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CLINICAL GUIDELINES

Guidelines for the provision of nutrition support therapy in the adult critically ill patient: The American Society for Parenteral and Enteral Nutrition

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Abstract

Background: This guideline updates recommendations from the 2016 American Society for Parenteral and Enteral Nutrition (ASPEN)/Society of Critical Care Medicine (SCCM) critical care nutrition guideline for five foundational questions central to critical care nutrition support.

Methods: The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) process was used to develop and summarize evidence for clinical practice recommendations. Clinical outcomes were assessed for (1) higher vs lower energy dose, (2) higher vs lower protein dose, (3) exclusive isocaloric parenteral nutrition (PN) vs enteral nutrition (EN), (4) supplemental PN (SPN) plus EN vs EN alone, (5A) mixed-oil lipid injectable emulsions (ILEs) vs soybean oil, and (5B) fish oil (FO)–containing ILE vs non-FO ILE. To assess safety, weight-based energy intake and protein were plotted against hospital mortality.

Results: Between January 1, 2001, and July 15, 2020, 2320 citations were identified and data were abstracted from 36 trials including 20,578 participants. Patients receiving FO had decreased pneumonia rates of uncertain clinical significance. Otherwise, there were no differences for any outcome in any question. Owing to a lack of certainty regarding harm, the energy prescription recommendation was decreased to 12–25 kcal/kg/day.

Conclusion: No differences in clinical outcomes were identified among numerous nutrition interventions, including higher energy or protein intake, isocaloric PN or EN, SPN, or different ILEs. As more consistent critical care nutrition support data become available, more precise recommendations will be possible. In the meantime, clinical judgment and close monitoring are needed. This paper was approved by the ASPEN Board of Directors.

[Corrections added on February 10, 2022, after first online publication: The statistics in the main narrative text regarding Figures 2 through 11, 13, 15, 17 through 21, 23, and 24 were modified to match the statistics in the images. The images for Figures 2, 3, 6, 8, 9, 11, 13, 20, 21, 23, and 24 were replaced. Some text within Tables 3, 4, 6, 7, and 8 was replaced.]

KEYWORDS
adult, bacteremia, critical care, critical illness, energy, enteral nutrition, guideline, intensive care unit, length of stay, lipid, mechanical ventilation, mortality, nutrition, nutrition support, parenteral nutrition, pneumonia, protein, randomized controlled trial

PURPOSE

Most critically ill patients are unable to provide their own nutrition. In these patients, artificial nutrition is often provided. The purpose of this guideline is to summarize the evidence within nutrition support to guide practitioners in their provision of artificial nutrition to critically ill patients and provide/update recommendations for several foundational questions that are central to the provision of nutrition support for most critically ill adult patients.

Existing American Society for Parenteral and Enteral Nutrition (ASPEN) clinical guidelines are reviewed for potential updating every 5 years or when significant new additions to the literature have occurred, whichever occurs first. Whereas the earlier guideline provided extensive practice guidance for a large group of clinical decisions that had few randomized controlled trials (RCTs), resulting in many "expert consensus" recommendations,[1] the current guideline restricted the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) process to questions that trials had explored. This resulted in fewer questions overall and some recommendations that did not translate directly into nutrition support prescription. Following the publication of this guideline, a separate Clinical Recommendations paper will ensue to answer expert opinion questions from the previous guideline and other questions for which there is insufficient evidence. To assist the reader in making practice decisions, a "Clinical Application" row has been added beneath each GRADE question in Table 1 that provides guidance for how to incorporate the GRADE recommendations into practice. To increase the external validity and comparability to today's intensive care unit (ICU) patient, only RCTs between January 1, 2001, and July 15, 2020, were included to reflect more current nutrition support practices in the modern era, a time when routine care includes maintenance of glycemic control, avoidance of overfeeding energy, and improved catheter care. Particular importance was given to the nutrition aspects of the exposures (ie, energy, protein, and lipid injectable emulsion [ILE]) provided to patients in the trials as well as timing and route of nutrition delivery.

GUIDELINE LIMITATIONS

These ASPEN clinical guidelines are based on a general consensus among a group of health professionals who, in developing such guidelines, have examined benefits of nutrition practices against risks inherent with such therapy. A task force of multidisciplinary experts in clinical nutrition comprising clinical epidemiologist/methodologists, dietitians, a pharmacist, and physicians was convened by ASPEN. These individuals participated in the development of the guidelines and jointly authored this document. Any recommendations in this guideline do not constitute medical or other professional advice and should not be taken as such. To the extent that the information published herein may be used to assist in the care of patients, this is the result of the sole professional judgment of the attending healthcare professional whose judgment is the primary component of quality medical care. The information presented here is not a substitute for the exercise of such judgment by the healthcare professional. Circumstances in clinical settings and patient indications may require actions different from those recommended in this document, and in those cases, the judgment of the treating professional should prevail. This paper was approved by the ASPEN Board of Directors.

The guidelines offer recommendations that are supported by review and analysis of the current literature as well as a blend of expert opinion and clinical practicality. The current literature has limitations that include variability in study design; limited description of actual intake levels of energy, protein, and ILE; heterogeneity in patient samples and treatment strategies; and limited information on nutrition status and difficulty in blinding. Because of the electrolyte and fluid instability of most critically ill patients and impracticality of blinding the type or details of feeding (enteral nutrition [EN] vs parenteral nutrition [PN], protein supplements, infusion pump rate, etc), most studies were not blinded to the ordering process or nurse administering the feedings or details of the feeding contents.

TARGET POPULATION

The target population is critically ill adult patients in surgical or medical ICUs who are unable to maintain volitional oral intake and are supported by PN or EN.

INCLUSION CRITERIA

The criteria for inclusion are RCTs that enrolled patients over 16 years of age, had an intervention that included EN or PN, reported clinically important outcomes (mortality, ICU or hospital length of stay [LOS], quality of life, or complications), and were published in English.

EXCLUSION CRITERIA

Studies that included only biochemical, nitrogen balance, metabolic, microbial, or nutrition outcomes; that included quasi-randomization; or that enrolled only patients 16 years or younger were excluded.

TABLE 1 Guideline questions, evidence grades, recommendations summary, and clinical applications

Guideline question 1. In adult critically ill patients, does provision of higher vs lower energy intake impact clinical outcomes?	**Evidence GRADE**: Moderate	**GRADE recommendation**: No significant difference in clinical outcomes was found between patients with higher vs lower levels of energy intake. We suggest feeding between 12 and 25 kcal/kg (ie, the range of mean energy intakes examined) in the first 7–10 days of ICU stay.	**Strength of GRADE recommendation**: Weak
Discussion on clinical application for question 1: Until data become available that enable more precise recommendations on energy intake, clinicians should rely on clinical judgment. When EN or PN is associated with problems in glycemic control, respiratory acidosis, or high serum triglyceride concentrations, consider whether feedings should be reduced. Lipid-based sedation also provides a source of energy that should be considered in the total daily intake. Gastrointestinal tolerance may limit how much EN can be provided. Feeding less than the EN formula volume needed to deliver dietary reference intake levels may risk inadequate vitamin, mineral, and trace element intake.			
Guideline question 2. In adult critically ill patients, does provision of higher as compared with lower protein intake impact clinical outcomes?	**Evidence GRADE**: Low	**GRADE recommendation**: There was no difference in clinical outcomes in the relatively limited data. Because of a paucity of trials with high-quality evidence, we cannot make a new recommendation at this time beyond the 2016 guideline suggestion for 1.2–2.0 g/kg/day.	**Strength of GRADE recommendation**: Weak
Discussion on clinical application for question 2: Few studies have investigated the impact of higher protein doses provided with equivalent energy; thus, the impact on outcomes is not known. Until more data are available, we suggest clinicians should individualize protein prescriptions based on clinician judgment of estimated needs.			
Guideline question 3. In adult critically ill patients who are candidates for EN, does similar energy intake by PN vs EN as the primary feeding modality in the first week of critical illness impact clinical outcomes?	**Evidence GRADE**: High	**GRADE recommendation**: There was no significant difference in clinical outcomes. Because similar energy intake provided as PN is not superior to EN and no differences in harm were identified, we recommend that either PN or EN is acceptable.	**Strength of GRADE recommendation**: Strong
Discussion on clinical application for question 3: Our findings indicate that when similar energy is delivered by PN or EN early in critical illness for relatively short periods of time, clinical outcomes are similar. Given these data, cost and convenience of providing EN vs PN may be larger determinants of route of feeding early in critical illness than differences in clinical outcomes. The question of PN use arises when EN is not feasible or tolerated or in patients with significant gastrointestinal disease, who were not the populations studied for question 3. The two reported trials gave ~18–20 kcal/kg/day and 0.6–0.8 g/kg/day protein, and both used a premixed PN solution. Avoidance of energy overfeeding may be the most important decision to make regarding PN use. Optimal glycemic control and catheter care are also important factors in the provision of PN to reduce infectious complications. Clinical judgment about an individual patient's metabolic tolerance to the dextrose (monitor glycemic control), ILE (monitor serum triglyceride concentrations), and amino acid dose is key to delivery of appropriate PN feedings.			
Guideline question 4. In adult critically ill patients receiving EN, does provision of SPN, as compared with no SPN during the first week of critical illness, impact clinical outcomes?	**Evidence GRADE**: High	**GRADE recommendation**: There was no significant difference in clinical outcomes. Based on findings of no clinically important benefit in providing SPN early in the ICU admission, we recommend not initiating SPN prior to day 7 of ICU admission.	**Strength of GRADE recommendation**: Strong
Discussion on clinical application for question 4: The data in this guideline compared SPN within the first week of ICU care and excluded patients with malnutrition. These findings imply that the average critically ill patient will not be harmed by waiting a week to initiate SPN. Further, the patient's tolerance to EN may improve in that time window. However, the needs of malnourished patients or patients who have limited lean muscle mass were not included in these trials and may differ from those of nonmalnourished patients. Patient-specific clinical judgment should be used regarding the initiation of SPN in the first 7 days for these special cases.			

