Critical Care

Updates in Nutrition Support for Critically Ill Adult Patients

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Specialized nutrition support is often employed in critically ill patients who are unable to maintain volitional intake. The Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) recently updated guidelines for the provision of nutrition support in critically ill patients. The purpose of this review is to summarize key changes from the previous guidelines as they relate to recently published literature, which will aid the hospital pharmacist in optimizing nutrition support therapies in the critical care setting.

INTRODUCTION

The Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) recently updated guidelines regarding the provision of nutrition support in critically ill patients.¹ This review aims to discuss key studies published over the past 5 years that have impacted guideline recommendations on the delivery of energy, protein, and intravenous fat emulsions (IVFE) in critically ill adults. Several important studies relating to these topics, which were published after guideline revision was in progress, will also be reviewed.

ENERGY

Nutritional Assessment and Timing of Nutrition Therapy

Much debate exists regarding the optimal nutrition regimen for critically ill patients. There is little debate that initiating enteral nutrition (EN) with 24 to 48 hours is appropriate for most intensive care unit (ICU) patients who do not have contraindications to EN. However, questions surrounding optimal nutritional goals and when patients may benefit from early parenteral nutrition (PN) have been addressed by recent guidelines. One important factor to establish for all ICU patients to guide decisions for energy goals is whether or not a patient is at “high nutrition risk.”

The guidelines suggest that a validated score, such as the NUTRITION Risk in the Critically ill (NUTRIC) score or Nutritional Risk Screening 2002 (NRS 2002), be utilized to determine nutrition risk in ICU patients.¹

The NUTRIC score, which incorporates age, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA), co-morbidities, days from hospital to ICU admission, and interleukin-6 (IL-6), was developed to link starvation, inflammation, and clinical outcomes.² Patients are scored from 0 to 10, with scores 6 and higher indicating high nutrition risk.² In a medical-surgical ICU population, NUTRIC was predictive of 28-day mortality, with high nutrition risk patients in the ICU for more than 3 days benefiting more from nutrition support than low nutrition risk patients. There was effect modification in the logistic regression model on the risk of mortality by NUTRIC score and caloric target attainment, suggesting aggressive nutrition could improve outcomes in high-risk patients.² The original NUTRIC score is limited by the incorporation of IL-6, which is not readily available in many institutions. Another study evaluated a modified-NUTRIC score omitting IL-6 and found that scores 5 and higher still indicated high nutrition risk.³ Rahman et al evaluated this modified-NUTRIC

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score and found that mortality increased by 1.4 (95% CI, 1.3-1.5) for every point increase on the modified-NUTRIC score. Similar to the NUTRIC validation study, mortality was decreased in patients with elevated modified-NUTRIC scores who received adequate nutrition, implying that increased nutritional intake can decrease mortality in high-risk patients.⁴ Still, even the modified-NUTRIC score is limited by other variables required for its calculation that may not be easily obtained, particularly APACHE II, which can be difficult to calculate at bedside and may lack validity in certain ICU subsets, such as trauma.⁵

The NRS 2002 is also recommended by the European Society for Clinical Nutrition and Metabolism guidelines.⁶ Like the NUTRIC score, the NRS 2002 considers nutrition status, including body mass index (BMI), recent weight loss, and recent nutritional intake, in addition to disease severity. Scores greater than 3 (out of a possible 6 points) indicate patients are nutritionally at risk and scores 5 and higher indicate patients are at high nutrition risk.^{1,6,7} Data regarding severity of illness and undernutrition were taken from randomized controlled trials (RCTs), converted to a numeric score, and validated against 128 RCTs in which nutrition support positively impacted clinical outcomes, as distinguished from trials in which nutrition support did not affect clinical outcomes.^{7,8} Two RCTs also found the NRS 2002 identified patients most likely to benefit from nutrition support.^{9,10} Although recommended by current guidelines, the NRS 2002 has been criticized as inappropriately categorizing all ICU patients as being at high nutrition risk.^{2,4}

