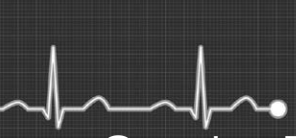

Concise Definitive Review

Series Editor, Jonathan E. Sevransky, MD, MHS

Feeding the Critically Ill Patient

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Objective: Critically ill patients are usually unable to maintain adequate volitional intake to meet their metabolic demands. As such, provision of nutrition is part of the medical care of these patients. This review provides detail and interpretation of current data on specialized nutrition therapy in critically ill patients, with focus on recently published studies.

Data Sources: The authors used literature searches, personal contact with critical care nutrition experts, and knowledge of unpublished data for this review.

Study Selection: Published and unpublished nutrition studies, consisting of observational and randomized controlled trials, are reviewed.

Data Extraction: The authors used consensus to summarize the evidence behind specialized nutrition.

Data Synthesis: In addition, the authors provide recommendations for nutritional care of the critically ill patient.

Conclusions: Current evidence suggests that enteral nutrition, started as soon as possible after acute resuscitative efforts, may serve therapeutic roles beyond providing calories and protein. Although many new studies have further advanced our knowledge in this area, the appropriate level of standardization has not yet been achieved for nutrition therapy, as it has in other areas of critical care. Protocolized nutrition therapy should be modified for each institution based on available expertise, local barriers, and existing culture in the ICU to optimize evidence-based nutrition care for each critically ill patient. (*Crit Care Med* 2014; 42:2600–2610)

Key Words: critically ill patient; enteral nutrition; parenteral nutrition; stress metabolism

In this era of evidence-based medicine, recommendations for nutrition therapy of the critically ill patient are supported by observational studies, a preponderance of small randomized controlled trials (RCTs), meta-analyses, and a foundation of mechanistic data. Admittedly, higher quality larger RCTs are needed before stronger clinical inferences can be made. Nonetheless, the signal that emerges from current existing data suggests that nutrition therapy provided early after admission to the ICU favorably alters outcome for the critically ill patient (1, 2). Every critically ill patient, regardless of preexisting malnutrition, has a highly variable metabolic/immune response to injury or illness, which may be attenuated by appropriate focused nutrition therapy. Artificial nutrition support has evolved into a primary therapeutic intervention designed to achieve metabolic optimization and attenuation of stress-induced immune responses rather than simply providing nutrients to prevent "malnutrition."

Not all critically ill patients, however, will derive the same benefit from nutrition therapy. Previously well-nourished patients with a mild degree of critical illness and a relatively short stay in the ICU may derive little benefit from early nutrition therapy. On the other hand, patients with moderate to severe nutrition risk might benefit from early enteral nutrition (EN) or be harmed by ongoing iatrogenic underfeeding (3). Even in these patients, the benefit of nutrition therapy likely depends on factors such as route, dosing, timing, content of nutrient substrate, interruptions in delivery, and efforts to promote patient mobility (3).

A number of controversies limit the widespread application and consequent potential benefits from nutrition therapy. Clinicians may continue to see provision of a nutrition regimen as adjunctive support and not true primary therapy. Recent studies on trophic feeding have been misinterpreted by some clinicians to imply that nutrition therapy is not important in the first week of hospitalization following admission to the ICU (4–6). Many practitioners may still believe that obese patients in the ICU have

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nutritional reserve and therefore do not require specialized nutrition therapy during their critical illness. Some units continue to practice an overreliance on use of parenteral nutrition (PN). Steps to identify degree of nutrition risk and determine the need for nutritional therapy are not well established and validated, and many medical centers do not routinely implement protocols for delivery of specialized nutrition therapy in critical illness.

This report reviews nutrition therapy in the critically ill adult patient unable to sustain volitional oral intake.

WHY IS EN THERAPY IMPORTANT?

The value of early EN is supported by mechanistic data delineating its physiologic effects, which provide both nonnutritional and nutritional benefits to the critically ill patient (3) (**Fig. 1**). EN should be started as soon as it is safely possible following admission to the ICU in order to achieve the nonnutrition benefits and minimize the development of a protein-calorie deficit that frequently occurs during the first week of critical illness (7). The nonnutrition benefits are derived from several physiologic mechanisms that maintain structural and functional gut integrity, thus preventing increases in intestinal permeability (8). Immune mechanisms elicited by EN result in attenuation of oxidative stress and the inflammatory response while supporting the humoral immune system (8). Enteral feeding modulates metabolic responses that help decrease insulin resistance (3). By contrast, the nutritional benefits are derived from delivery of exogenous nutrients, which provide sufficient protein and calories, deliver micronutrients and antioxidants, and maintain lean body mass.