(Continues)

TABLE 1 (Continued)

Guideline question 5A. In adult critically ill patients receiving PN, does provision of mixed-oil ILEs (ie, medium-chain triglycerides, olive oil, FO, mixtures of oils), as compared with 100% soybean-oil ILE, impact clinical outcomes?	**Evidence GRADE**: Low	**GRADE recommendation**: Because of limited statistically or clinically significant differences in key outcomes, we suggest that either mixed-oil ILE or 100% soybean-oil ILE be provided to critically ill patients who are appropriate candidates for initiation of PN, including within the first week of ICU admission.	**Strength of GRADE recommendation**: Weak
Guideline question 5B. In adult critically ill patients receiving PN, does provision of FO-containing ILE, as compared with non–FO-containing ILE, impact clinical outcomes?	**Evidence GRADE**: Low	**GRADE recommendation**: Because there was only one outcome found with a significant difference that was not supported by data covering the other key downstream outcomes, we suggest that either FO- or non–FO-containing ILE be provided to critically ill patients who are appropriate candidates for initiation of PN, including within the first week of ICU admission.	**Strength of GRADE recommendation**: Weak
Discussion on clinical application questions 5A and 5B: In addition to 100% soybean-oil ILE, mixed oil– and FO-containing ILE products are now available in the United States, but health-system formulary availability of these formulations may vary. In general, ILE is a safe and effective energy source that can be included with the PN formulation at the time of initiation, including within the first week of ICU admission. Optimizing ILE provision helps avoid excessive dextrose provision and hyperglycemia. Monitoring serum triglyceride concentrations will give information about the adequacy of lipid clearance. The energy provided by lipid-based sedation should be considered in the overall estimate of lipid and energy intake. It is also important to give adequate levels of the essential fatty acids to meet requirements if the PN will be needed for >10 days. The essential fatty acid content of the mixed-oil ILE and FO-containing ILE is lower than that of the soybean-oil ILE.			

Abbreviations: EN, enteral nutrition; FO, fish oil; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; ICU, intensive care unit; ILE, lipid injectable emulsion; PN, parenteral nutrition; SPN, supplemental PN.

TARGET AUDIENCE

These guidelines are intended for use by clinicians, including but not limited to dietitians, nurses, nurse practitioners, pharmacists, physicians, and/or physician assistants who provide nutrition care for critically ill adult patients; nutrition researchers interested in critical illness; and hospital committees with a charge to evaluate nutrition support policies.

DEFINITIONS

Nutrition support refers to the provision of either EN provided by an enteral access device and/or PN provided intravenously. Critically ill patients may also receive IV fluid intake or sedative medications, some of which provide energy.

METHODS

The GRADE process was used to develop the key questions using the PICO (population, intervention, comparator, outcome) format and to plan data acquisition and assessment for these guidelines.[2] The task force of experts defined keywords to be used for the literature search, developed key PICO questions that address major contemporary practice themes, and determined the time frame for the literature search, target population, and the specific outcomes to be addressed. These PICO questions defined the limits of the literature search. We plan to revisit this guideline within 5 years or as important evidence becomes available.

Literature search

All citations were culled from the PubMed/MEDLINE database and limited to those posted between January 1, 2001, and July 15, 2020. Search terms are included in Figure 1. Our search strategy was designed to collect citations if (1) they were indexed in MEDLINE and contained at least one term from both group 1a and group 1b, (2) they were indexed in MEDLINE and contained at least one term from both group 2a and group 2b within the citation title or abstract, or (3) they were indexed in the PubMed non-MEDLINE database and contained at least one term from both group 2a and group 2b. The search strategy was then further restricted to only those citations that were

Group 1a (MeSH Terms): "Nutritional Support"[Mesh], "Malnutrition"[Mesh], "Nutrition Assessment"[Mesh], "Energy Intake"[Mesh], "Energy Metabolism"[MeSH], "Dietary Proteins"[Mesh], "Parenteral Nutrition Solutions"[Mesh], "Probiotics"[Mesh], "Antioxidants"[Mesh], "Amino Acids"[Mesh]

Group 1b (MeSH Terms): "Critical Illness"[Mesh], "Intensive Care Units"[Mesh], "Critical Care" [MeSH], "Acute Lung Injury"[Mesh], "Respiratory Distress Syndrome, Adult"[Mesh]

Group 2a (Text Terms): malnutrition, malnourished, "inadequate intake", "nutritional assessment", "malnutrition screening", "energy needs", "energy requirement", "caloric requirement", "energy expenditure", kcal, kilocalorie, calorie, "kcal/kg", "kcals/kg", "protein needs", "protein requirement", "amino acid requirement", "protein intake", "estimated protein", "estimated amino acid", "enteral nutrition", "enteral feeding", "enterally fed", "tubefeed", "tube feed", "tube-feeding", "tube feeding", "j-tube", "g-tube", "jejunal feeding", "gastric feeding", "parenteral nutrition", "parenteral feeding", "parenteral feed", "parenterally fed", "IV feeding", "intravenous feeding", "IV fed", "intravenously fed", "immunonutrition", "probiotic", "vitamin c", "ascorbic acid", "glutamine", "arginine", "branched chain amino"

Group 2b (Text Terms): "critical illness", "Critically Ill", "ICU", "intensive care

Group 3 (Restrictions): Clinical Study[ptyp], Clinical Trial[ptyp], Clinical Trial, Phase I[ptyp], Clinical Trial, Phase II[ptyp], Clinical Trial, Phase III[ptyp], Clinical Trial, Phase IV[ptyp], Controlled Clinical Trial[ptyp], Comparative Study[ptyp], Randomized Controlled Trial[ptyp], English[lang]

FIGURE 1 Search terms for literature search. lang, language; MeSH, Medical Subject Heading; ptyp, publication type

cross-referenced to the terms listed in group 3. Analogous strategies were used to search the Embase and Cochrane Central databases.

Data acquisition

Each abstract was independently screened by two authors to determine whether the study met the inclusion criteria. Articles that met all three inclusion criteria were reviewed using a standardized data abstraction form (DAF) that was developed based on specific questions for the guideline using the GRADE approach for RCTs. Data retrieval included demographic information, methods used to assess energy and protein requirements, the amount of energy and protein received (ie, exposure variables), various clinical outcome variables, and assessment of quality of the investigation. Trials with quasi-randomization were excluded. Each article was independently reviewed by two task force members, results were compared, differences were resolved by consensus, and a final DAF was created for each trial. For purposes of consistency in analysis and comparisons of findings between studies, for questions 1–4 the "intervention" group was designated as those individuals randomized to receive greater and/or earlier energy and/or higher protein intake; the "control" group was defined as patients randomized to receive less energy or protein or delayed feedings. For questions 5A and 5B, respectively, the intervention group was defined as patients provided mixed-oil ILE or fish-oil (FO) ILE vs soybean-oil (SO) ILE.

Evidence quality assessment

Five main factors are considered when assessing the quality of the evidence in the GRADE approach. *Risk of bias* refers to limitations in study design (quasi-randomization, lack of blinding, lack of comparability of groups at baseline) or execution (lack of intent-to-treat [ITT] analysis, inadequate delivery of exposure, excess loss to follow-up). The Cochrane Risk of Bias 2 tool (RoB2)[3] was used to assess bias. It is important to note that bias, in the context of this new tool, *is a comment not on the study itself but on the ability of the study to answer our specific question for each individual outcome* (ie, a study may have high risk of bias for one outcome and low risk of bias for another, depending on the question asked and the design of the study). *Inconsistency* refers to substantial unexplained heterogeneity in results across the trials from which the recommendation is drawn. This is assessed by examining the consistency of study outcomes. *Indirectness* is a subjective term that refers to how directly applicable the available evidence is to the guideline question. This is assessed by examining limitations in our ability to apply our findings to our population and question of interest. *Imprecision* denotes the degree to which we are confident the estimated effect size reflects the true effect size. This is assessed by examining the width of CIs and assessing power to detect an effect. *Publication bias* reflects the likelihood that the nature of the study findings determined its publication status, thereby skewing the combined study findings away from the direction of the findings of studies that were omitted from the literature.

The GRADE process distinctly separates the evaluation of the quality of the body of evidence from the strength of the recommendation statements. This separation enables incorporation of the weight of the risks vs the benefits that occur from adopting the recommendation. Thus, a recommendation may be "strong" despite comparatively weak published evidence if the net benefits outweigh the harms from its adoption. Also, a forest plot that combines included trials may display a difference that is statistically significant (at $P \leq 0.05$) but is not a clinically meaningful difference to support a strong recommendation. Table 2 describes the standard language and rationale for the GRADE assigned to a recommendation. Of note, the clinical applications developed for each question were not part of the GRADE process—that is, they do not represent an "expert consensus" of the GRADE data. Rather, they are provided to assist practitioners in the clinical application of our findings that did not directly translate into nutrition support prescription.

