Invited Commentary

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Recent Critical Care Nutrition Trials and the Revised Guidelines: Do They Reconcile?

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Although the latest publication of the revised "Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient" includes >90 recommendations and cites 480 references, the fact remains that 2 years have passed since the predetermined end date of December 31, 2013, for inclusion of studies in the 2016 publication of the guidelines.[1] This may concern nutrition support clinicians who want assurance that the most up-to-date evidence is being incorporated into their nutrition therapy recommendations, which ultimately affect patient outcomes. In the intervening 2 years, the Guidelines Task Force has remained abreast of results published from recent trials and suggests thoughtful consideration of all significant findings from rigorously conducted research to evaluate how they apply to your institution or patient population. As stated in the preliminary remarks section of the guidelines, clinical judgment for individual patients supersedes consensus recommendations. In this article, the authors review notable clinical trials published after the inclusion end date and discuss how their findings relate to the recommendations in the guidelines. On the basis of this review, the authors believe that no research data have been published that would change the substance of the recommendations of the Guidelines Task Force; however, individually, clinicians may decide to adjust their local protocols to reflect these newly published results.

Parenteral Nutrition Considerations

The CALORIES Trial[2] has prompted considerable discussion regarding how it may influence decisions regarding early parenteral nutrition (PN) in the intensive care unit (ICU), in apparent contrast to the revised guidelines. This trial randomly assigned 2400 patients to either parenteral or enteral delivery of nutrition initiated within 36 hours of ICU admission and continued for up to 5 days, with primary outcome of all-cause 30-day mortality. By 30 days, the parenteral and enteral groups had similar mortality rates of 33.1% and 34.2%, respectively (relative risk in the PN group, 0.97; 95% confidence interval [CI], 0.86–1.08; $P = .57$). In addition to no difference in the primary outcome, there were no significant differences between groups for mean number of treated infectious complications, 90-day mortality, rates of adverse events, or rates of 14 other secondary outcomes. Caloric intake was similar in both groups, and neither achieved target intake in most patients.[2] The implications of the CALORIES Trial are that in high-risk patients, we would expect outcome benefits from either enteral nutrition (EN) or PN. It goes without saying that when PN is performed by more modern standards, its outcome can equal EN over a 5-day course of therapy. These results do not change the preference of EN over PN but should simply lower the threshold for administering PN when EN is insufficient. For those high-risk patients included in the CALORIES Trial,[2] the guidelines would wholly address their needs. For the low-risk patient, we maintain that there are no convincing data to support an aggressive approach to feeding, either EN or PN, in the first week of critical illness. In fact, there are now many trials published suggesting that early aggressive feeding in the low- to moderate-risk patient may cause net harm with either increased morbidity[3-6] or increased mortality.[3,7] The Bost et al[8] systematic review could find no benefit of early supplemental PN over late supplemental PN and, in fact, stated that due to our lack of understanding of the mechanisms to explain greater infectious morbidity and unresolved organ failure, the use of early PN cannot be justified.[8] However, the dynamic trajectory of illness in the ICU patient warrants reassessment on a daily basis to identify a deteriorating condition and greater nutrition risk deserving attention.

Another updated recommendation related to PN that has additional support from a recent meta-analysis[9] involves avoiding