Four distinct bodies of evidence exist in the literature from which the clinical value of early EN in the critically ill patient may be derived: 1) Numerous small RCTs and multiple meta-analyses comparing early versus delayed EN suggest that enteral feedings started within the first 24–48 hours reduce infection, hospital length of stay, and mortality compared with similar feeds started after that point (2, 9, 10). 2) Meta-analyses of RCTs comparing EN with standard therapy where no specialized nutrition therapy is provided, conducted in the setting of elective surgery and surgical intensive care, have shown that EN initiated the day after surgery reduced infection, hospital length of stay, and mortality compared to controls where patients awaited return of bowel function and requested oral intake (11, 12). 3) Observational cohort studies in critically ill patients evaluating the concept of caloric deficit have shown that delays in initiation of EN or processes which interrupt feedings create a caloric deficit between calories expended (i.e., caloric requirements) and actual calories delivered by the nutrition regimen. A caloric deficit that exceeds

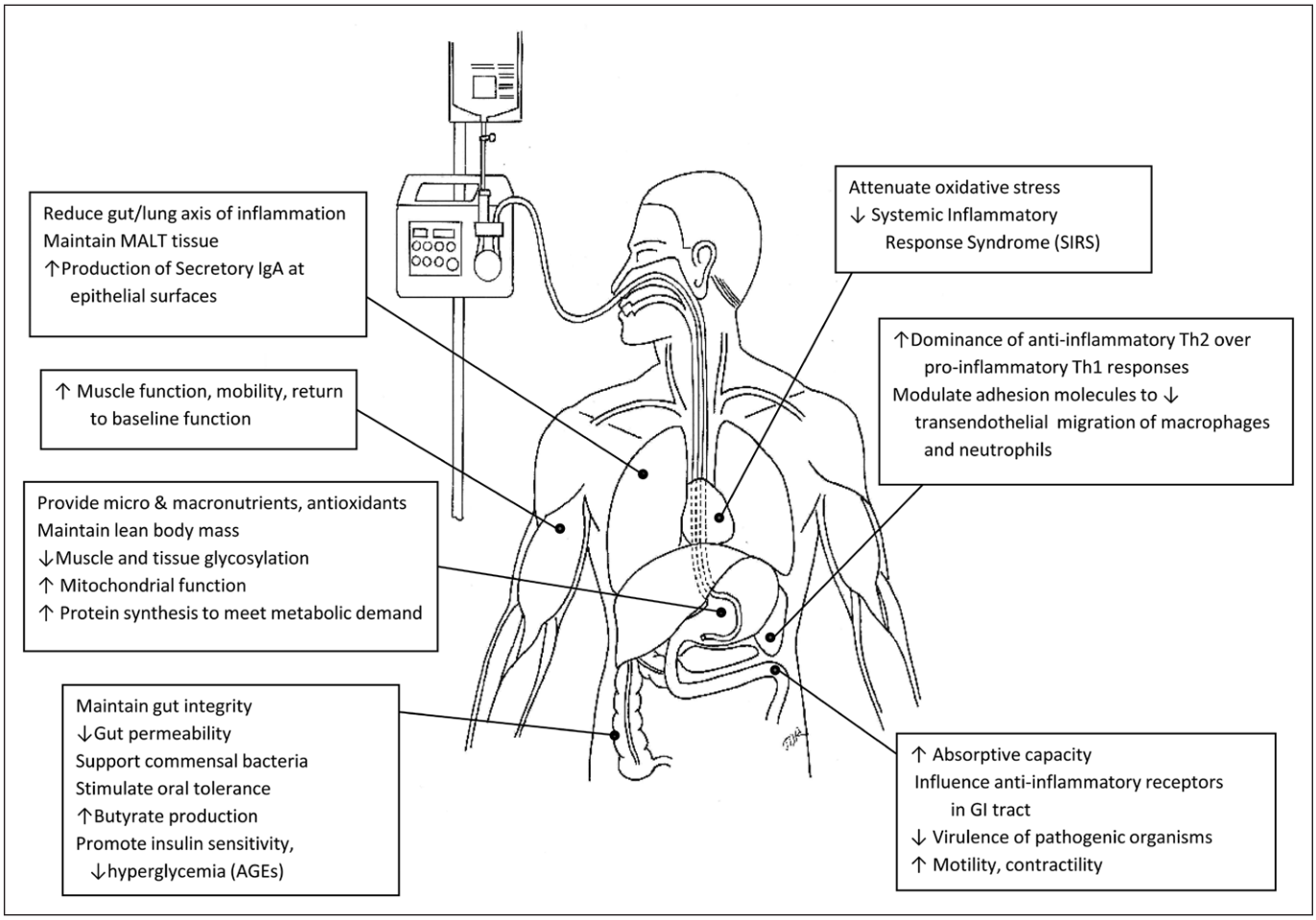

Figure 1. Nutritional and nonnutritional benefits of early enteral nutrition. AGEs = advanced glycolytic endproducts, GI = gastrointestinal, MALT = mucosal-associated lymphoid tissue.

4,000–10,000 calories has been associated with increased organ failure, infection, hospital length of stay, and total complications (7, 13). Large-scale observational studies have shown that increasing nutrient delivery through both earlier initiation and more aggressive administration of enteral feeding to reduce the caloric deficit is associated with improved outcomes (increased ventilator-free days and reduced 60-day mortality) (14). 4) Prospective studies have evaluated the impact of nurse-driven enteral feeding protocols to increase EN delivery and reduce the caloric deficit (both RCTs and trials evaluating patients before and after protocol implementation). Such studies have shown that patients placed on an EN protocol experience earlier initiation and increased delivery of EN, which is subsequently associated with decreased infection, hospital length of stay, and mortality compared with patients not placed on such a protocol (15, 16).