TABLE 2 Language for guideline recommendations[a]

Quality of evidence	Weighing risk vs benefits	Strength of recommendation	Guideline recommendation language
Very low to high	Net benefits outweigh harms	Strong	We recommend
Very low to high	Net harms are considerable and may outweigh the benefits	Weak	We suggest

Note: In very rare cases, a clinical panel may decide that they should not make a recommendation, but in almost all cases, the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) process encourages panels to make a recommendation regardless of the evidence. Wherever possible, these recommendations are evidence based. When this is not possible, they are deemed expert opinion, which is not a category of GRADE.

Statistical analysis

Outcomes for which there were three or more studies with comparable data were meta-analyzed using a random-effects model and an alpha significance level of 0.05. Trials that met the inclusion criteria and had data that were pertinent to the question but presented in a dissimilar manner relative to other included trials were discussed in the text but not meta-analyzed. The risk difference (RD) between the intervention and control groups for the outcome variables was calculated. The RD provides information about the absolute effect of the exposure on the risk of the clinical outcome in those in the intervention compared with those in the control group. The risk for any group is derived by dividing the number of events by the number of patients at risk for the event. The RD is a straightforward subtraction of the risk of the occurrence of the event in the control group from the risk of the event in the intervention group. When there is no difference between the intervention and the control groups, the RD = 0. A 95% CI for an RD that contains 0 indicates the difference between the groups is not statistically significant.

This impact and clinical significance of an RD are altered by the underlying risk of having an event such that an RD for low-risk events may be more clinically significant than the same RD for events for which the underlying risk is higher. For example, if the risk in the control group is 0.02 (2%) and the risk in the intervention group is 0.04 (4%), the intervention has doubled the risk (RD = 0.02). Conversely, if the risk in the control group is 0.75 (75%) and the risk in the intervention group is 0.77 (77%), the clinical risk has barely increased, yet the RD is the same (RD = 0.02). For this reason, it is always important to consider underlying risk when interpreting a significant RD.

When trial data could not be combined to estimate the effect size, they were reported in a summary table for each question as the author presented the data. All statistical analyses were performed in Stata 16 (StataCorp; College Station, TX). Summary statistics were calculated and forest plots constructed using random-effects models. Publication bias was assessed through funnel plots and Egger statistics but only presented for main document forest plots with at least 10 studies (see Supporting Appendix). The GRADEPRO Guideline Development Tool (Cochrane Collaboration, 2020) was used to estimate the strength of the body of evidence for each outcome in each question and create summary tables. This was then used to infer the overall quality of the evidence relative to its ability to answer the respective PICO question.

Safety analysis

For questions 1 and 2, to facilitate recommendations for specific cut points in energy and protein provision, a post hoc safety analysis (see Supporting Appendix) was performed with the goal to assess qualitatively hospital mortality across the available range of energy per kilogram. The randomization groups for each study were separated and ordered along an x-axis by energy received per kilogram. This was then plotted against hospital mortality, and linear trend lines were qualitatively assessed. Studies were restricted to RCTs that met our inclusion criteria and to those that provided information on energy received per kilogram. Further between-study differences, such as country and medical system, and whether or not the study comprised all admissions to the ICU vs a subgroup were dealt with through stratification. We also examined stratifications by median splits of Acute Physiology and Chronic Health Evaluation (APACHE) II and body mass index (BMI). Additional forest plots were run to explore combining energy exposure trials that used different interventions (higher vs lower energy exposure, EN vs PN, supplemental PN [SPN] vs standard care) in their study designs. Stratifications of studies that intended hypocaloric interventions or intensive nutrition interventions and forest plots that were ordered by and stratified by the between-group separation of energy received per kilogram were also examined.

RESULTS

Our search strategy detected 2320 citations. Of these, 138 citations were downloaded for further assessment. After review, 80 articles met the inclusion criteria for data abstraction, of which 36 trials contained data that could be used to answer the questions posed and, thus, had DAFs completed.

Question 1. In adult critically ill patients, does provision of higher vs lower energy intake impact clinical outcomes?

Recommendation: No significant difference in clinical outcomes was found between patients with higher vs lower levels of energy intake. We suggest feeding between 12 and 25 kcal/kg (ie, the range of mean energy intakes examined) in the first 7–10 days of ICU stay.

Quality of evidence: Moderate

Strength of recommendation: Weak

Rationale: This broad-range recommendation reflects two major components of our forest plots that limit their interpretation. First, a more specific cut point for energy goals could not be generated, as this would require examination between the outcomes at different levels of energy per kilogram. Unfortunately, this was not possible because of the overlap between the trials' energy exposure (Table 3) and limited within-study energy differences between intervention and control. Second, the forest plot analysis assumes a linear relationship between the exposures of interest (ie, energy intake) and outcomes; however, energy/outcome relationships have not been demonstrated to be linear. To address these limitations, a safety analysis (see Supporting Appendix) was performed to visually inspect our data for evidence of benefit or harm (Figures S1–S59). Our broad recommendation reflects the range of mean energy exposures in our data and the findings from the safety analysis. This decision was made based on having no evidence of benefit for and a lack of certainty regarding harms of energy provision consistent with those recommended in past guideline recommendations.

To be included in the analysis for this question, the trial needed to randomize energy exposure without causing a secondary competing intervention, such as a shift from EN to PN. Although this question was meant to be a broader question on general energy intake from any source, as a sensitivity analysis, protein dose was also considered as a potential competing intervention. The forest plots below therefore contain both combined results and results stratified by whether the trial was isonitrogenous between allocation group. Thirteen trials[4–16] representing data from 8690 patients were included to answer this question (Table 3). In acknowledgment of the lack of difference between PN and EN, reported in question 3, the safety analysis also included a series of plots that combined these studies from questions 1, 3, and 4 in its analysis.

Methodological quality and intervention design varied between trials. One trial[11] reported important baseline differences, including imbalances in baseline diabetes mellitus prevalence, that were not controlled for in their analysis. Two trials[9,17] lacked a true ITT design, removing participants from analysis after they withdrew consent. Because withdrawal counts were low and did not likely impact the outcomes, they are included in this analysis. Most trials included all patients admitted to the ICU,[4–6,9–11,14,15,17] but some restricted enrollment to patients with acute respiratory distress syndrome (ARDS)[7,13] or those requiring mechanical ventilation.[8,12] Duration of the intervention varied from 6 to 28 days. Energy delivery was reported as kilocalories per kilogram per day[7,10–12,16] or as mean or median kilocalories per day,[4,5,8,14,15] and three trials did not include data on energy or protein intake delivered.[9,14,17] Among the trials reporting energy received as kilocalories per kilogram, intake in the higher-fed group ranged from 17 to 30 kcal/kg.[6,10] Higher intakes in those reporting data as mean or medians ranged from 1252 to 2085 kcal/day.[6,15] Lower-fed groups were similarly heterogenous. In addition, differences in energy delivered between the higher- and lower-energy arms varied considerably (from 5 kcal/kg/day in the study by Charles et al[6] to 9 kcal/kg/day in the study by Braunschweig et al,[7] respectively, and from 200 kcal in the study by Arabi et al[5] to 1100 kcal/day in the study by Rice et al,[14] respectively). For studies that did not provide energy measurements in kilocalories per kilogram per day or that provided measurements of kilocalories and kilograms separately, preventing conflation of their standard error, energy measurements in kilocalories per day were provided. As stated earlier, although the collapse of trials into higher vs lower energy intake was necessary to permit forest plot comparisons across all included trials, it assumes that the impact of energy exposure (measured in kilocalories per kilogram) has a linear relationship with outcome, which conflicts with previous study outcomes. Further, these forest plots did not enable determination of cut points or inflection points in the data. For that, one has to look at the relationship at different levels of energy per kilogram, and the overlap between the studies' energy exposure made it impossible to do that within a forest plot. Because of the above-described issue of indirectness, quality of evidence was rated as moderate. This was based upon our critical outcome, hospital mortality. The strength of our recommendation was rated as weak, based upon our lack of certainty regarding harms and benefits.

No significant differences were found between higher vs lower energy intake groups for any clinical outcome. Trials examining the relationship between higher vs lower energy intake had heterogenous findings, with some supporting benefits to higher levels of energy delivery,[9,11] others indicating harm,[5,7,15] and most finding no significant difference between groups.[4,6,8,10,12–14,16] Six trials[4–6,10,12,16] delivered isonitrogenous energy but did not impact the effect of energy exposure on any of our chosen outcomes (Figures 2–11). Taken together, the current evidence suggests that higher energy exposure (maximum reported here was 30 kcal/kg/day[12]) and lower energy exposure (lowest reported here was 300 kcal/day[14]) are similar in their effect (or lack of effect) on outcomes in the critically ill population. The risk of bacteremia was not different in patients with higher vs lower energy intake (RD = 0.01; 95% CI, −0.02 to 0.03; $P = 0.58$) (Figure 2). Neither the isonitrogenous nor the non-isonitrogenous trials demonstrated significant differences in risk of bacteremia between higher and lower energy intake.

The risk of pneumonia was not different in higher vs lower energy intake groups (RD = 0.01; 95% CI, −0.01 to 0.02; $P = 0.48$), with non-significant findings relative to isonitrogenous vs non-isonitrogenous intake (Figure 3).

