feeding has not reduced infectious complications, ventilator-free days, ICU or hospital LOS, or mortality [12]. However, providing caloric intake of 25–30 kcal/kg/day is also quite difficult in the critically ill patient due to multiple factors and may actually result in increased adverse outcomes when correcting for overall protein provision. This is evidenced by Arabi et al.'s study that demonstrated near goal caloric intake was associated with increased hospital mortality, ICU acquired infections, mechanical ventilation, ICU, and hospital LOS [15]. In addition, restricting caloric intake to <25 % recommended daily intake has also been shown to increase adverse outcomes. An important consideration remains that, in more recent trials examining this question as opposed to earlier trials, protein provision has been relatively equivalent in the groups being compared regardless of total caloric provision. There is increasing sentiment that suggests that outcome, especially mortality, may be more related to provision of protein as opposed to full feeding of calories [22]. The optimal caloric intake in the critically ill patient has yet to be established, but it does appear that protein should rarely be limited and traditional targets should be the goal. While hypocaloric feeding strategies do not seem to improve outcome, these studies demonstrate that hypocaloric nutrition can achieve similar outcomes thereby providing advantage in situations where enteral nutrition is difficult to provide secondary to interruptions in delivery and/or intolerance of goal feeds. In summary, evidence suggests that caloric intake of greater than 25 % but less than 70 %, as calculated by the recommended daily intake of 25 kcal/kg/day, appears to be a safe target in the critically ill patient.

Immunomodulating Diet

Critically ill patients are at risk for severe infections leading to sepsis and death. The pro-inflammatory state with increased oxidative stress may contribute to morbidity and mortality in these critically ill patients. This oxidative

stress occurs when reactive oxygen species and anti-oxidant defense mechanisms become unbalanced. Multiple studies have demonstrated a relationship between reactive oxidative species, nitric oxide, and inflammatory cytokines and sepsis in the critically ill patient, resulting in sepsis induced organ dysfunction [23]. Recent literature has striven to identify specific antioxidant species as markers for targeted therapy. Therapeutic adjuncts targeted toward the diminishment of this inflammatory response have remained elusive but "immunonutrition" as compromised of various combinations of glutamine, arginine, nucleic acids, favorable omega-3 to omega-6 fatty acid ratios, and additional micronutrient supplementation have resulted in moderate success in some trials and warrant discussion. Due to current composition of available formulas which are comprised of many or all of the above constituents, difficulty remains in ascertaining which components of these formulas are potentially beneficial in specific patient populations. To provide some clarity, the most common constituents will be discussed individually in the following sections.

Glutamine

Glutamine is the preferred nutrient of enterocytes and enhances glutathione levels, thereby acting as an antioxidant. Decreases in glutamine have been shown to be associated with immune dysfunction and increased mortality. In addition, glutamine has been shown to be decreased in critically ill patients [24]. Glutamine may be supplemented enterally or parenterally in the critically ill patient. The most recent ASPEN guidelines (2009) give a grade A recommendation for immune-modulating regimens, including glutamine, to be administered enterally to surgical ICU patients and a grade B recommendation for medical ICU patients [1]. The 2006 ESPEN guidelines also give a grade A recommendation for glutamine supplementation in burn and surgical patients [10]. In accordance with these recommendations, Heyland et al's meta-analysis recommended enteral glutamine in trauma and burn patients however reported insufficient data to support use of enteral glutamine in other critically ill patients [7]. However studies published since these recommendations may call into question glutamine supplementation and revisions to future guidelines are expected. Van Zanten et al. in the MetaPlus trial demonstrated no difference in infections with immune-modulating enteral nutrition in a heterogeneous ICU population consisting of medical, surgical, and trauma patients [25]. The formula utilized in this study included glutamine, antioxidants, and omega-3 fatty acids but not arginine. This trial also reported higher 6 month mortality in patients receiving this diet [25]. The

SIGNET trial in 2011, also a randomized, double blinded, multi-institution controlled trial, and demonstrated no benefit for glutamine supplementation for critically ill patients [26]. In the REDOXS trial by Heyland et al., not only did the authors find no improvement in clinical outcomes with supplementation of glutamine, but found an increase in mortality in critically ill patients with multi system organ failure [27]. Therefore, while early studies suggested a benefit with decreased length of mechanical ventilation and decreased infectious complications, several large randomized controlled trials recently have called these benefits into question. These studies have shown that some patients have high baseline levels, while others have low baseline glutamine levels which dramatically change with glutamine supplementation. For such patients, as well as those with organ failure, or patients on steroids, glutamine supplementation may be inappropriate [25, 27, 28]. At current, given recent data, glutamine supplementation cannot be recommended in critically ill patients. Due to the heterogeneity of the patients studied in several of the trials as well as the diverse composition of the experimental formulas utilized, further research is needed to specify in which, if any, patient populations glutamine may be beneficial.