APPROPRIATE ASSESSMENT VARIABLES WITH INITIATION OF NUTRITION THERAPY

When initiating early EN, the usual issues of nutritional assessment, such as dose, composition, and level of infusion within the gastrointestinal tract, may be less important than just getting some EN started. Later, subsequent assessment within 24–72 hours helps identify the patient at high nutrition risk where a more sophisticated and tailored nutrition prescription can be provided. A number of published scoring systems have been developed for nutritional assessment (17). Systems such as the Mini-Nutritional Assessment, Malnutrition Universal Screening Tool, Nutritional Risk Index, and Subjective Global Assessment focus almost entirely on nutritional status alone and the presence of malnutrition and have not really been validated for use in the ICU (17). Two more recent scoring systems focus instead on the concept of nutritional risk. The Nutritional Risk Score 2002 (18) and the NUTrition Risk in the Critically ill Score (19) (**Table 1**) assess both disease severity and nutritional intake to determine nutritional risk and have either been derived from RCTs in critical care (18) or been validated in the ICU setting (19). Prospective data involving both of these scoring systems have shown that high-risk patients who receive sufficient nutrition therapy closer to target goal requirements experience

TABLE 1. Nutrition Assessment Scoring Systems Used to Determine Nutrition Risk

Impaired Nutritional Status		Severity of Disease	
NRS 2002: factors used to determine score[a] (18)			
Absent score 0	Normal nutritional status	Absent score 0	Normal nutritional requirements
Mild score 1	Weight loss > 5% in 3 mo (or) food intake below 50–75% of normal requirement in preceding week	Mild score 1	Hip fracture chronic patients in particular with acute complications: cirrhosis, chronic obstructive pulmonary disease, chronic hemodialysis, diabetes, oncology
Moderate score 2	Weight loss > 5% in 2 mo (or) BMI 18.5–20.5 + impaired general condition (or) food intake 25–50% of normal requirement in preceding week	Moderate score 2	Major abdominal surgery, stroke, severe pneumonia, hematologic malignancy
Severe score 3	Weight loss > 5% in 1 mo (15% in 3 mo) (or) BMI < 18.5 + impaired general condition (or) food intake < 25% of normal requirement in preceding week	Severe score 3	Head injury, bone marrow transplantation, intensive care patients (APACHE II ≥ 10)
Total score = (points for nutritional status) + (points for disease severity) + (points for age)			

Factors	NUTRIC Points			
NUTRIC score: factors used to determine score (19)	0	1	2	3
Age (yr)	< 50	50–74	≥ 75	
APACHE II score	< 15	15–19	20–27	≥ 28
Baseline Simplified Organ Failure Assessment score	< 6	6–9	≥ 10	
No. of comorbidities	0–1	≥ 2		
Days in hospital to ICU admit	0	≥ 1		
Interleukin-6 (mcg/mL)	0–399	≥ 400		
Total score = (total from six separate factors)				

BMI = body mass index, APACHE = Acute Physiologic and Chronic Health Evaluation, NUTRIC = NUTrition Risk in the Critically ill.
[a]If age ≥ 70 yr, add one point.

positive outcome benefits (reduced complications, infection, and mortality) (19, 20).

Relatively simple weight-based equations to predict energy expenditure such as 25–30 kcal/kg/d are appropriate for estimating full caloric requirements in most critically ill patients. Published predictive equations have not been proven to be more beneficial than the weight-based equations (21). However, at extremes of body mass index (BMI), estimates are less accurate (**Fig. 2**), intuitively increasing the need for indirect calorimetry (IC) (22). Unfortunately, greater use of IC is limited by cost, lack of expertise in test interpretation, time spent by the respiratory therapist, intertest variability, and lack of evidence that data obtained from IC alters clinical outcomes. One recent study has emphasized the need to meet not just caloric requirements but to provide sufficient formula to meet daily protein requirements (23). Protein requirements may be approximated by employing weight-based equations using actual body weight (1.2–2.0 g protein/kg/d) (24).

Appropriate adjustments in the calorie and protein goals for the obese critically ill patients have not been standardized. Patients at the extremes of BMI (< 20 or > 40) have been shown to be at high risk with increased morbidity and mortality compared with normal weight controls (25). The curve for mortality versus BMI in the critically ill patient may be U-shaped, suggesting that those patients in the nadir of the curve (overweight, class-1 [BMI, 30–35], or class-2 [BMI, 35–40] obesity) may actually be protected by their obesity. Such findings may be misleading in these patients, as risk may be better defined by the presence or absence of the metabolic syndrome, sarcopenia, reduced functional status, or other comorbidities (25, 26).

Based on limited data from retrospective cohort studies and small RCTs, a reasonable strategy for the obese critically ill patient on either EN or PN is to provide high-protein, hypocaloric feeding (where patients receive 2.0–2.5 g protein/kg ideal body weight/d and 65–70% of caloric requirements) to maintain lean body mass, promote loss of fat mass, and still improve clinical outcome (27–29). Alternatively, there may be some concern that failure to meet caloric requirements during the acute phase of critical illness may not be best therapy. Larger RCTs are needed to determine the optimal caloric and protein requirements in this patient population.