The risk of any infection was not different in patients with higher vs lower energy intake (RD = 0.01; 95% CI, −0.04 to 0.05; $P = 0.74$), including in the groups separated by isonitrogenous or non-isonitrogenous feeding (Figure 4).

Mean ICU LOS was not different in the higher- vs lower-energy group (RD = 0.19; 95% CI, −1.62 to 2.00 days; $P = 0.84$), including no difference by isonitrogenous status (Figure 5).

Hospital LOS was not different between lower and higher groups (RD = −0.88; 95% CI, −4.89 to 3.14 days; $P = 0.67$), regardless of isonitrogenous feeding (Figure 6).

TABLE 3 Data summary for question 1: In adult critically ill patients, does provision of higher vs lower energy intake impact clinical outcomes?

First author, year	Population	Comparison (*n*) of higher vs lower energy	Intake provided	Infections, *n* (%)	Time on mechanical ventilation, median (IQR) or mean ± SD, days	Length of stay, median (IQR) or mean ± SD, days	Mortality, *n* (%)
Arabi, 2011[5]	Adult med/surg ICU patients Mean BMI: 28.5 vs 28.5	90%–100% goal energy (*n* = 120) vs 60%–70% goal energy (*n* = 120)	Energy (kcal/day): 1252 ± 433 vs 1067 ± 306 Protein (g/day): 48 ± 21 vs 44 ± 19	Sepsis: 56 (47) vs 53 (44)	13.2 ± 15.2 vs 10.6 ± 7.6	ICU: 14.5 ± 15.5 vs 11.7 ± 8.1 Hospital: 67.2 ± 93.6 vs 70.2 ± 106.9	28-day: 28 (23) vs 22 (18) ICU: 26 (22) vs 21 (18) Hospital: 51 (43) vs 36 (30) 6-month: 52 (44) vs 38 (33)
Arabi, 2015[4]	Adult med/surg ICU patients Mean BMI: 29.7 vs 29	70%–100% goal (*n* = 446) vs 40%–60% goal (*n* = 448)	Energy (kcal/day): 1299 ± 467 vs 835 ± 297 Protein (g/day): 59 ± 25 vs 57 ± 24	Pneumonia: 90 (20) vs 81(18) Any infection: 169 (38) vs 161(36)	10 (5–16) vs 9 (5–15)	ICU: 13 (8–20) vs 13 (8–21) Hospital: 30 (14–63) vs 28 (15–54)	28-day: 97 (22) vs 93 (21) ICU: 85 (19) vs72 (16) Hospital: 123 (28) vs 108 (24) 90-day: 127 (29) vs 121 (27) 180-day: 140 (32) vs 131 (30)
Braunschweig, 2015[7]	ALI patients in med ICU BMI ≥ 30, 45% vs 47%	Intensive therapy[b] (*n* = 40) vs standard care (*n* = 38)	Energy (kcal/kg/day): 25.4 ± 6.6 vs 16.6 ± 5.6 Protein (g/day): 82 ± 23 vs 60.4 ± 24	Any infection: 5(12) vs 8(21)	6 (4–10) vs 7 (3–14)	ICU: 15.5 ± 12.8 vs 16.1 ± 11.5 Hospital: 27.2 ± 18.2 vs 22.8 ± 14.3	Mortality: 16 (40) vs 6 (16)
Chapman, 2018[12]	Adult patients in 46 ICUs who were mechanically ventilated and eligible for EN Mean BMI: 29.2 vs 29.3	1.5-kcal/ml (*n* = 1971) vs 1.0-kcal/ml (*n* = 1986) formula administered at 1 ml per kilogram of IBW	Energy based on IBW (kcal/kg/day): 30.2 ± 7.5 vs 21.9 ± 5.6 Energy based on ABW (kcal/kg/day): 23.9 (7.8) vs 17.4 (5.5)	Bacteremia: 228 (12) vs 221 (11)	NR	NR	Hospital: 468 (24) vs 470 (24) 28-day: 450 (23) vs 455 (23) 90-day: 523 (27) vs 505 (26)
Charles, 2014[6]	Adult patients in surg ICU Mean BMI: 28.1 vs 32.9	Standard 25–30 kcal/kg (*n* = 42) vs 12–15 kcal/kg (*n* = 41)	Energy (kcal/kg/day): 17.1 ± 1.1 vs 12.3 ± 0.7 Protein (g/kg/day): 1.1 ± 0.1 vs 1.1 ± 0.1	Bacteremia: 8 (19) vs 10 (24) Pneumonia: 20 (48) vs 18 (44) Any infection: 32 (76) vs 29 (71)	NR	ICU: [c] 13.5 ± 1.1 vs 16.7 ± 2.7 Hospital: [c] 31 ± 2.5 vs 35.2 ± 4.9	Mortality: 4 (10) vs 3 (7)
Desachy, 2008[8]	Mechanically ventilated patients Mean BMI: 25 vs 27	Immediate EN (*n* = 50) vs gradual EN (*n* = 50)	Energy (kcal/day): 1715 ± 331 vs 1297 ± 331 Protein (g/day): 82 ± 23 vs 60.4 ± 24	Pneumonia: 0(0) vs 0(0)	NR	ICU: 15 ± 11 vs 15 ± 11 Hospital: 56 ± 59 vs 51 ± 75	ICU: 6(12) vs 8(16) Hospital: 14(28) vs 11(22)

(Continues)

TABLE 3 (Continued)

First author, year	Population	Comparison (*n*) of higher vs lower energy	Intake provided	Infections, *n* (%)	Time on mechanical ventilation, median (IQR) or mean ± SD, days	Length of stay, median (IQR) or mean ± SD, days	Mortality, *n* (%)
Doig, 2013[17]	Critically ill patients with short-term contraindication to EN in 31 med/surg ICUs Mean BMI: 27.9 vs 28.5	Early PN (*n* = 681) vs standard care (*n* = 682) (both groups also received EN)	Energy (kcal/kg/day): NR Protein: NR	Pneumonia: 43 (6) vs 45(7) Bacteremia: 39 (6) vs 33(5) Any infection: 74(11) vs 78(11)	NR	ICU: [a]8.6 (8.2-9) vs 9.3(8.9–9.7) Hospital: [a]25.4 (24.4–26.6) vs 24.7 (23.7-25.8)	ICU: 81(12) vs 100(15) Hospital:140(21) vs 151(22) 60-day: 146(22) vs 155(23)
Doig, 2015[9]	Patients in 13 med/surg ICUs Mean BMI: 28 vs 28	Standard care (*n* = 165) vs 2 days with 20 kcal/h then gradual increase to usual (*n* = 166)	Energy (kcal/kg/day): NR Protein: NR	Pneumonia: 22 (13) vs 14 (8) Bacteremia: 8 (5) vs 2 (1) Any infection: 27(16) vs 13(8)	[a]7.45 (7.16 to 7.65) vs 7.86 (7.54 to 8.18)	ICU: [a]10.0 (9.2–10.9) vs 11.4(10.5–12.4) Hospital: [a]21.7 (20.0–23.5) vs 27.9 (25.7–30.3)	ICU: 15(9) vs 9(5) Hospital: 30(18) vs 15(9) 60-day: 35 (21) vs 15 (9) 90-day: 35 (21) vs 21 (13)
Peake, 2014[10]	Adult critically ill patients in surg ICU Mean BMI: 27.8 vs 26.2	1.5 kcal/ml (*n* = 57) vs 1.0 kcal/ml (*n* = 55)	Energy (kcal/kg/day): 27.3 ± 7.4 vs 19.0 ± 6.0 Protein (g/kg/day): 1.0 ± 0.3 vs 1.1 ± 0.3	NR	NR	ICU: 9.6 (5.9–22.6) vs 11.8(6.9–22.8) Hospital: 34.5(16.9–83.6) vs 30.6(15.2–undefined)	ICU: 6 (11) vs 9 (16) Hospital: 10(19) vs 14 (27) 28-day: 11(20) vs 18(33) 90-day: 11(20) vs 20(37)
Petros, 2016[11]	Adult patients in med ICU Mean BMI: 27.1 vs 28.6	Normocaloric (*n* = 54) vs hypocaloric (*n* = 46) EN or PN	Energy (kcal/kg/day): 19.7 ± 5.7 vs 11.3 ± 3.1 Protein (g/kg/day): NR	Any infection: 6(11) vs 12(26)	7.44 (2.90–16.80) vs 10.60 (4.81–28.60)	NR	ICU: 12(22) vs 10(22) Hospital: 17(32) vs 17(37) 28-day: 18(33) vs 18(39)
Rice, 2011[14]	Adult patients with respiratory failure in med ICU Mean BMI: 28.2 vs 29.2	Normocaloric (*n* = 102) vs trophic EN (*n* = 98)	Energy (kcal/day): 1418 ± 686 vs 300 ± 149 Protein (g/day): 54.4 ± 33.2 vs 10.9 ± 6.8	Pneumonia: 18 (18) vs 14(14) Any infection: 33(32) vs 30 (31)	NR	ICU-free days: 21(9.3–24) vs 21(6.5–24) Hospital-free days: 16.5(0–21) vs 12(0–21)	Hospital: 20 (20) normocaloric vs 22(22) trophic
Rice, 2012[13]	Adults with ALI in 44 ICUs Mean BMI: 30.4 vs 29.9	25–30 kcal/kg full EN feeding (*n* = 492) vs trophic (*n* = 508)	NR	Bacteremia: 46(9) vs 59(12) Pneumonia: 33(7) vs 37(7)	NR	ICU-free days in 28 days: [a]14.7(13.8–15.6) vs 14.4(13.5–15.3)	60-day: 109(22) vs 118(23)
Rugeles, 2016[16]	Adult patients expected to require EN for >96 h in med/surg ICU Mean BMI: 25 vs 25	Normocaloric (*n* = 60) vs hypocaloric (*n* = 60)	Energy (kcal/kg/day): [a]19.2 ± 4.3 vs 12.1 ± 2.6 Protein (g/kg/day): [a]1.3 ± 0.3 vs 1.3 ± 0.3	NR	9(8.3) vs 9(8.3)	ICU: 10.5(8.0) vs 12(7.3)	28-day: 16(27) vs 18(30)