Based on these data, the 2016 SCCM/A.S.P.E.N. guidelines categorize patients with an NRS 2002 score of 5 or higher or a modified-NUTRIC score 5 or higher (or >6 if using the original NUTRIC score) as being at high nutrition risk. It is suggested to avoid specialized nutrition support in low-risk patients over the first week of hospitalization, although high-risk patients should receive nutrition support, initiated within the first 24 to 48 hours after admission, preferably with EN. A significant and controversial deviation from the previous guidelines is the timeframe to initiate PN in patients unable to receive EN. Previously it was recommended to withhold PN for 7 days in these patients,¹¹ but the new guidelines recommend prompt initiation of PN in nutritionally at-risk patients unable to tolerate EN.¹ An exception is patients with sepsis, who should not receive exclusive or supplemental PN early in their disease course, irrespective of nutrition risk.¹ Data supporting the

use of PN in early sepsis are lacking, and concern exists for potential morbidities, including increased ICU and hospital stays, infection rates, and duration of organ support.^{1,12,13} Although the timing of nutrition support in high nutrition risk patients, specifically early PN, may be controversial due to changes from previous recommendations, it is supported by data showing improved outcomes with early aggressive nutrition support in this patient population. With greater recognition of the need for nutrition risk assessments, further evidence regarding the use of NUTRIC or NRS 2002 to determine appropriateness for initiating EN and PN may be forthcoming.

Nutritional Requirements

The decision to utilize full feeding (>80% goal), trophic feeding (10-20 mL/h or 10-20 kcal/h up to a maximum of 500 kcal/day), or permissive underfeeding (50%-80% of goal) in various ICU populations has been controversial, with much recent literature focused on this topic (Table 1).^{1,14-19} The benefits of EN in critically ill patients are well known and include maintenance of the functional and structural integrity of the gut, decreased infectious complications, shorter hospital stays, and lower mortality.¹ The specific amount of EN required for improved outcomes continues to be questioned. Trophic feeding has been theorized to provide a sufficient amount of EN to maintain gut integrity while decreasing incidence of EN intolerance. Rice et al evaluated trophic feeding versus full-feeding in medical ICU patients with acute lung injury (ALI) for the first 6 days of mechanical ventilation.¹⁴ Ventilator-free days, ICU stay, and mortality rates were not significantly different between groups, although patients who received trophic feeding experienced fewer elevated gastric residual volumes (GRV). In a similarly designed trial in patients with ALI, initial trophic feeding was again compared with full enteral feeding for the first 6 days of mechanical ventilation.¹⁵ No differences were seen between groups in ventilator-free days, mortality rates, or infection. The full-feeding group experienced more days with elevated GRV, constipation, and vomiting, but no differences were seen in diarrhea, aspiration, abdominal distention, or cramping. No benefits or harms were observed in these trials, but their results must be interpreted carefully. Although both studies sought to compare trophic to full feeding, the fully fed groups received only 75% to 80% of their prescribed caloric goal, which is more appropriately described as permissively underfed than "fully fed." Trophic feeding inherently results in both lower energy and protein