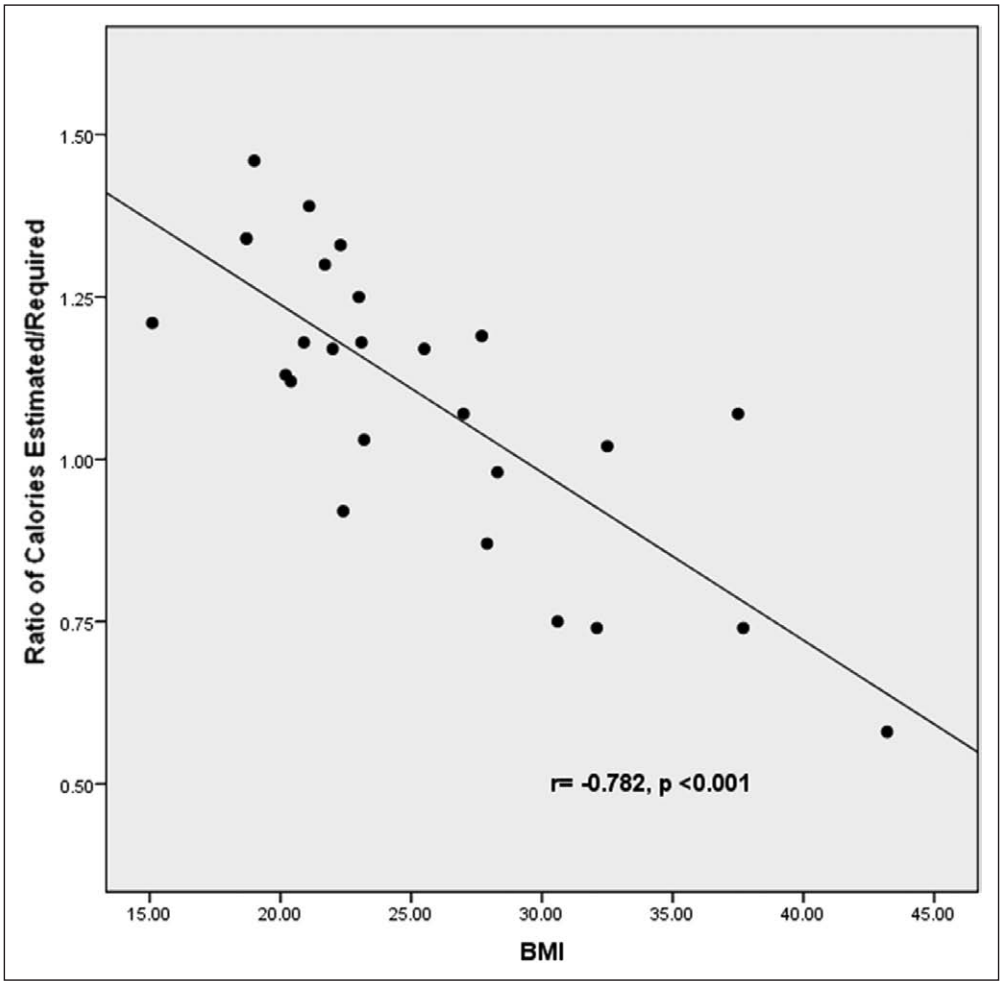

Figure 2. Impact of body mass index (BMI) on estimating energy expenditure. At the extreme ends of the range of BMI, clinicians are less accurate in estimating caloric requirements as a percentage of energy expenditure measured by indirect calorimetry. For example, such error might result in overfeeding patients with a low BMI, while underfeeding obese patients with higher BMI (17). Used with permission from Current Opinion in Clinical Nutrition and Metabolic Care (17).

Once EN is initiated, assessment strategy should focus on assuring that risk for aspiration is minimized, that the rate of delivery is advanced quickly to goal, and that the patient appears to be tolerating the feeding regimen well. Ischemic bowel in the patient on enteral feeding occurs very rarely, unpredictably, and often later in hospitalization (not during the acute resuscitative phase) (although the stable patient is not well defined and clinical judgment is required) (30). It is appropriate and safe to provide EN on pressor agents in the stable patient after adequate resuscitation variables have been met (although the stable patient is not well defined and clinical judgment is required) (31). It is appropriate and safe to feed patients by nasoenteric tube with open abdomen and to continue providing EN with increased protein at 1.5–2.0 g/kg/d through continuous renal replacement therapy (1). Gastric feeding is successful and usually well tolerated in the vast majority of ICU patients (32). Gastric access can often be

obtained quickly, further facilitating earlier initiation of enteral feeds. Decisions on enteral access device, the level of infusion within the gastrointestinal tract, and whether simultaneous aspiration of the stomach is required are all predicated on the degree of tolerance of gastric feeding and risk of aspiration.

Not all ICU patients are candidates for nutrition therapy. It is not appropriate to provide EN to a patient with sufficient oral intake (or who is expected to achieve adequate oral intake within a few days), low stress, or minimal risk, or the patient who is preterminal, hemodynamically unstable, or has discontinuous bowel.

WHAT IS THE OPTIMAL DOSE OF EN?