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soybean oil (SO)–based intravenous fat emulsion (IVFE) for the first week of critical illness. This recommendation did not change significantly from the 2009 guidelines[10] but now provides additional information about prescribing IVFE if there are concerns about fatty acid deficiency. In addition, mention is made of alternative fat sources that may appear on the US market soon. Of the 4 meta-analyses in the past 3 years, 2 were already available[11,12] for review by the Guidelines Task Force, but the 2 Manzanares et al[9,13] papers were not yet published. Similar to the results reported by Pradelli and Palmer—which showed benefit from fish oil–containing lipid emulsion (LE) on clinical outcomes such as ICU stay and lung oxygenation[11] as well as hospital stay[11,12]—Manzanares[9] found a trend toward a decrease in ventilation requirement and mortality when fish-oil containing LEs were administered enterally or parenterally. This meta-analysis[9] combined all SO-sparing LEs (ie, those containing medium chain triglycerides, olive oil [OO], fish oil alone, or in any combination) for comparison with SO and demonstrated trends for improved clinical outcomes (days of mechanical ventilation and mortality) with the SO-sparing LEs. In this trial, the subgroup analyses of fish oil–containing LE showed no effect on infectious complications or ICU length of stay (LOS).[9] The updated systematic review and meta-analysis[13] included 4 new trials of critically ill patients, now totaling 10 randomized controlled trials and 733 patients, who received fish oil containing LE, again, either parenterally or enterally. The investigators aggregated 5 trials that reported infections as an outcome and found that fish oil–containing LE significantly reduced infections (relative risk = 0.64; 95% CI, 0.44–0.92; $P = .02$; heterogeneity, $I^2 = 0\%$).[13] The high-quality trials showed a significant reduction in hospital LOS, but the low-quality trials had no effect; it is important to note that the test for subgroup differences in hospital LOS was significant ($P = .001$).[13] One additional paper that describes a secondary analysis of an international prospective observational study published in *Critical Care Medicine*[14] reported a clear benefit of OO or fish oil–containing LE in critically ill patients who received exclusive total PN for at least 5 days. Evaluating different LEs, researchers found SO-based lipid or SO–medium chain triglycerides offered no advantage over no lipid; furthermore, they reported that although 60-day mortality may be lower with no lipid, SO-OO or the use of fish oil appeared superior to no lipid for outcomes such as ICU discharge rate and time on mechanical ventilation. This conclusion supports the findings from the Manzanares et al[9] meta-analysis. The data presented by Edmunds et al[14] are observational, compiled from a larger multicenter study, and while some would consider the observational nature of this trial a limitation, the fact that these data come from routine clinical care settings is actually a strength, especially in relation to the guidelines, as the study serves as an example of how the guidelines can reach practical application. As Calder[15] summarized, the investigators were able to demonstrate significant clinical benefits or a strong trend toward these benefits for fish oil–containing IVFE in a trial with a low number of patients; this observation emphasizes the clinical usefulness of fish oil–containing LEs.[15]

In summary, as the guidelines were in the final stages, concessions regarding PN were made in response to comments that arose from the peer review process as well as favorable trial results published just before the cutoff date for inclusion in the guidelines. Though not without their weaknesses, 2 trials with results available in 2013—1 by Doig et al,[16] which administered PN vs standard feeding (described as delayed EN, delayed PN, or no nutrition), and 1 by Heidegger et al,[17] which utilized supplemental PN for insufficient EN vs EN alone—suggest that PN can safely be administered in patients with an appropriate risk profile to reduce ventilator days[16] and/or nosocomial infections.[17] In the guideline sections discussing nutrient delivery recommendations, the Task Force emphasized that the differences in route of feeding (EN vs PN) primarily reflect older studies, and it should be expected that the outcome differences would diminish with improvements in glycemic control, protocolized management of risk, and availability and use of new IV LEs in the near future.

EN Considerations

Dosing and Nutrition Adequacy

A definition of nutrition adequacy for critically ill patients remains elusive, and optimal dosing levels are yet to be determined. Recent studies have challenged the conventional idea that enhancing calorie and protein provisions for critically ill patients improves patient outcomes. Several recommendations in the revised guidelines are dedicated to EN dosing and nutrition adequacy (see section C, Dosing of EN, and section D, Monitoring Tolerance and Adequacy of EN). As a result of recent studies, the strongest recommendation put forth by the task force with high quality of evidence is incorporated into section C2: "Either trophic or full nutrition by EN is appropriate for patients with acute respiratory distress syndrome (ARDS)/acute lung injury (ALI) and those expected to have duration of mechanical ventilation greater than 72 hours."[1] Though the large multicenter randomized study in ARDS/ALI patients that generated the signal for this recommendation showed no difference in outcomes between trophic feeding and full feeding in the first week,[18] careful interpretation is essential, as the data here apply to patients at low nutrition risk. It should be emphasized that recommendations are not generalizable to all critically ill patients. Several randomized studies since the deadline of inclusion for the revised guidelines have attempted to address this nutrition adequacy debate.