Table 1. Summary of recent studies evaluating nutritional requirements

Study	N	Study design	Intervention	Nutrition received	Outcomes
Rice 2011 ¹⁴	200	Single-center, randomized, open-label trial	Trophic feeding (10-20 mL/h) vs full feeding (25-30 kcal/kg IBW/day nonprotein calories; 1.2-1.6 g protein/kg IBW/day)	Trophic: average of 15.8% prescribed kcal vs Full: average 74.8% prescribed kcal ($p<.001$)	No differences in ventilator-free days (23 vs 23; $p=.90$), ICU-free days (21 vs 21; $p=.64$), or mortality (22.4% vs 19.6%; $p=.62$) Trophic feeds associated with fewer elevated GRV (2% vs 8%; $p<.001$)
The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network 2012 ¹⁵	1,000	Multicenter randomized, open-label trial	Trophic feeding (10-20 mL/h) vs full feeding (25-30 kcal/kg IBW/day nonprotein calories; 1.2-1.6 g protein/kg IBW/day)	Trophic: 25% prescribed goal vs Full: 80% prescribed goal ($p<.001$)	No difference in ventilator-free days (14.9 vs 15.0; $p=.89$) No difference in 60-day mortality (23.2% vs 22.2%; $p=.77$) No difference in infections (VAP: 7.3% vs 6.7%, $p=.72$; <i>Clostridium difficile</i> : 3% vs 2.6%, $p=.77$; bacteremia: 11.6 vs 9.3%, $p=.24$) Trophic feeds associated with fewer days with elevated GRV (2.2% vs 4.9%; $p<.001$), vomiting (1.7% vs 2.2%; $p=.05$), and constipation (2.1% vs 3.1%; $p=.003$)
Arabi 2011 ¹⁶	240	Single-center, randomized, controlled trial	Permissive underfeeding (60%-70% of caloric goal) vs target feeding (90%-100% caloric goal) using Harris-Benedict equation	Permissive underfeeding: 59.0% caloric goal vs Target group: 71.4% caloric goal ($p<.0001$)	Lower hospital mortality with permissive underfeeding (30.0% vs 42.5%; RR, 0.71 [95% CI, 0.50-0.99]; $p=.04$) No significant differences in 28-day mortality (18% vs 23.3%; RR, 0.79 [95% CI, 0.48-1.29]; $p=.34$)
Singer 2011 ¹⁷	130	Single-center, prospective, randomized pilot	Tight targeted caloric intake (determined by repeated IC) vs standard nutrition (25 kcal/kg/day)	Tight caloric intake: 2,086 kcal/day vs Standard: 1,480 kcal/day ($p=.01$)	Standard group had shorter durations of mechanical ventilation (16.1 vs 10.5 days; $p=.03$), fewer infectious complications (37 vs 20 occurrences; $p=.05$), decreased ICU stay (17.2 vs 11.7 days; $p=.04$), but higher mortality rates (47.7% vs 32.3%; $p=.058$)
Arabi 2015 ¹⁸	894	Multicenter, unblinded, randomized trial	Moderate caloric intake (40%-60% of goal) vs standard caloric intake (70%-100% goal) per the Penn State or 1992 Ireton-Jones equations Protein 1.2-1.5 g/kg/day (both groups)	Caloric intake: Moderate caloric intake: 46% goal vs Standard: 71% ($p<.001$) Protein: mean 0.7 g/kg/day (both groups)	No differences in 90-day mortality (27.2% vs 28.9%; RR, 0.94 [95% CI, 0.76-1.16]; $p=.58$), length of ICU stay (13 vs 13 days; $p=.46$), hospital stay (28 vs 30 days; $p=0.24$), or days free from mechanical ventilation (77 vs 75 days; $p=.48$)
Braunschweig 2015 ¹⁹	78	Single-center, prospective randomized, controlled trial	Intensive nutrition (EN within 6 hours of hemodynamic stability, volume-based EN, optimization of oral diets) vs standard therapy	Energy: Intensive therapy 84.7% kcal goal vs Standard 55.4% kcal goal ($p<.0001$) Protein: Intensive therapy 76.1% goal vs Standard therapy: 54.4% ($p<.0001$)	No differences in hospital length of stay (27.2 vs 22.8 days; $p=.33$), ICU length of stay (15.5 vs 16.1 days; $p=.83$), days on ventilator (6 vs 7 days; $p=.85$), or infections (12% vs 21%; $p=.29$) Higher mortality seen with intensive medical therapy (40% vs 15.8%; $p=.017$)

Note: EN = enteral nutrition; IC = indirect calorimetry; IBW = ideal body weight; GRV = gastric residual volume; RR = relative risk; VAP = ventilator-associated pneumonia.

intake; even patients assigned to “full feeds” did not receive goal protein. Therefore, an alternative conclusion to these trials has been described: Achieving closer to caloric targets while providing insufficient protein does not improve clinical outcomes.²⁰ Indeed, adequate protein provision, not total energy, may be more significant in improving clinical outcomes in the critically ill population, which could explain why no outcome differences were seen. These studies were also largely comprised of medical ICU patients and excluded patients more likely to be at increased nutrition risk, thus these results may not be applicable to other ICU populations. Trophic feeding may be a safe initial EN regimen in low- to moderate-risk patients, but it may be inappropriate for patients at high nutrition risk, especially for more than 7 days.¹ Additional research in this area is necessary.