Several issues in the literature, such as caloric deficit, permissive underfeeding, and trophic feeding, raise the questions as to what is the appropriate dose and optimal goal for nutrition therapy. Intentional "permissive" underfeeding for the nonobese patient on EN is thought to be a simpler strategy with better tolerance and less risk for aspiration or hyperglycemia (33, 34). Early studies supporting this concept were shown to have significant flaws in methodologic design. An RCT by Ibrahim et al (34) evaluating permissive underfeeding used bolus gastric feeding, which severely limited EN delivery while maximizing risk from aspiration. In both retrospective and prospective observational studies by Krishnan et al (33), Ash et al (35), and Arabi et al (36), those patients who received the most nutrition therapy had the worst outcome. This counterintuitive effect may be explained by the highest tertile/quartile groups receiving significantly more calories from PN and propofol (added to the EN) and failure of investigators to adjust for the confounding bias of duration of exposure to EN and timing of advancement to oral diet (33, 35–37).

A more recent large well-designed study of trophic feeding in patients with acute respiratory distress syndrome (ARDS), where patients randomized to receive 10–20 mL/hr (approximately 20 kcal/hr representing 25% of goal calories) for the first 6 days before advancing to goal, was shown to have similar outcome to patients randomized to full feeds (who ended up receiving 80% of goal calories and < 60 g protein/d) (4). This study has strong internal validity. Similar short-term outcome between groups may be explained by the fact that study patients were younger than average ICU patients (mean, 52 yr), had a normal or slightly elevated BMI (mean, 29.9–30.4), and a relatively short ICU stay (average ICU length of stay 6–7 d) and thus were at low to moderate nutritional risk (4, 19). Patients with BMI less than 20, severe chronic lung or liver disease, or refractory septic shock were excluded from the study. The results confirm those of a similarly designed single-center study that enrolled a more heterogeneous patient population of 200 critically ill patients with acute respiratory failure (38). This phase 2 study, which had similar relatively short ICU lengths of stay, also demonstrated no difference in clinical outcomes. Not surprisingly, both studies demonstrated reduced prevalence of gastrointestinal intolerances with the trophic feeding strategy although the overall prevalence of intolerances was relatively low in both groups. Although the strategy of trophic feeding may be an appropriate alternative in some patient populations, it was not shown to be superior to a regimen of full feeding. Extrapolating the results of this study to other patient populations in the ICU may not be appropriate. Although longer term outcomes, including comprehensive measurements of strength and physical functioning, were similar between the two feeding strategies (39), advocating such iatrogenic underfeeding as the generalized routine strategy in higher risk patients may lead to erosion of lean muscle mass resulting in impaired recovery and worse clinical outcomes. Since nurse-driven protocols are designed to meet the needs of a heterogeneous group of ICU patients, embedding the recommendation for intentional underfeeding all ICU patients over the first week into an enteral feeding protocol cannot be recommended. The option of providing trophic feeding should thus be derived from specific criteria and include timely review for advancement.

A patient identified to be at high risk may benefit from more aggressive, more complete nutrition therapy (delivering as close to target goal calories as possible with > 1.5 g protein/kg/d) (19, 20) (**Fig. 3**). High nutrition risk is defined by disease severity (which reflects inflammation), preexisting deterioration of nutritional status (reduced nutrient intake prior to admission, low BMI, or recent weight loss prior to admission) (19, 20), and anticipated prolonged length of stay in the ICU (40). Such patients may benefit from aggressive utilization of prokinetic agents and diverting the level of infusion more distal from the stomach to the small bowel, if initial attempts at providing EN are insufficient in reaching target goals (41). These patients may be harmed by prolonged underfeeding. Adequate feeding to target goal protein and calories becomes more important as risk increases (19, 20) (Fig. 3).

Although the Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients (EPaNIC) study was a randomized trial comparing early versus late supplemental PN (42), the authors used a post hoc analysis of the data to show worse outcomes with increasing calorie and protein delivery by either enteral or parenteral route (43). Although the adverse effect (reduced likelihood of being discharged alive) was shown

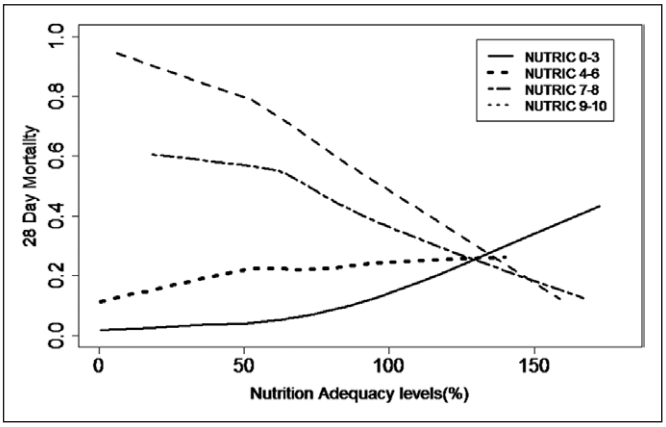

Figure 3. Effect of adequacy of nutrition therapy on mortality by range of NUTRIC score. Patients with higher NUTrition Risk in the Critically ill (NUTRIC) scores of 7–10 showed significant reductions in 28-day mortality with greater adequacy of nutrition therapy. No significant correlation was seen in patients with lower NUTRIC scores of 0–6 (19).