In a single-center randomized study, Petros et al[19] compared hypocaloric (50% of estimated energy expenditure) with full nutrition (100% of estimated energy expenditure) during the first week of critical illness in a medical ICU. Limitations of the study included the use of supplemental PN to make up calorie deficits in both groups, though the primary route of

feeding was not significantly different between groups. In addition, as in most nutrition intervention studies, patients with preexisting malnutrition were excluded. The authors concluded that hypocaloric feeding was associated with more frequent nosocomial infections than normocaloric feeding (26.1% vs 11.1%; $P = .036$) but had no significant effect on ICU or hospital mortality rate. Hypocaloric feeding in the first 7 days after ICU admission was associated with less insulin demand and less gastrointestinal intolerance as compared with normocaloric feeding. The authors noted the potential confounding effect of a higher number of patients with chronic disease (diabetes and pulmonary disease) in the hypocaloric group.[19] The application of this study to the body of literature on nutrition adequacy is limited by its small sample size, as it lacked sufficient power to demonstrate a statistically significant difference in clinical outcomes between groups.

Within 1 week of the publication of the Petros et al[19] study, the findings of the single-center randomized INTACT Trial by Braunschweig et al[7] were published. Patients with ALI from medical or surgical ICUs were randomized to receive either an intensive nutrition protocol for enhanced enteral infusions and oral food intake or standard care, defined as nutrition care provided by their physicians and registered dietitians. Primary outcome was nosocomial infections, and secondary outcomes were days to weaning from mechanical ventilation, ICU and hospital LOS, and mortality. The study was stopped early due to increased mortality in the study group vs the standard care group, 16 of 40 (40%) vs 6 of 38 (16%).[7] Of note is the fact that severity of illness, according to APACHE II score, was significantly lower in the study group than the standard care group (23.4 vs 27.7; $P = .03$). Supplemental PN was used similarly in both groups in this study to achieve caloric goals; however, the study group received 84.7% of their estimated needs (9% from PN), while the standard care group received only 55.4% (7% from PN; $P < .0001$ for overall energy needs). The investigators felt that their ability to effectively deliver goal energy intake early in the ALI diagnosis, particularly in the study group, contributed to higher mortality rates than those observed in other prospective randomized controlled trials.[7] While much can be learned from this trial, the sample size was too small to make definitive practice changes based on this study alone.

In keeping with enhanced caloric delivery, Peake et al[20] investigated whether the use of a concentrated EN formula, 1.5 kcal/mL, improved the delivery of calories when compared with a 1.0-kcal/mL formula over the first 10 days in the ICU in a multicenter randomized double-blind study. The study patients received more calories on average when compared with the control group (27.3 vs 19 kcal/kg/d; $P < .001$) with a trend toward reduced 90-day mortality (20% vs 37%; $P = .057$).[20] Other outcomes of ICU and hospital LOS and ventilator-free days did not differ between the 2 groups. Though the study was well designed, the sample size was small, leaving the need for larger studies to determine appropriate EN dosing in critically ill patients.

Previous studies accounted for caloric differences between groups but failed to mention the differences in already suboptimal protein provisions. In the studies discussed above, protein provision was generally very low in all groups, meeting <50% of estimated protein needs. Two newer randomized controlled trials[21,22] attempted to determine if a caloric difference affected clinical outcomes in the setting of similar protein doses between groups. In a small pilot study of surgical ICU patients, Charles et al[21] randomized patients to hypocaloric versus normocaloric feeding with similar protein provision. The investigators found no significant differences in infectious outcomes or the secondary outcomes of glucose control, ICU and hospital LOS, and mortality.[21] In similar fashion, the large multicenter randomized trial by Arabi et al[22] found no significant difference with respect to 90-day mortality between a moderate calorie restriction (40%–60% of estimated needs) and a normocaloric (70%–100% of estimated needs) feeding regimen in a primarily medical ICU population (75% of patients enrolled from medical ICUs). Protein provision was similar between groups, albeit low, at <70% of estimated protein needs.[22]