Arginine

Arginine not only enhances T-cell function but also functions as an antioxidant [24]. During stress, arginine is decreased secondarily in part to increased metabolism via nitric oxide synthetase [24]. Decreased levels of arginine lead to decreased T-cell function as well as increased levels of infection [24]. Therefore, arginine has been investigated as a possible supplementation in the ICU population. However, multiple small studies and meta-analysis have demonstrated no difference in infectious complications or mortality [7]. Subgroup analysis in a few studies have found an increase in mortality in patients with severe sepsis and this has somewhat limited the incorporation of arginine into the support delivered in the more randomized controlled trials [1, 7, 10]. Currently, ASPEN guidelines (2009) state that arginine containing products are safe to use, however caution should be used in severe sepsis and in the hemodynamically unstable patient [1]. ESPEN also states that in patients with severe sepsis, no benefit could be established and may be harmful [10]. However, studies have shown that surgical, as opposed to medical, patients may benefit from arginine supplementation as evidenced by Heyland et al's study that demonstrated decreased morbidity and hospital LOS when arginine containing formulas were utilized [29]. Therefore, there is likely a variable response to arginine depending on the specific

patient population and, based on the available evidence, there still appears to be a role for arginine in the perioperative setting and in the surgical intensive care unit.

Fatty Acids

Omega-3 fatty acids have been shown to decrease inflammatory states by the ability to displace omega-6 fatty acids from the cell membranes of immune cells [1, 24]. This results in reduced systemic inflammation by producing less potent inflammatory mediators (PGE_3, TxA, LTB_5) and decreasing neutrophil attachment and migration [30]. In patients with acute lung injury (ALI), decreased omega-3 levels are seen which presents an opportunity for supplementation [21]. Most studies on omega-3 supplementation have focused on patients with ALI and acute respiratory distress syndrome (ARDS) considering omega-3's positive effects specifically on pulmonary mechanics. Historically, studies have demonstrated a reduction in ventilator days, organ failure, ICU LOS and mortality [1]. ASPEN, ESPEN, and Heyland et al.'s analysis all recommend supplementation with omega-3 fatty acids based on three randomized clinical trials [1, 7, 10]. However, two recent randomized, double blinded, multi-center, and controlled trials have brought these recommendations into doubt. The OMEGA study was prematurely terminated after finding no improvement in ventilator-free days and trend toward an increase in 60 day in-hospital mortality [21]. Consistent with these results, the MetaPlus study found that supplementation with an immune-modulating enteral nutrition (including omega-3 fatty acids and glutamine) did not show a benefit in infectious complications and demonstrated potential harm with a trend towards increased 6 month mortality [25]. In addition, Stapleton et al demonstrated that omega-3 fatty acids, alone, did not reduce markers of pulmonary or systemic inflammation in patients with ALI [31]. However, omega-3 fatty acids, combined with arginine, may have benefit in surgical patients. A meta-analysis by Drover et al demonstrated that fish oil, combined with arginine, resulted in decreased surgical site infections (SSI) [32]. In addition, the meta-analysis by Braga also demonstrated a decrease SSI and hospital LOS when combinations of fish oil and arginine were used [33]. These would suggest that the synergistic effect of arginine and fish oil may result in benefit while other supplements including glutamine, nucleic acids, and antioxidants may be of lesser importance. As many of these studies have great heterogeneity in both patient population and composition of the immune-modulating formulations, care must be taken regarding recommendations for supplementation.

Conclusion

While nutrition support in the critically ill patient remains an accepted and important component of clinical practice, specific guidelines regarding the timing, quality, and make-up of the support that is delivered are clearly in evolution. Despite a recent increase in the available body of literature pertaining to nutrition support in the ICU, practice has been difficult to standardize due to conflicting results, heterogeneous patient populations, and the overall complexity of the critically ill patient. ASPEN and ESPEN guidelines delineate recommendations for surgical versus medical patients, however many studies cited within these recommendations include both patient populations. Questions also arise regarding additional subgroups including the obese patient as well as patients with severe pre-existing malnutrition. Despite clinical practice recommendations, barriers exist, and compliance remains difficult for a variety of reasons including the individualized inflammatory and metabolic response to insult, the presence of pre-existing co-morbidities, difficulties regarding fuel integration and the innumerable physical and logistical difficulties in delivering ICU level healthcare. The renewed interest and emergence of multiple trials in recent years investigating the foundational principles of nutrition support are encouraging and the expectation would be for the continued evolution of future concepts and guidelines regarding appropriate support.

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