to correlate with increasing percent of goal feeding delivered by the parenteral route alone, authors hypothesized that any specialized nutrition therapy (EN or PN) early in critical illness may be detrimental and recommended withholding "forced mandatory feeding" during the first week of critical illness (43) (which appeared to lead directly to similar recommendations by the 2012 Surviving Sepsis Campaign guidelines) (5). A physiologic mechanism proposed to support this argument is that any feeding inhibits autophagy, thereby preventing its protective effects on cell structure and function from recycling of amino acids and energy homeostasis to regenerate adenosine triphosphate (ATP) (6, 43). However, the effects of autophagy in critical illness are contradictory and difficult to predict (44). Both impaired autophagy and excess autophagy can lead to cell death (44). Energy balance dependent on ATP generated from autophagic proteolysis is poor (44), and net protein synthesis is greater in a setting where exogenous feeding inhibits autophagy and stimulates mammalian Target of Rapamycin pathways (45, 46). Furthermore, prospective studies demonstrating a benefit from withholding all nutrition therapy early in the course of critical illness are uniformly lacking.

FORMULA SELECTION

Although 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 various specialty formulas in an individual patient under specific circumstances. Formulas with arginine, fish oil, and nucleotides are effective in reducing infection and hospital length of stay in the elective major surgery patient but have not consistently been shown to change outcomes in the critically ill patient in a medical ICU (2, 47). Early data supporting the use of formulas with an anti-inflammatory lipid profile demonstrated that omega-3 fish oil delivered by continuous infusion showed clinical benefit in patients with acute lung injury or ARDS on mechanical ventilation (48). More recent studies, however, where omega-3 fatty acids were provided via bolus infusion, did not appear to achieve the same physiologic effects or outcome benefits, and there was some signal that this method of delivery might have been harmful (49, 50). Besides the issue of bolus versus continuous infusion (where bolus infusion failed to alter arachidonic acid levels), the studies involving formulas with an anti-inflammatory lipid profile had other methodological differences (such as control groups getting significantly more protein) which may also have contributed to the divergent results. The addition of supplemental enteral glutamine (to a dose of 0.5 g/kg/d) has been shown in the past in small single-center trials to have outcome benefits for patients with burns or trauma (2). However, this strategy needs to be reevaluated in light of recent trials showing that enteral glutamine in generalized medical ICU patients may cause net harm (AV Zanten, MetaPlus Trial, personal communication, March 20, 2014) (51).

Many enteral formulas are designed with appropriate physiologic rationale for specific patient populations, but outcome benefits in the ICU are not reported and utilization should be on an individual case-by-case basis. Such formulations include small peptide medium-chain triglyceride formulas to promote more efficient nitrogen and lipid absorption in patients with gut dysfunction, a high-protein low-calorie formula for obese patients, and organ-failure formulas for patients with liver disease or acute kidney injury. The physiologic basis for provision of pulmonary or glucose control formulas is not applicable to the current critical care setting.

Numerous trials have shown a benefit from the provision of antioxidant cocktails to ICU patients on continuous feeding (52). A recent, large, blinded RCT failed to demonstrate benefit from antioxidant combination, including selenium supplementation. However, the dose of selenium used was relatively low, and studies demonstrating benefit from selenium investigated cocktails containing selenium at higher doses (52–54). Use of probiotics has shown benefit in the ICU setting when commercially available products are provided, reducing ventilator-associated pneumonia, likelihood to acquire antibiotic-associated diarrhea, pseudomembranous colitis, and possibly overall infections (55–57). The benefits of probiotics appear to be widely variable, species-specific, and may be dose-dependent, all of which should be taken into account when deciding which product to use. It is difficult to provide more specific recommendations at this time.

A number of metabolically active ancillary agents have been proposed for use in the critically ill patient, based on their appropriate physiologic effects (58). β-blockers decrease the hyperdynamic response. Statins have a general pleiotropic effect and can possibly lower septic risk while serving as an antioxidant. Anabolic agents such as insulin, human recombinant growth hormone, glucagon-like peptide 2, and anabolic steroids have been shown to have trophic effects on the gut and/or to build lean body mass. Leucine stimulates protein synthesis, citrulline serves as a substrate for endogenous arginine synthesis and subsequent nitric oxide production, and carnitine may be beneficial in transport of long-chain fatty acids into the mitochondria for oxidation. However, rigorous, well-designed studies demonstrating benefit in clinical outcomes with any of these metabolically active ancillary agents is lacking. In fact, a large randomized clinical trial of growth hormone in ICU patients requiring mechanical ventilation showed increased mortality (59). With respect to growth hormone and anabolic steroids, giving high doses in a nonpulsatile manner may be harmful, but lower doses provided in a way that preserves pulsatility perhaps later in critical illness in association with exercise (to reduce anabolic resistance) warrants further exploration. As such, use of all of these agents in this manner in the ICU setting should be considered experimental and should neither be used outside a research protocol setting nor extrapolated for use in the general heterogeneous ICU patient population (58).