The practice of permissive underfeeding in the medical or mixed medical-surgical ICU is supported by multiple small studies that suggest improved clinical outcomes compared with full feeding, potentially due to fewer complications from hyperglycemia, electrolyte imbalances, and feeding intolerances. Arabi et al found that permissive underfeeding was associated with lower (but non-statistically significant) 28-day mortality compared to target feeding.¹⁶ Fully fed patients received only 71% of their prescribed nutrition compared with 59% in the underfed group, so differences between the interventions were smaller than intended; this makes it difficult to determine whether outcome differences were actually due to nutrition strategies. A study of mostly medical ICU patients conducted by Singer and colleagues showed mixed results. They found that patients who were underfed for up to 14 days had shorter durations of mechanical ventilation, fewer infectious complications, and decreased ICU stay but non-significantly higher mortality rates compared with patients receiving target caloric intakes.¹⁷

More recently, Arabi and colleagues evaluated the effects of permissive underfeeding versus standard enteral feeding in a mixed ICU population.¹⁸ Patients were stratified to receive moderate caloric or standard caloric intake for up to 14 days, with full protein doses prescribed in both patient groups. No significant differences in mortality, length of stay, or days free from mechanical ventilation were seen, which implies there is no harm in permissive underfeeding in this study population. Although both groups achieved their prespecified nutrition targets, many would argue that both groups were underfed, as permissively underfed patients received 46% of goal kcal and standard patients

received 71% of prescribed kcal. Based on the reported mean body weight, patients received an average protein intake of 0.7 g/kg/day, which is significantly below recommended targets of 1.2 to 2 g protein/kg/day.¹ The study population was fairly young (mean age of 50 years), consisting of primarily medical ICU patients who were likely not at high nutrition risk (mean BMI of 29), and approximately 70% were recruited from one institution. These results must be interpreted cautiously with close consideration of the patient types who were not included, such as elderly, malnourished, and non-medical ICU patients (ie, trauma, surgery, or burn).

In contrast to underfeeding strategies, a recent trial of medical and surgical ICU patients conducted by Braunschweig and colleagues evaluated intensive medical nutrition therapy (IMNT), which included early EN, volume-based feeding strategies, and optimization of oral diets, compared with standard nutrition support in patients with ALI.¹⁹ No differences were seen in hospital or ICU lengths of stay, mechanical ventilation days, or infections, but higher mortality was observed in the IMNT group, causing early cessation of the trial. The mean age of patients studied was 55 years, approximately 63% of patients were considered to have a normal nutritional status, and patients in the intervention group had significantly lower APACHE II scores than the control group (23.4 vs 27.7; $p = .03$), indicating that the treatment group may be less likely to benefit from aggressive nutrition support. The degree of heterogeneity between groups is difficult to determine, as information was not provided concerning the distribution of ICU subtype, etiology of patients' ALI, treatments received for ALI, or use of medications that could affect feeding tolerance (paralytic infusions, vasopressors, prokinetic agents, corticosteroids). Due to these limitations, few conclusions can be made from this trial, and further studies are needed to clarify whether IMNT is actually harmful in a well-nourished ICU population with ALI.

In summary, patients at high nutrition risk (NRS 2002 ≥ 5 , modified-NUTRIC score ≥ 5 , or NUTRIC score > 6) should receive specialized nutrition support, preferably with EN. Nutrition support is recommended to be initiated as quickly as possible and advanced to goal as quickly as possible over 1 to 2 days in this patient population, whereas patients with acute respiratory distress syndrome (ARDS), with ALI, or expected to require 72 hours or more of mechanical ventilation are recommended to receive EN via either full or trophic feeding.¹ More research is required to make definitive recommendations regarding trophic, permissive underfeeding, or

intensive nutrition strategies in critically ill patients. Additionally, the routine use of validated nutrition scores could assist with determining patients who may benefit most from various feeding strategies.

PROTEIN

The stress response during critical illness leads to uncontrolled catabolism, which underscores the importance of establishing optimal nutrition support regimens for ICU patients.²¹ Current guidelines recommend a protein intake of 1.2 to 2 g/kg actual body weight per day for most patients in addition to ongoing evaluation of adequacy of protein provision.¹ The use of serum protein markers, such as prealbumin and C-reactive protein, to assess protein adequacy is not validated in critically ill patients and is therefore not recommended. While nitrogen balance (NB) has historically served as a surrogate marker for protein adequacy, its utility has been questioned due to a lack of evidence correlating nitrogen equilibrium with improved clinical outcome.²² However, limited evidence from a prospective study in patients requiring continuous renal replacement therapy (CRRT) found that for every 1 g/day increase in NB, the probability of survival increased by 21% (odds ratio [OR], 1.211; 95% CI, 1.017-1.443; $p = .03$).²³ Additionally, an increasing number of studies indicate that providing adequate protein, and not necessarily total energy, may be one of the most important nutrition interventions to improve outcomes in critically ill adults.¹