(Continues)

TABLE 3 (Continued)

First author, year	Population	Comparison (*n*) of higher vs lower energy	Intake provided	Infections, *n* (%)	Time on mechanical ventilation, median (IQR) or mean ± SD, days	Length of stay, median (IQR) or mean ± SD, days	Mortality, *n* (%)
Singer, 2011[15]	Adult med/surg ICU Mean BMI: 27.8 vs 27.4	Indirect calorimetry-measured requirement (*n* = 65) vs 25 kcal/kg/day (*n* = 65)	Energy (kcal/day): 2086 ± 460 vs 1480 ± 356 Protein (g/day): 76 ± 16 vs 53 ± 16	Bacteremia: 13(20) vs 8(12.3) Pneumonia: 18(27.7) vs 9(13.8)	16.1 ± 14.7 vs 10.5 ± 8.3	ICU: 17.2 ± 14.6 vs 11.7 ± 8.4 Hospital: 33.8 ± 22.9 vs 31.8 ± 27.3	ICU: 16(25) vs 17(26) Hospital: 21(32) vs 31(48)

Abbreviations: ABW, actual body weight; ALI, acute lung injury; BMI, body mass index (kg/m^2); EN, enteral nutrition; IBW, ideal body weight; ICU, intensive care unit; IQR, interquartile range; med, medical; NR, not reported; PN, parenteral nutrition; surg, surgical.
[a]Mean (95% CI).
[b]Intensive nutrition therapy: EN prescribed within 6 h of hemodynamic stability, monitored and adjusted to make up for interruptions in feeding.
[c]Mean ± SE.

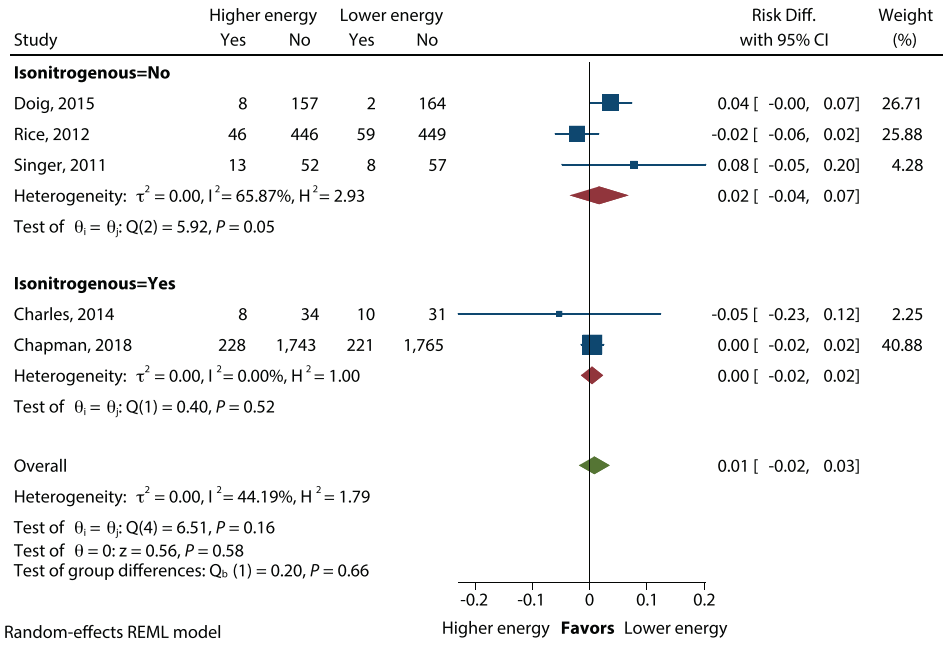

FIGURE 2 Mean difference in bacteremia in patients with higher vs lower energy intake. Diff., difference; REML, restricted maximum likelihood

Mean ventilator days did not differ between patients fed higher vs lower amounts of energy (RD = 2.05; 95% CI, −1.33 to 5.43 days; *P* = 0.23) (Figure 7). With only one isonitrogenous and two non-isonitrogenous trial, the subanalysis was not meaningful.

ICU mortality was not different by higher- or lower-fed intervention arms (RD = 0.00; 95% CI, −0.03 to 0.03; *P* = 0.98), regardless of isonitrogenous or non-isonitrogenous feeding (Figure 8).

Hospital mortality was not different by higher- or lower-fed intervention arms (RD = 0.02; 95% CI, −0.02 to 0.05; *P* = 0.31), regardless of isonitrogenous or non-isonitrogenous feeding (Figure 9).

Mortality by day 28 was not different in higher- or lower-fed intervention arms (RD = −0.00; 95% CI, −0.02 to 0.02; *P* = 0.51) (Figure 10).

Mortality by day 90 was not different in higher- or lower-fed intervention arms (RD = 0.01; 95% CI, −0.01 to 0.04; *P* = 0.27) (Figure 11).

Four trials[4,10,12,16] that provided data on ICU and/or hospital LOS and days on mechanical ventilation did so in a way that could not be compared statistically and are not included for these outcomes in the forest plots. The results were not significantly different for any of these four studies, suggesting their inclusion would not likely have altered the effect size of the outcomes reported above.

This recommendation differs from the prior version of this guideline, in which varied guidance was given based on nutrition risk or ARDS.[1] The 2016 guideline recommended different early EN strategies based on nutrition assessment. The previous guideline recommended against

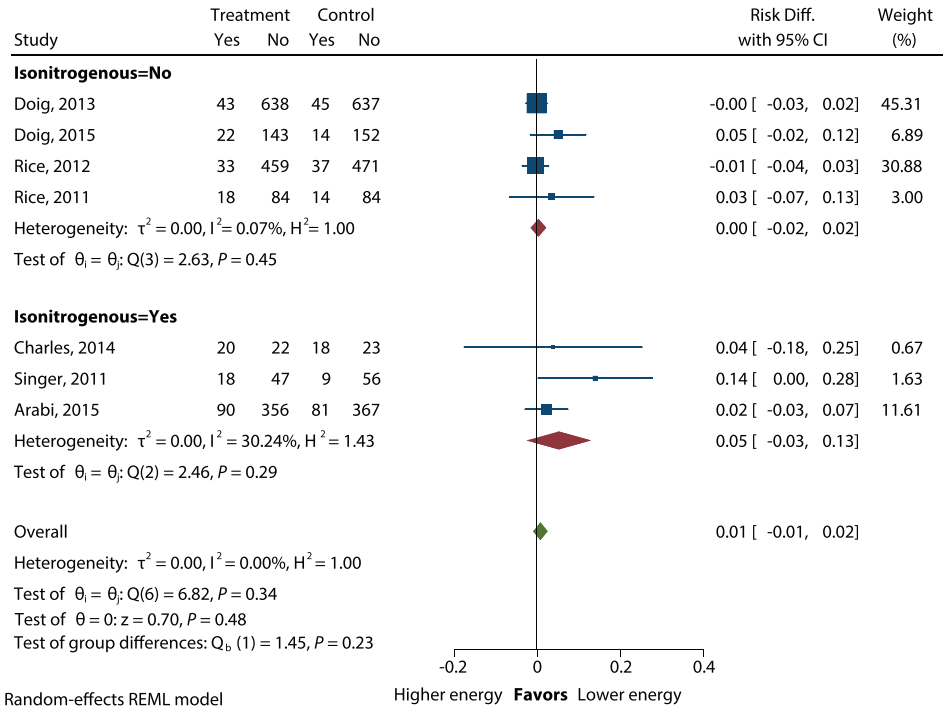

FIGURE 3 Mean difference in pneumonia in patients with higher vs lower energy intake. Diff., difference; REML, restricted maximum likelihood