STRATEGIES TO PROMOTE DELIVERY

Gut dysfunction in critical illness involves segmental dysmotility, reduced villous height and absorptive surface, disrupted excretion of digestive enzymes, reduced production of trophic epithelial hormones and secretory IgA, and alterations in gut microbiota (60). The majority of ICU patients

can be fed through the gut dysfunction, with the feeding itself leading to improved gut integrity, better contractility, increased brush border enzymes, and restoration of the commensal bacteria (8, 60).

Because many factors impede delivery of early EN in the ICU setting, patients routinely get approximately 50% of the calories and protein that are required (61, 62). Reluctance to initiate early feeds arises from the difficulties in defining full resuscitation and stabilization as well as the perception that early enteral feeding is not a priority. Cessation of delivery of EN for reasons related to nursing care, tests and procedures, or perceived intolerance is estimated to be inappropriate 66% of the time (61). A common misconception exists that feeding is inappropriate in the setting of high gastric residual volumes (GRVs) (63), stable blood pressure while on pressor therapy (31), or hypoactive bowel sounds with evidence of ileus (60). Eliminating use of gastric residual volume as a clinical monitor surprisingly has been shown to promote increased EN delivery without adverse sequelae in certain patient groups (64). However, some clinicians may be reluctant to forego use of gastric residual volume in surgical ICU or other difficult-to-feed patient populations.

Institutional practice can be changed by adopting specific strategies to promote delivery of EN. Routine underdelivery of prescribed calories can be countered successfully by simply setting a higher than needed goal and overordering calories (prescribe goal calories at 120%, such that patients end up getting 100% of requirements). Volume-based feeding is a strategy that identifies the total goal volume of EN (based on requirements or target calories) to be delivered over an entire 24 hours (65). Traditional rate-based feeding is calculated from the total 24-hour goal volume divided into an appropriate hourly rate delivered throughout the day. Interruptions in delivery in the latter system because of diagnostic tests or procedures result in lost volume as patients are restarted at the same rate when they return to the floor. Following any period of cessation with volume-based feeding, nurses are empowered to increase the rate to make up for lost time, such that the rest of the entire volume is delivered over the period of time remaining (65). "Top-down" or "de-escalation" therapy represents maximal therapy with multiple strategies initiated at the start of enteral feeding to promote tolerance, followed by de-escalation of therapy (and removal of some strategies) over the next few days (e.g., the "Enhanced Protein-Energy Provision via the Enteral Route in Critically Ill Patients" protocol) (66). Such strategies include starting at goal rate with prokinetic therapy, using volume-based feeding, monitoring the caloric deficit, elevating the head of the bed, setting a higher cutoff value for GRV (400–500 mL) or eliminating their routine use in all critically ill patients, incorporating postpyloric infusion with a small peptide formula, and adding supplemental protein during the first few days of feeding (1, 4, 64, 66). Development and implementation of nurse-driven enteral feeding protocols (containing set orders to initiate feeds, set the goal and ramp-up rate, determine appropriate GRVs, etc.) have also been shown to increase delivery of EN (67). Such protocols should be modified by the individual institution depending on local expertise, culture of the ICU, and nursing practice to enhance utilization.

Although not yet available for critical care nutrition, the concept of a nutrition bundle ties together key elements from societal guidelines, identifying those few most important action items for recommendation, that when performed together are most likely to impact outcome (**Table 2** for potential bundle elements). Large-scale prospective databases have long been used to provide audit and feedback to programs, allowing comparison with other ICUs and institutions. An international audit/feedback system database (http://www.criticalcarenutrition.com) based on compliance with the Canadian Clinical Practice Guidelines showed that greater compliance was associated with greater delivery of EN (68).

TABLE 2. Potential Elements for Nutrition Bundles

Nutrition bundle: patient-specific
Initiate EN within 24–48 hr of admission to the ICU
In appropriate high-risk patients, early, rapid advancement of EN targeting calorie and protein goals by 48–72 hr
Elevate head of bed 30–45° when patient illness allows
In appropriate patients, administer commercially available probiotic solution by infusion per nasoenteric tube and swabbing the oropharynx twice daily (effects may be species- and diagnosis-specific)
Consider initiating prokinetic agent upon initiation of EN, stop as tolerance is achieved
Nutrition bundle: appropriate system-specific
Implement and enforce nurse-driven protocols with institution-specific strategies (i.e., volume-based and top-down) to enhance EN delivery
Full nutrition assessment by nutrition specialists within 72 hr of ICU admission
Monitor and display caloric balance (or caloric deficit) on all patients
Judicious use of parenteral nutrition in clearly defined patients initiated at appropriate times only
Participate and submit information into database to promote performance audit and feedback

EN = enteral nutrition.

Challenging traditional dogma is just the beginning of overcoming barriers which prevent change in practice. Barriers to implementation of EN protocols and aggressive early feeding derive from perceived lack of supporting evidence, poor implementation processes, systems characteristics (financial regulations, organizational structure, lack of resources), individual provider behavior, and patient complexity (69, 70). Moving forward, strategies designed to reduce the barriers will likely improve our abilities to deliver nutrition to critically ill patients.