A higher protein goal is supported by several recent observational studies demonstrating an association between adequate protein intake (ie, at least 1.2 to 1.5 g/kg/day) and improved clinical outcomes in critically ill patients (Table 2).²⁴⁻²⁶ The impact of energy and protein provision on clinical outcomes was evaluated in ICU patients with severe sepsis ($n = 100$) or burns ($n = 13$).²⁴ Patients with a 24-hour urine output of less than 500 mL or who required renal replacement therapy were excluded. Patients were stratified according to the amount of protein they received during the study period (low, medium, high). Nitrogen balance was different only between the low versus high groups (mean protein equivalents: -0.59 vs -0.2 g/kg/day; $p < .01$). Patients in the high-protein group had a significantly lower risk of hospital mortality. Although overall ICU mortality did not differ, the Kaplan-Meier survival probability at day 10 differed among protein groups (low, 49%, medium, 79%, and high, 88%; $p = .021$). Energy provision was not associated with ICU mortality. These

data should be interpreted cautiously owing to the observational study design and the differences in findings between the nominal and time-to-event analyses. EN may not have been provided as aggressively in patients not expected to survive. This study also took place during 2 separate time periods with major differences in methods noted (ie, differences in indirect calorimeters used and frequency of measurements). Finally, although not reported to be significantly different between study periods, ICU mortality was higher during period 1 versus 2 (29% vs 16%). Weijs et al evaluated the impact of early (day 4) energy and protein provision on mortality in medical and surgical ICU patients who were on mechanical ventilation for 72 hours or longer.²⁵ Most patients (73%) received energy entirely from EN, while the remaining received either PN alone (1%) or EN plus PN (26%). Overall hospital mortality was higher in patients with sepsis (48.7 vs 33.9%; $p = .003$); however, neither protein nor energy intakes were associated with mortality. In the cohorts of patients with sepsis or overfeeding, protein intake was not associated with mortality. In the cohort of patients without sepsis, results differed based on whether or not patients were overfed (per indirect calorimetry measurements). In those who were not overfed, protein intake of greater than or equal to 1.2 g/kg/day was independently associated with a significant reduction in hospital mortality. However, in patients without sepsis who were overfed, protein intake was not associated with mortality. This suggests harm from overfeeding may outweigh the benefits of achieving adequate protein intake and ICU patients without sepsis may gain more from adequate protein intake than patients with sepsis. However, due to the post hoc analysis design, these results are only hypothesis-generating and should be validated in future randomized, controlled trials. Whereas Allingstrup et al excluded patients with renal failure, this study included this patient population. In fact, current guidelines recommend the same protein goals of 1.2 to 2 g/kg actual body weight for critically ill patients with acute kidney injury to account for lean body mass catabolism.¹ While authors note that protein goals were not reduced for renal replacement therapy, goals were not increased in patients receiving CRRT – a population in which protein doses of up to 2.5 g/kg/day are recommended.¹ It would be expected that more patients in the cohort of patients with sepsis would have required CRRT, although these numbers were not reported.

In a retrospective analysis of existing data from the International Nutrition Survey 2013, the influence

Table 2. Summary of recent studies evaluating protein intake in critically ill adults