Peer reviewers of the guidelines raised concern about recommendations to underfeed or provide for only 80% of identified calorie needs in the first 7 days of critical illness. Trials such as the Wei et al trial published in 2015,[23] which was not available to the Guidelines Task Force, are used to argue that all patients in the ICU must be fed within 48 to 72 hours or risk survival and quality of life. The Wei et al trial is a retrospective post hoc analysis focusing on a very small subset (n = 475) of elderly patients on mechanical ventilation who were studied as part of a larger randomized controlled trial[24] addressing provision of glutamine and antioxidants to critically ill patients (N = 1223). In this trial, not only were calories inadequate, but protein delivery was extremely low at an average of only 50 g/d of protein in a population with multiple organ failures and a mean body weight >50 kg. The unexpected observation of a relationship between suboptimal calorie and protein intake in the first week of ICU stay and longer survival and faster physical recovery to 3 months is exactly why rigorous randomized studies must guide recommendations for clinical practice.[23] Even if this trial had been published before our December 2013 cutoff, the GRADE process would minimize the impact of the Wei trial in the overall evaluation of quality of the evidence, placing it at the same level as expert opinion. Multiple observational trials have reported an association between decreased delivery of nutrition therapy in the ICU and compromised outcome, but these associations have been disproven by randomized studies.[7,18,19,21,22]

Conventional feeding strategies have been recently challenged in the acute pancreatitis population as well. The multicenter randomized controlled study in Dutch ICUs by Bakker et al[25] compared early nasoenteric EN with initiation of an oral diet within 72 hours after presentation in patients with acute pancreatitis at high risk for complications. Baseline characteristics were similar between groups except for body mass index (BMI). Patients in the early EN group had a significantly

higher BMI (29 ± 5 vs 27 ± 5; $P = .01$). There was no significant difference in the primary outcomes for major infection or death. However, the on-demand oral diet group had a significantly shorter time to tolerance of an oral diet than the EN group (6 vs 9 days; $P = .001$). Though the BMI difference between groups could be confounding, a post hoc subgroup analysis based on BMI <25 or >35 showed no significant difference between groups for the composite primary end point of major infection or death. The authors concluded that there is no benefit to early EN over on-demand oral diet in patients with acute pancreatitis at high risk of complications.[25]

EN Formula Selection

A substantial body of evidence from a meta-analysis was available for the recommendation to use immune-modulating EN (IMEN) as the first choice following gastrointestinal surgery.[26] A new report provides strong evidence supporting this recommendation. In a very recent multiple-treatment meta-analysis[27] involving 74 studies and 7572 patients, according to the surface under the cumulative ranking curve, IMEN was ranked first for reducing the incidence of 7 complications: any infection, 0.86; overall complication, 0.88; mortality, 0.81; wound infection, 0.79; intra-abdominal abscess, 0.98; anastomotic leak, 0.79; and sepsis, 0.92. IMEN was ranked second for ventilator-associated pneumonia and catheter-associated urinary tract infection, behind immune-modulating PN. Furthermore, results of this study imply that IMEN is efficacious for reducing the incidence of complications in gastrointestinal surgery, irrespective of the timing of administration.[27] A meta-analysis by Osland et al[28] in the population of patients undergoing elective surgery for gastrointestinal malignancies reported a reduction in total complications with use of IMEN given postoperatively (odds ratio = 0.70; 95% CI, 0.52–0.94; $P = .02$), but a reduction in anastomotic dehiscence was seen only when the immune-modulating formula was given perioperatively.[28]