ROLE OF PN IN THE ICU SETTING

Because PN has a much narrower risk-to-benefit ratio than EN in the critical care setting, identifying the appropriate candidate and choosing the optimal timing of initiation for PN is often very difficult. Although data are lacking, it is reasonable to initiate exclusive PN during the first week of hospitalization in the critically ill patient for whom EN is not feasible, if the patient shows signs of malnutrition (BMI < 18.5, actual weight < 90% ideal body weight, or > 10–15% weight loss over previous 6 mo) (1) and is expected to be unable to receive any EN for a number of days. If the patient was previously well nourished and determined to be at low to moderate risk at admission to the ICU (and EN is not feasible) (19, 20), initiation of exclusive PN should be considered only after the first 7 days of hospitalization (1).

Three large well-designed RCTs have shown conflicting results on the benefit of adding supplemental PN to hypocaloric EN in the early phase of critical illness (41, 42, 71). The largest EPaNIC study by Casaer et al (42) showed net harm from early supplemental PN initiated on day 3 compared to late PN started after 7 days. Since both groups got an equal volume of EN delivery over the first week, any differences in outcome would be attributed to the timing of receipt of the PN calories and protein. However, infusion of a large IV glucose load prior to PN in the early group only and other issues of methodology (use of tight glucose control) limit interpretation and the applicability of results to patient care (42). By contrast, two subsequent trials by Heidegger et al (41) and Doig et al (71) suggest that early PN may be safe but has limited to no outcome benefit over hypocaloric EN alone. Although the optimal timing remains unclear, adding supplemental PN to hypocaloric EN should be considered in the high-risk patient, at some point after the first few days in the ICU if enteral feeds are providing less than 60% of caloric and protein goal requirements (mimicking the control group who received late PN in the EPaNIC protocol) (41, 42). There may be little, if any, role for supplemental PN in the low-risk patient getting hypocaloric EN.

In the appropriate candidate, additional factors may help maximize the benefit from PN. RCTs in nonobese patients on PN have shown that permissive underfeeding in which 80% of caloric requirements are provided may reduce insulin resistance, avoid the potential for overfeeding, and improve outcome (72). In the past in the United States, the only parenteral lipid formulation available is a more inflammatory soy-based product, and as such simply withholding lipids over the first week of hospitalization may improve outcome (2). Outside the United States, newer types of lipid emulsions (olive oil, fish oil, and the combination soy, medium-chain triglycerides, olive oil, and fish oil) show promise in reducing the inflammatory profile of the parenteral lipids, and their use has been shown to have better outcome than parenteral soy-based therapy (62). Just recently, an alternative olive oil–based lipid emulsion has been introduced and approved for use in the United States (73). Whereas previous trials suggested a benefit from supplemental parenteral glutamine (74), recent RCTs have questioned the benefit of adding glutamine IV to the PN regimen in ICU patients (75–77). A large study in medical ICU patients demonstrated no benefit and potential worse outcomes with combined enteral and parenteral glutamine supplementation. The detrimental effect was especially evident in the subgroup of patients with renal failure and multisystem organ failure (51).

FUTURE TRENDS

Newly recognized physiologic mechanisms in critical illness and emerging alternative management strategies will likely impact the manner in which specialized nutrition therapy is provided in the future. Combining early EN with aggressive resistance exercise and early mobility in the ICU has been shown to promote the uptake and utilization of protein with maintenance of muscle mass and enhancement of function. Prospective randomized trials on the effect of exercise in the ICU have shown reduced ICU length of stay, duration on mechanical ventilation, and total hospital length of stay (78, 79). The use of probiotics in critically ill patients is likely to increase, as manipulation of intestinal microbiota has already shown the potential to reduce ventilator-associated pneumonia, likelihood for acquiring antibiotic-associated diarrhea or *Clostridium difficile*, and risk of colonization with vancomycin-resistant enterococci (55–57, 80, 81). A newly described persistent inflammatory catabolism syndrome (PICS) highlights the long-term adverse metabolic and immune sequelae from a prolonged ICU length of stay, where a patient progresses to a chronic critical illness characterized by a pattern of chronic inflammation, catabolism, degradation of lean body mass, and a shift in immune responses to an ineffective production of myeloid-derived suppressor cells by the bone marrow (82). Such patients are often transferred from the ICU to long-term acute care facilities and never return to baseline function (82). Whether aggressive early nutrition therapy attenuates PICS, restores bone marrow function, or improves long-term outcome is yet to be tested.

CONCLUSIONS

Clearly, more large RCTs are needed to form a better evidentiary basis for these recommendations. However, to date, the existing data suggest that early EN represents a primary therapeutic intervention designed to achieve metabolic manipulation rather than simply supportive therapy designed to prevent the ravages of malnutrition alone. Nutrition therapy should be started as soon as possible after initial resuscitative efforts, immediately following acute lifesaving maneuvers to restore oxygenation and circulatory status. Emphasis should focus on

nutrition strategies that improve outcome. The appropriate level of standardization has not yet been achieved for nutrition therapy, as it has in other areas of critical care. Protocolizing nutrition therapy now, modified for each institution (based on available expertise, local barriers, enabling factors, existing culture, and potential leadership in the ICU), is important to ensure that each patient is afforded the opportunity to get optimal evidence-based nutrition care.

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