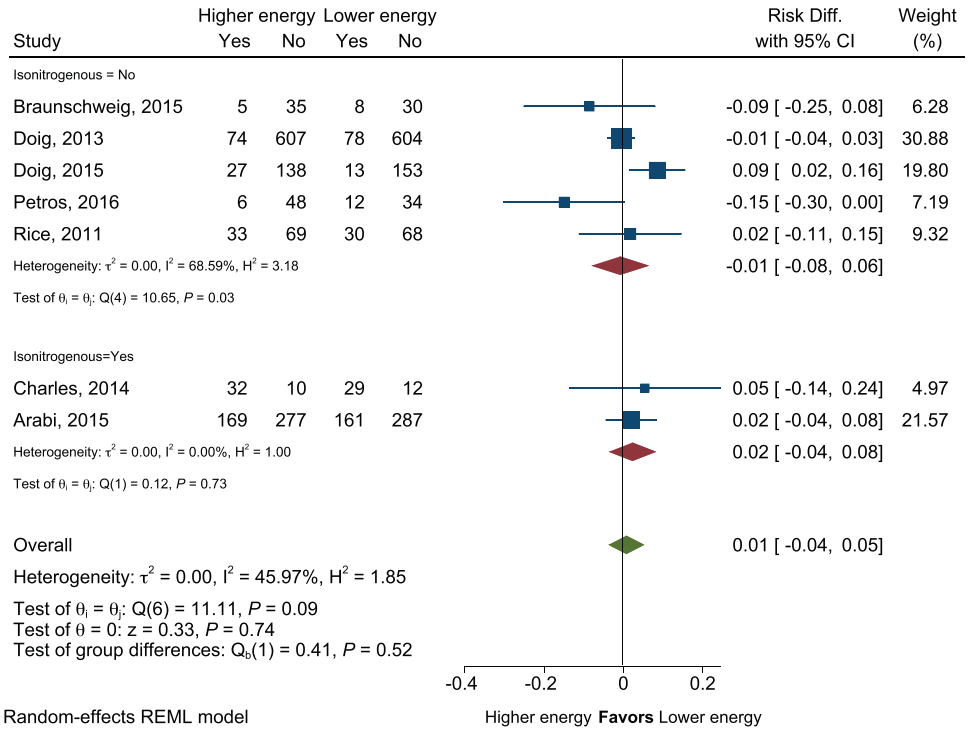

FIGURE 4 Mean difference in any infection in patients with higher vs lower energy intake. Diff., difference; REML, restricted maximum likelihood

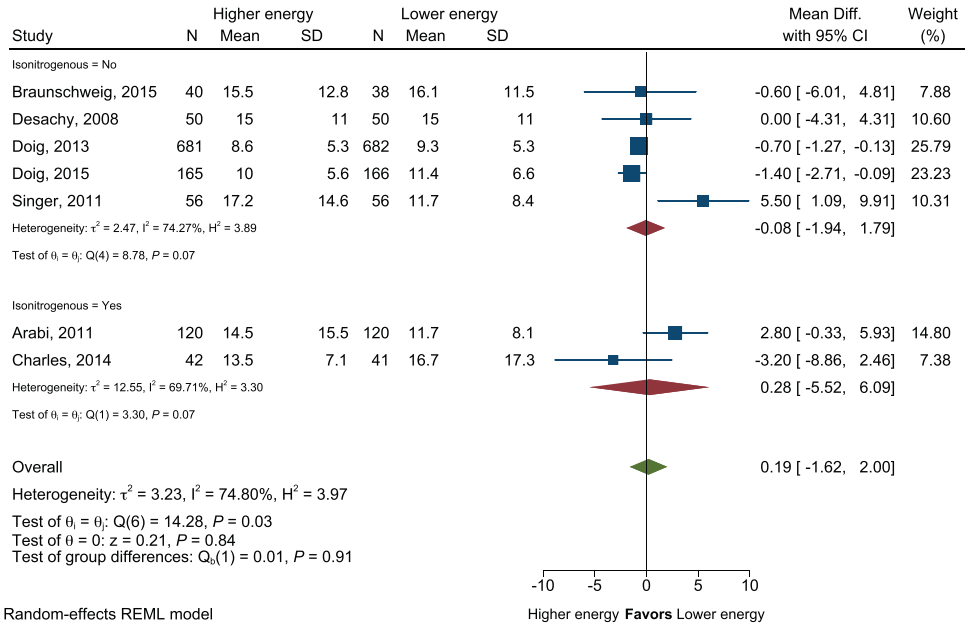

FIGURE 5 Mean difference in intensive care unit length of stay in patients with higher vs lower energy intake. Diff., difference; REML, restricted maximum likelihood

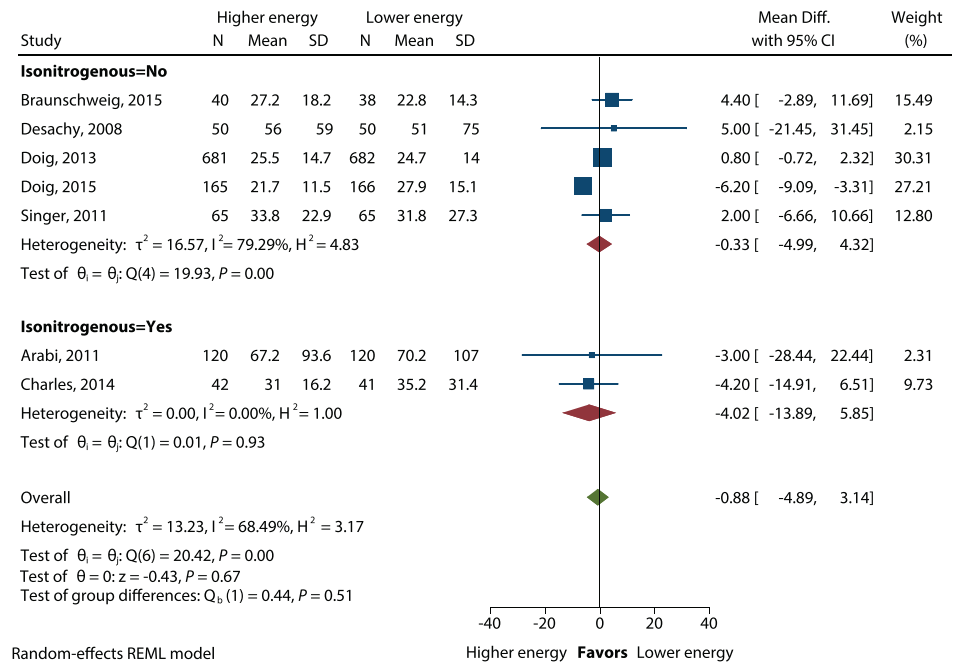

FIGURE 6 Mean difference in hospital length of stay in patients with higher vs lower energy intake. Diff., difference; REML, restricted maximum likelihood

specialized nutrition therapy in patients with low nutrition risk, in favor of either trophic or full-dose EN in those with ARDS, and in favor of achieving >80% of estimated energy needs by 48–72 h in those patients with high nutrition risk. This was based on the theory that patients will differ in their need for nutrition based on nutrition risk score. To date, this has been neither supported nor refuted through RCT data. Considering this and the fact that the current guideline found no statistically or clinically significant differences in outcomes relative to energy intake, we have chosen to not retain this distinction of nutrition risk in this guideline. Also of note, whereas the mean BMI of patients included in clinical trials in the 2016 guideline was not reported, the trials from the past 20 years included for this question reported a mean BMI in the overweight or obese range (Table 3).

Despite extensive research, inconsistency in energy provided and in how higher- and lower-fed groups were defined inhibited meaningful

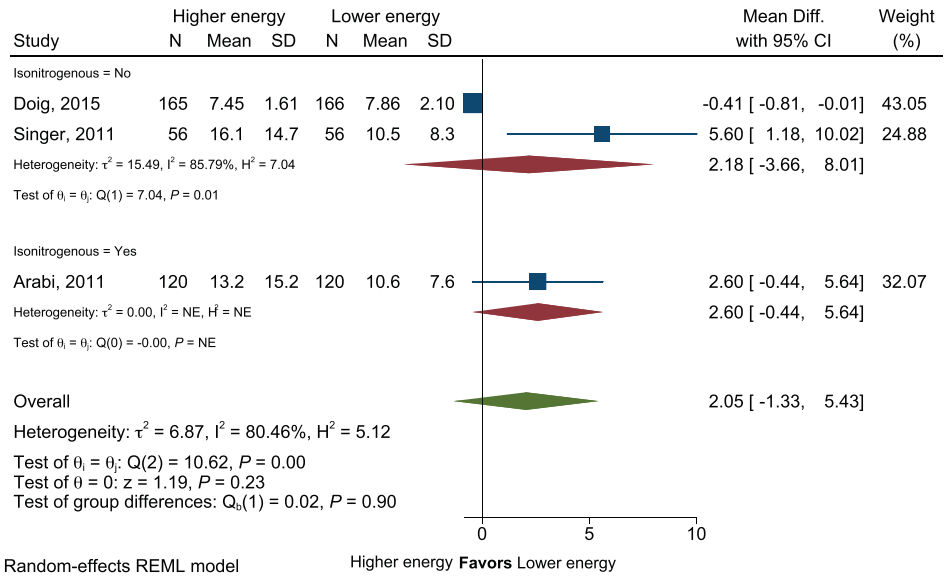

FIGURE 7 Mean difference in ventilator days in patients with higher vs lower energy intake. Diff., difference; NE, not estimable; REML, restricted maximum likelihood