However, with the 2014 publication of the highly anticipated MetaPlus Trial,[29] we were given a reason to pause and reconsider high-protein IMEN for mechanically ventilated critically ill patients, particularly in the population of critically ill with a medical diagnosis, such as pneumonia or infections of the urinary tract, bloodstream, central nervous system, eye, ear, nose, and throat, as well as skin and soft tissue. This study was a randomized double-blind multicenter trial conducted over 2 years in 14 ICUs in the Netherlands, Germany, France, and Belgium. The trial enrolled 301 adults who were expected to require mechanical ventilation and EN for >72 hours and randomized them to a high-protein IMEN formula or a standard high-protein formula within 48 hours of admission to the ICU, which continued throughout the ICU stay for a maximum of 28 days. Immune-modulating nutrients included glutamine, omega-3 fatty acids, selenium, and antioxidants. The primary outcome was incidence of new infections based on definitions of the Centers for Disease Control and Prevention,[30] and secondary outcomes were mortality, Sequential Organ Failure Assessment scores, days on mechanical ventilation, and ICU and hospital LOS. Researchers planned an intent-to-treat analysis, as well as subgroup analysis for medical, surgical, and trauma subpopulations. Even with higher-than-average target energy intakes of 70% for the high-protein IMEN group and 80% for the high-protein standard group within the first 3 days of feeding, there were no statistically significant differences in the primary or secondary outcomes, except for a higher 6-month mortality rate in the medical subgroup. The authors pointed out that while supplemental PN (SPN) was not quantified, current practice in participating centers was to refrain from using SPN if EN intake was 60%–80% of goal, which likely minimized any marked effect from the SPN. These findings do not support the use of high-protein IMEN in the critically ill population and suggest possible harm in the medical population with an increase in mortality rate. The researchers pointed out that the 6-month mortality rate of 28% in this trial is low when compared with that reported in other large trials, such as the REDOXS[24] at 35% and the SIGNET[31] at 43%. The difference is attributed to the lower protein intakes in those trials and possibly the strictly enteral and continuous administration of immune-modulating nutrients, although doses were lower than those in the other similar trials. The MetaPlus Trial[29] was not published by the time of our literature reviews; however, the Guidelines Task Force had updated its position on IMEN using currently available evidence to suggest that IMEN formulations (arginine with eicosapentaenoic acid, docosahexaenoic acid, glutamine, and nucleic acids) should not be used routinely in medical ICU patients, including those with ALI or ARDS. Consideration for these formulations should be reserved for patients with traumatic brain injury and for perioperative patients in the surgical ICU. The current broad recommendation for EN is stated in section E, Selection of Appropriate Enteral Formulation. Recommendation E2 states, "Based on expert consensus, we suggest using a standard polymeric formula when initiating EN in the ICU setting. We suggest avoiding the routine use of all specialty formulas in the critically ill patient in a medical ICU and disease-specific formulas in the surgical ICU."[1] We were able to provide a recommendation for the routine use of an IMEN formula (containing both arginine and fish oils) in the surgical ICU for the postoperative patient who requires EN therapy due to sufficient evidence from systematic reviews and meta-analyses in the 1–3 years prior to the guideline cutoff for literature reviews of December 2013.[28,32,33]

Conclusion

The GRADE approach (Grades of Recommendation, Assessment, Development, and Evaluation) to evaluating the quality of evidence for the revision of the guidelines provided a structured method to assess a large body of literature.[34] Despite this systematic and transparent process, controversies and criticisms as described in this article are likely to persist in the heterogeneous critical care domain that, to date, is predominantly supported by observational studies, small randomized controlled trials, and meta-analyses.

New and valuable studies have been performed since the Guidelines Task Force evaluation; however, the overall signal from the revised guidelines remains the same. The controversies that exist in critical care nutrition demonstrate how difficult it can be to apply data at the bedside in the evolving complexity of the critically ill patient. There is an ongoing need for new studies to clarify these controversies and improve our ability to optimize outcomes with nutrition therapies. The Guidelines Task Force assumed the burden of assimilating the evidence; however, it is the responsibility of clinicians to understand and determine how to incorporate the evidence into their institutions' culture and practice.

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