Study	N	Study design	Energy target	Protein target	Protein received, mean	Outcomes
Allingstrup 2012 ²⁴	113	Single-center, prospective, observational	Initial goal of 25-30 kcal/kg/day, then adjusted based on IC results	Initial goal of 1.2- 1.5 g/kg/day, then adjusted based on 24-hr urea nitrogen results	Low protein (<i>n</i> =37): 0.79 g/kg/day Medium protein (<i>n</i> =38): 1.06 g/kg/day High protein (<i>n</i> =38): 1.46 g/kg/day	ICU mortality was associated with protein intake (HR, 0.98 [95% CI, 0.96-0.99]; <i>p</i> =.01) ICU mortality was not associated with total energy provision (HR, 0.99 [95% CI, 0.99-1.00]; <i>p</i> =.20)
Weijs 2014 ²⁵	843	Single-center, prospective, observational, post hoc analysis	Initial goal based on Harris-Benedict (with correction factors of 10% for activity and 20% for stress), then adjusted based on IC results	1.2-1.5 g/kg/day of preadmission body weight or adjusted body weight if BMI was <20 or >30 kg/m ²	Patients without sepsis who were <i>not</i> overfed: 0.69 g/kg/day (<i>n</i> =419)	In patients without sepsis (who were <i>not</i> overfed), protein intake of ≥1.2 g/kg/day was independently associated with a significant reduction in hospital mortality (OR, 0.42 [95% CI, 0.21-0.83]; <i>p</i> =.013) In patients without sepsis (who <i>were</i> overfed), protein intake was <i>not</i> associated with mortality (OR, 0.91 [95% CI, 0.59-1.4]; <i>p</i> =.666)
Nicolo 2016 ²⁶	2,828	Retrospective analysis of existing data from 202 institutions	24 kcal/kg/day (mean prescribed goal across study sites)	1.2 g/kg/day	For patients in ICU ≥4 days [group 1] (<i>n</i> =2,828): <80% prescribed: 44 g/day, ≥80% prescribed: 75 g/day For patients in ICU ≥12 days [group 2] (<i>n</i> =1,584): <80% prescribed: 50 g/day, ≥80% prescribed: 76 g/day	Protein intake of ≥80% goal was associated with a significant reduction in mortality (adjusted OR, 0.68 [95% CI, 0.5-0.91]) while intake of ≥80% energy goal was not (adjusted OR 0.89 [95% CI, 0.71-1.12])

Note: BMI = body mass index; HR = hazard ratio; IC = indirect calorimetry; ICU = intensive care unit; OR = odds ratio.

of protein intake on 60-day mortality was evaluated in a primarily medical ICU population.²⁶ Patients were categorized by length of ICU stay (≥4 days [group 1] and ≥12 days [group 2]), and logistic regression analyses were performed to compare mortality outcomes between patients who received less than 80% and greater than or equal to 80% of prescribed goal. Protein intake of greater than or equal to 80% goal was associated with a significant reduction in mortality, while intake of greater than or equal to 80% energy goal was not. Similar results were seen in group 2. This study is limited by its retrospective

design; however, the included data were part of a comprehensive quality analysis survey, and investigators were able to account for all sources of measurable caloric and protein intake (eg, EN, PN, supplements, medications). These data were not included as energy and protein intakes once a patient was started on an oral diet. Thus, the results should accurately reflect what the patients actually consumed. Still, the average amount of protein consumed in patients requiring an ICU stay of 4 days or longer was only 60.5% of the 1.2 g/kg/day goal, which falls significantly short of current recommendations.¹

These recent studies suggest protein adequacy is of significant importance for critically ill patients, and prospective, randomized trials are needed to confirm these findings. Notably, standard EN formulas are not designed to meet the higher protein requirements of critically ill patients, and protein is largely underdelivered in clinical practice. Therefore, the routine use of protein supplements for ICU patients should be considered in order to achieve adequate protein intake.

INTRAVENOUS FAT EMULSIONS

There is much debate surrounding the use of intravenous fat emulsions (IVFEs) in the critical care population. Soybean oil (SO)-based IVFE was the first type to be developed as a source of essential fatty acids in patients requiring PN. The fatty acid profile of SO-based IVFE is made up of approximately 50% linoleic acid (ω -6), 25% oleic acid (ω -9), and 10% α -linolenic acid (ω -3), which are all unsaturated, long-chain triglycerides (LCT). The metabolic pathways of these fatty acids differ in that ω -6 fatty acids are broken down into more pro-inflammatory prostanooids and leukotrienes whereas ω -3 fatty acids break down into less pro-inflammatory products.²⁷ In vitro studies have demonstrated potential deleterious effects on immune function relating to SO-based fat emulsions,²⁸⁻³⁰ suggesting SO IVFE could be harmful in the critically ill population in which an overproduction of inflammatory mediators already exists. However, only one prospective, randomized study has demonstrated negative clinical outcomes with the use of SO IVFE.³¹ Trauma ICU patients who required PN were randomized to either receive IVFE ($n = 30$) or have IVFE withheld ($n = 27$) for 10 days, starting on or after postinjury day 5. Patients who received IVFE had longer mean hospital and ICU lengths of stay (39 vs 27 days [$p = .03$] and 29 vs 18 days [$p = .02$], respectively), mean days on mechanical ventilation (27 vs 15 days; $p = .01$), and higher infection rates (pneumonia, 73 vs 48%, $p = .05$; catheter sepsis, 43 vs 19%, $p = .04$). However, there were major differences in intake of nonprotein calories between patients who received IVFE and IVFE-free PN (28 vs 21 kcal/kg/day; $p = .0001$). The IVFE group may have been overfed, because these results do not account for protein calories. Increased total caloric intake is associated with increased carbon dioxide production, which may account for longer duration of mechanical ventilation and increased risk for bloodstream infections regardless of blood glucose concentrations.^{32,33} Nonetheless, this study led to the previous guideline recommendation to withhold SO-based