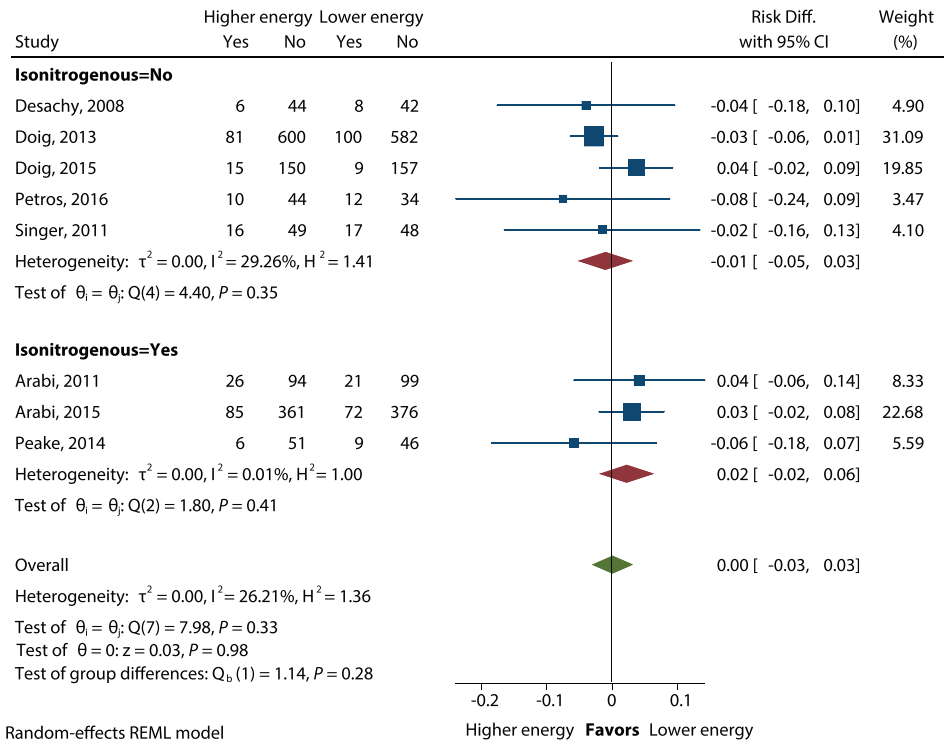

FIGURE 8 Mean difference in intensive care unit mortality in patients with higher vs lower energy intake. Diff., difference; REML, restricted maximum likelihood

clinical inference. To compare trials, at a minimum, the intervention and comparator groups need to be similar between studies. Table 3 reveals that trials that delivered 25–30 kcal/kg/day in the higher-fed group had comparison groups that were incomparable, and two trials[10,12] had a lower-fed group that received energy levels comparable to those of the higher-fed groups of most other studies. With such high heterogeneity, nothing can be inferred other than the average relative effect of feeding more vs less in critically ill patients. The safety analysis addressed this by breaking studies down into their randomization groups and plotting their energy intake per kilogram against hospital mortality.

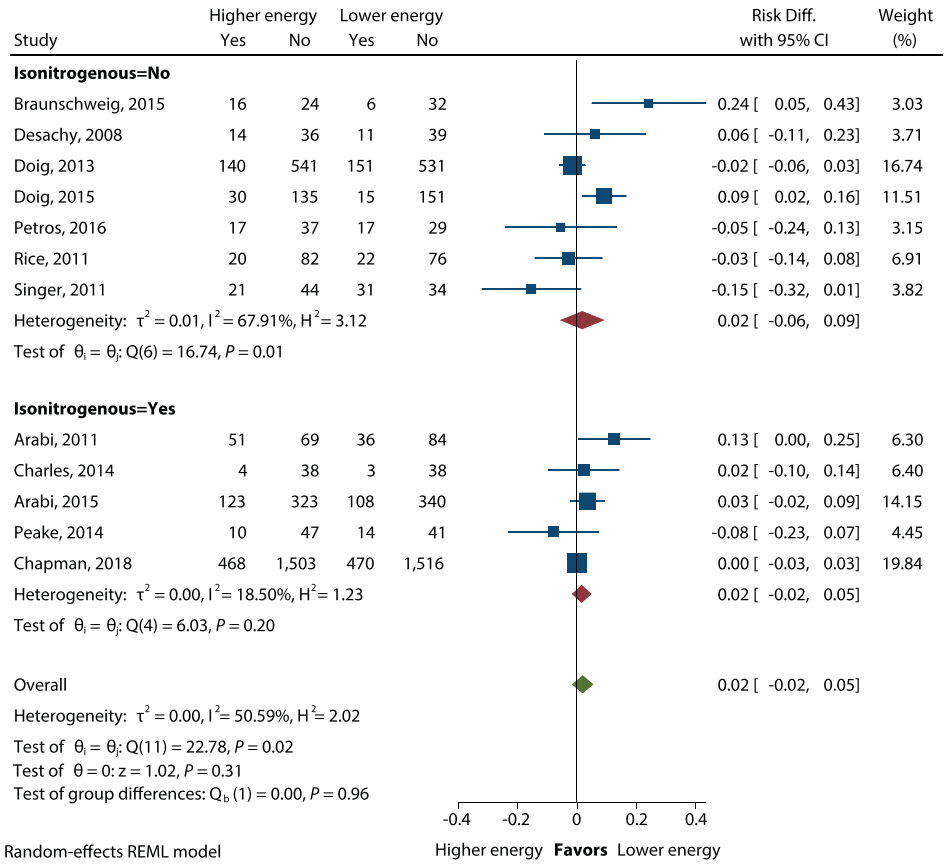

FIGURE 9 Mean difference in hospital mortality in patients with higher vs lower energy intake. Diff., difference; REML, restricted maximum likelihood

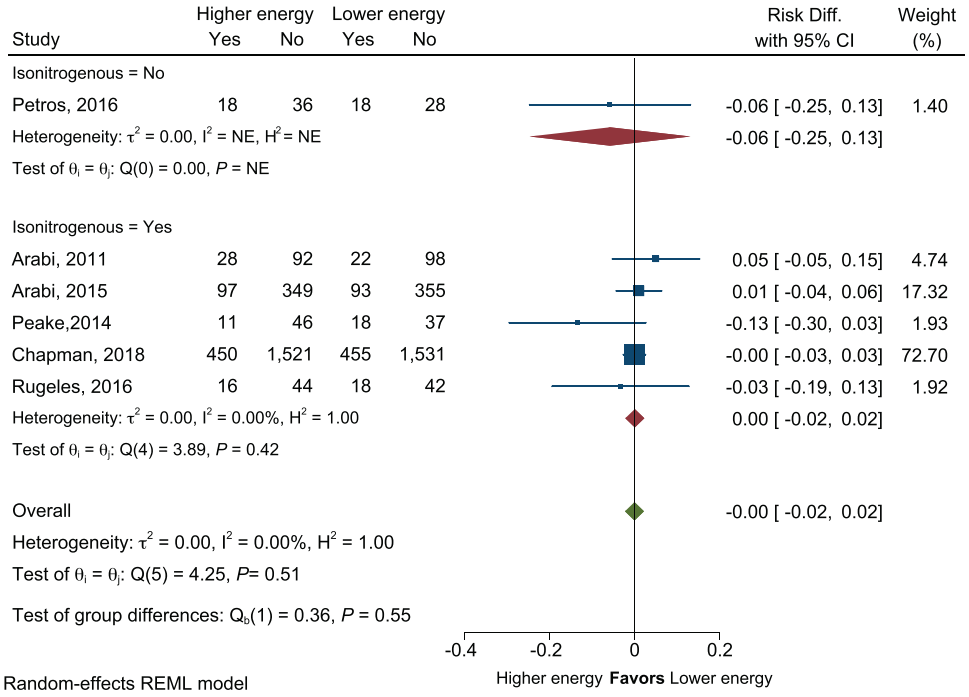

FIGURE 10 Mean difference in 28-day mortality in patients with higher vs lower energy intake. Diff., difference; NE, not estimable; REML, restricted maximum likelihood

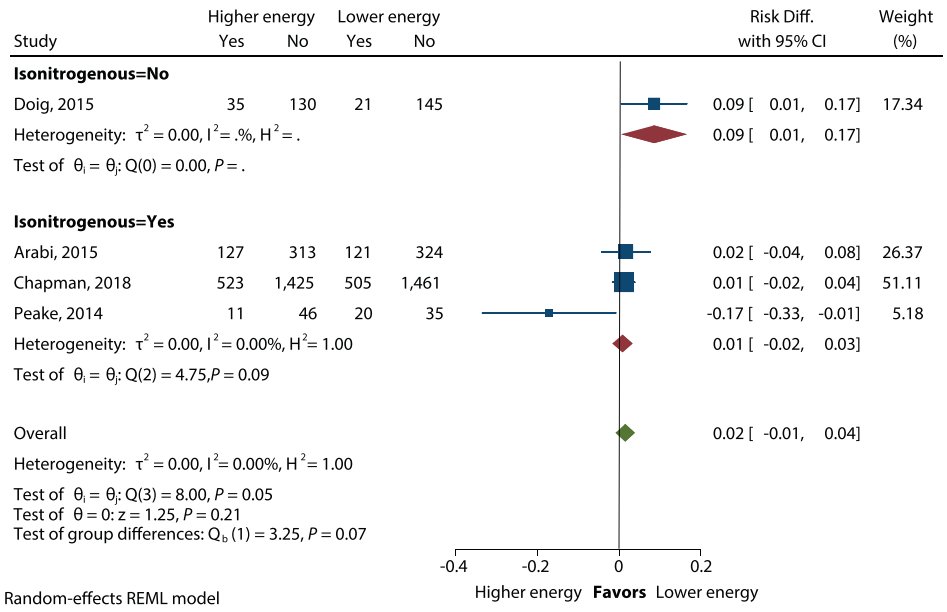

FIGURE 11 Mean difference in 90-day mortality in patients with higher vs lower energy intake. Diff., difference; NE, not estimable; REML, restricted maximum likelihood

The consistent positive slopes reported in this analysis combined with the consistent directionality toward increased mortality for the hospital (Figure 8) and ICU mortality (Figure 9) forest plots, even after stratification on whether the intended intervention was decreased (Figure S1) or increased (Figure S2) energy exposure compared with standard care, was the basis for our lack of certainty regarding the safety of higher levels of energy exposure. The lack of RCTs providing data on the consequences of withholding feeding coupled with the increased energy expenditure and metabolic demands of critical illness precludes us from a recommendation of withholding feedings at this time. The safety analysis implies that more tightly controlled energy intervention trials examining the impact of higher (25–30 kcal/kg/day) energy exposure vs lower (<12–15 kcal/kg per day) are urgently needed. This likely will require the use of SPN or PN, as gastric intolerance for EN is common in critical illness and often limits its delivery of the higher energy amounts. It may also be time to consider feeding trials in a carefully selected population in which the control group receives very low to no nutrition. Such a study would require careful design to minimize harm but would provide valuable information on the efficacy of nutrition support.