IVFE during the first week following initiation of PN in critically ill patients.¹¹ Smaller, retrospective studies have shown no difference in infectious outcomes based on the timing and/or frequency of exposure to SO IVFE.^{34,35} New guidelines have modified the previous recommendation to include withholding or, if there is concern for essential fatty acid deficiency (ie, in a patient who is at high nutrition risk), SO-based IVFE should be limited to a maximum of 100 g/week for the first week following initiation of PN.¹

Several recent studies have evaluated alternative IVFE sources in critically ill patients (Table 3).³⁶⁻³⁸ Umpierrez et al compared clinical outcomes between medical-surgical ICU patients requiring PN who were randomized to receive SO-based IVFE (containing 100% SO) versus an olive oil (OO)-based IVFE (containing 80% OO and 20% SO).³⁶ OO is thought to be a neutral source of fatty acids in terms of pro-inflammatory potential and provides an equal caloric value to SO while sparing exposure to ω -6 fatty acids.²⁷ However, authors found similar nosocomial infection rates between SO and OO groups or markers of stress or inflammation between groups. This study population was primarily composed of patients in the surgical ICU following major gastrointestinal surgery (48.4%) or trauma (39.6%); however, it was not a severely ill population with a mean APACHE II score of only 15.1. Both groups received a similar energy, protein, and fat intake per day. Notably, PN was initiated an average of 12.6 days from admission, which was significantly later than patients in the Battistella study with “early” exposure to SO-based IVFE. This study design did not allow for evaluation of differences in infection rates based on timing of IVFE exposure, and it is possible that differences may have been seen if patients were exposed to IVFE earlier.

Another study evaluated the incidence of hospital-acquired infections between ICU patients requiring PN who were randomized to receive IVFE in the form of SO versus fish oil (FO).³⁸ Although currently only available in the United States for investigational or compassionate use, IV FO is rich in ω -3 fatty acids, providing a potentially anti-inflammatory IVFE option.²⁷ The SO group received a product containing a 1:1 ratio of medium chain triglycerides (MCT) versus LCT, which is relatively half of the LCT dose provided by the SO-based product used in the United States. The FO group received a product containing a 5:4:1 ratio of MCT, LCT, and FO, respectively. Both groups received similar intakes of energy, protein,

Table 3. Summary of recent alternative intravenous fat emulsion studies

Study	N	Study design	Intervention	Nutrition received (control vs treatment)			Outcomes
				Energy, kcal/kg/day	Protein, g/kg/day	Fat, g/kg/day	
Umpierrez 2012 ³⁶	100	Prospective, double-blind, randomized	SO (<i>n</i> =49) vs OO (<i>n</i> =51)	22 vs 22	1.21 vs 1.16	Not reported ^a	No difference in nosocomial infection rates (43% vs 57%; <i>p</i> =.16)
Grau-Carmona 2015 ³⁸	159	Prospective, multicenter, randomized	SO (<i>n</i> =78) vs FO (<i>n</i> =81)	23.2 vs 22.6	1.41 vs 1.43	1 vs 1	Higher cumulative nosocomial infection rates in patients receiving SO vs FO (21% vs 37%; RR, 1.77 [95% CI, 1.06-2.95]; <i>p</i> =.035)
Edmunds 2014 ³⁷	451	Secondary analysis of a prospective, multicenter study	Lipid free (<i>n</i> =70) vs SO (<i>n</i> =223) vs MCT (<i>n</i> =65) vs OO (<i>n</i> =65) vs FO (<i>n</i> =19)	Not reported ^b			Shorter time to termination of mechanical ventilation alive for FO vs SO (HR, 1.67 [95% CI, 1-2.81]; <i>p</i> =.05) and OO vs SO (HR, 1.43 [95% CI, 1.06-1.93]; <i>p</i> =.02) Shorter time to ICU discharge alive for FO vs SO (HR, 2.4 [95% CI, 1.43-4.03]; <i>p</i> =.001), OO vs SO (HR, 1.76 [95% CI, 1.3-2.39]; <i>p</i> <.001), and FO vs lipid-free PN (HR, 1.84 [95% CI, 1.1-3.34]; <i>p</i> =.05)

Note: FO = fish oil; ICU = intensive care unit; MCT = medium chain triglycerides; OO = olive oil; SO = soybean oil.

^aAverage dose per group not reported. The total study population received a mean daily dose of 0.59 g/kg.

^bOnly mean kcal/day reported: 1,036 (lipid-free PN) vs 1,466 (SO) vs 1,553 (OO) vs 1,517 (FO); *p* < .001.

and fat per day. Baseline characteristics were similar between groups with the exception of a greater number of patients with pancreatitis in the treatment versus control groups (14 [17.3%] vs 5 [6.4%]; *p* = .049). Of the patients with pancreatitis, 7 (50%) versus 1 (20%) died in the treatment versus control groups, respectively. No statistical results were provided, although the investigators acknowledged that this difference in mortality was not statistically significant. However, the potential clinical relevance of these results is worth noting. Despite this, cumulative nosocomial infection rates were significantly higher in patients receiving SO IVFE compared to FO IVFE, implying that IV FO may be beneficial to this critically ill population. Immunologic variables were not compared so it is unknown whether this difference in outcome was related to decreased exposure to SO or actual immunologic changes from FO exposure.

Finally, in a study of medical and surgical ICU patients, Edmunds et al compared the effects of various IVFE formulations on clinical outcomes.³⁷ All

patients were mechanically ventilated and required PN for greater than or equal to 5 days. Patients receiving FO or OO had both a shorter time to termination of mechanical ventilation alive and shorter time to ICU discharge alive compared to those receiving SO. Likewise, patients who received FO had a shorter time to ICU discharge alive compared to a control group of patients who received lipid-free PN. Outcomes evaluated differ slightly from the Battistella study; however, investigators found no significant differences in number of patients alive at termination of mechanical ventilation or ICU or hospital discharge in patients receiving SO versus lipid-free PN.³¹ Major limitations of the study include significant differences in baseline demographics and clinical characteristics among study groups. For example, mean BMI was significantly higher in patients receiving SO versus MCT (28.4 vs 23.8 kg/m²; *p* < .001), and patients in the lipid-free PN group received significantly fewer calories per day than all other groups. Additionally, several forms of IVFE were included in the FO group,

which contained various amounts of FO as well as ω -6 fatty acids, and infection rates were not evaluated.

Although no specific recommendations can be made regarding the optimal formula, dose, or timing of alternative IVFE at this time, these recent studies suggest several potential benefits for the critically ill population requiring PN. While OO-based IVFE seems to provide a neutral source of essential fatty acids and decreases exposure to ω -6 fatty acids, more evidence exists for outcome benefits with FO-based IVFE over SO. Indeed, results from a recent meta-analysis, which evaluated several previous studies not mentioned in this article, also suggest FO IVFE may be associated with reduced infections, duration of mechanical ventilation, and length of stay.³⁹

CONCLUSION

Recent updates to guidelines for nutrition support in critically ill adults offer new insights for treatment optimization.¹ Recognition of patients at high nutrition risk is an important advancement, which should be a consideration in managing nutrition support regimens in the ICU. Likewise, achieving adequate protein provision appears to be of significant therapeutic benefit and may have a positive impact on survival. Advancements in IVFE products may offer unique, anti-inflammatory alternatives for providing essential fatty acids with associated improvement in clinical outcomes. Pharmacists should remain informed on this ever-changing body of literature, which presents unique opportunities for nutrition therapy optimization in the ICU.

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