Question 2. In adult critically ill patients, does provision of higher as compared with lower protein intake impact clinical outcomes?

Recommendation: There was no difference in clinical outcomes in the relatively limited data. Because of a paucity of trials with high-quality evidence, we cannot make a new recommendation at this time beyond the 2016 guideline suggestion for 1.2–2.0 g/kg/day.

Quality of evidence: Low

Strength of recommendation: Weak

To be included in the analysis for this question, trials needed to (1) report protein intake in grams per kilogram per day (not only as percentage of goal), (2) have differences in protein intake of at least 0.2 g/kg/day between groups, and (3) have roughly equivalent energy intake between the groups. The expectation for equivalent energy intake is required to distinguish the impact of protein provision from differential energy or micronutrient provision. Four trials[18–21] met these criteria, with data from 697 patients (Table 4).

For the trials reporting protein delivered in grams per kilogram per day, patients randomized to the higher-protein arm had an intake ranging from 1.1[19] to 1.3 g/kg/day.[20] The largest trial by Doig et al[18] did not specifically report intake levels from patient feeding, but the intravenous amino acid dose prescribed by Doig was estimated to be about 1.75 g/kg/day. All trials provided comparable energy intake.

The quality of evidence varied among the trials. Many did not describe study design details. However, two had small sample sizes and were targeted to achieve the primary aim of increased protein[20] or protein/energy[21] intake rather than mortality, an outcome that would have required a larger sample size. Thus, the ICU mortality outcome below is reported on <85 events and the hospital mortality on <115 events. Ventilator days were variably reported as mean ± SD,[20] mean/10 ICU days,[18] and median (IQR)[21,19] and thus could not be combined into a summary statistic. Most trials also reported null findings for LOS outcomes in the higher-protein group, with one study (Fetterplace et al[21]) reporting increased hospital LOS in the higher-protein group. However, the interpretation of this finding is tempered

TABLE 4 Data summary for question 2: In adult critically ill patients, does provision of higher vs lower protein intake impact clinical outcomes?

First author, year	Population	Comparison (*n*) of higher vs lower protein	Intake provided	Infections, *n* (%)	Time on mechanical ventilation, median (IQR) or mean ± SD, days	Length of stay, median (IQR) or mean ± SD, days	Mortality, *n* (%)
Doig, 2015[18]	Patients in 16 med/surg ICUs Mean BMI: 28.9 vs 29.5	IVAA to 2 g/kg/day + standard care ($n = 239$) vs standard care ($n = 235$)	Total energy (kcal/kg/day): NR Protein (g/kg/day) during ICU stay: maximum of 2 vs NR	NR	7.3 (7–7.7) vs 7.3 (6.9–7.6) per 10 ICU days[a]	ICU:[a] 11.6(10.8–12.5) vs 10.7(10–11.5) Hospital:[a] 26(24.2–28) vs 24.8(23–26.6)	ICU: 28(12) vs 30(13) Hospital: 37(16) vs 43(18) 90-day: 42(18) vs 47(20)
Ferrie, 2016[19]	Patients requiring PN in med/surg ICU BMI: NR	1.2 g/kg PN ($n = 59$) vs 0.8 g/kg PN ($n = 60$)	Energy (kcal/kg/day) over 7 days: 23.1 ± 3.9 vs 24.9 ± 4.2 Protein (g/kg/day) over 7 days: 1.1 ± 0.2 vs 0.9 ± 0.2	NR	2.0(1.0–3.0) vs 2.0(1.0–5.0)	ICU: 5(3–8) vs 6(3.8–10) Hospital: 25 (16.8–41.3) vs 27.5(18.8–55.8)	ICU: 8(14) vs 6(10) Hospital: 12(20) vs 9(15) 6-month: 15(25) vs 9(15)
Fetterplace, 2018[21]	Patients in med ICU Mean BMI: 30 vs 29	1.5 g/kg EN ($n = 30$) vs 1.0 g/kg EN ($n = 30$)	Total energy (kcal/kg/day): 21 ± 5.2 vs 18 ± 2.7 Protein (g/kg/day): 1.2 ± 0.3 vs 0.8 ± 0.1	NR	6.2 (4.5–10.8) vs 5.1 (3.6–8.5)	ICU: 7.8(5.9–13.4) vs 7.5(4.9–12.7) Hospital: 22(9.9–43) vs 15(9.9–25)	28-day: 4(13) vs 5(17) 60-day: 4(13) vs 5(17)
van Zanten, 2018[20]	Overweight ICU patients (BMI ≥ 25) with med, surg, or trauma diagnosis Mean BMI: 30.3 vs 30.7	High-protein EN ($n = 22$) vs standard-protein EN ($n = 22$)	Energy (kcal/kg/day): 16.6(8.9–23.3) vs 14.4(10.9–18.8) Protein (g/kg/day): 1.3(0.7–1.9) vs 0.7(0.5–0.9)	NR	10 ± 8.7 vs 7.4 ± 5.4	ICU: 18.4 ± 13.4 vs 18.3 ± 12.7 Hospital: 28.5 ± 13.3 vs 28.2 ± 13.2	ICU: 1(5) vs 2(9) Hospital: 2(9) vs 3(14)

Abbreviations: BMI, body mass index (kg/m^2); EN, enteral nutrition; ICU, intensive care unit; IVAA, intravenous amino acid; med, medical; NR, not reported; PN, parenteral nutrition; surg, surgical.
[a]Mean (95% CI).

by non-isocaloric randomization groups. Although these shorter-term outcomes might logically be impacted by the level of protein intake, the high variability in outcomes left no discernable pattern. Underpowered mortality data (our critical outcome) and the same issue of indirectness discussed in question 1 necessitated an evidence quality rating of low. Based upon the limited data with which to assess the benefits and harms, this recommendation received a strength rating of weak.

Mortality in the ICU was not different in three trials with data from 637 patients (RD = −0.01; 95% CI, −0.06 to 0.04; $P = 0.81$) (Figure 12).

Hospital mortality was not different in three trials with data from 637 patients (RD = −0.02; 95% CI, −0.07 to 0.04) (Figure 13).

The 2016 ASPEN-SCCM guideline[1] recommended a protein dose of 1.2–2 g/kg/day for most critically ill patients and for higher amounts to be provided to patients with burns, obesity, or trauma. Our current guideline is driven by the limited available RCT data on the impact of varying protein intake. No trials specifically in patients with burns, obesity, or multitrauma were identified that met inclusion criteria.

Several ongoing clinical trials are currently testing a higher vs lower protein dose in critically ill patients (see Supporting Appendix). Assuming these trials deliver roughly equivalent energy intake in both arms concurrent with higher vs lower protein dose, data may soon be available to better inform optimal protein delivery in critically ill patients.

Question 3: In adult critically ill patients who are candidates for EN, does similar energy intake by PN vs EN as the primary feeding modality in the first week of critical illness impact clinical outcomes?

Recommendation: There was no significant difference in clinical outcomes between early exclusive PN and EN during the first week of

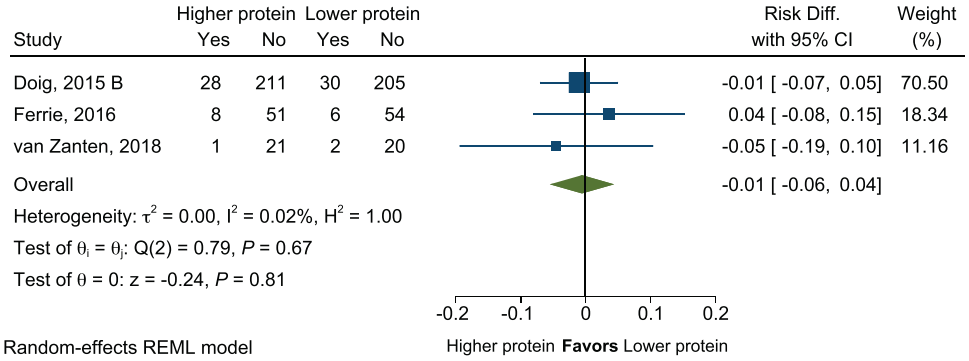

FIGURE 12 Mean difference in intensive care unit mortality in patients with higher vs lower protein dose. Diff., difference; REML, restricted maximum likelihood

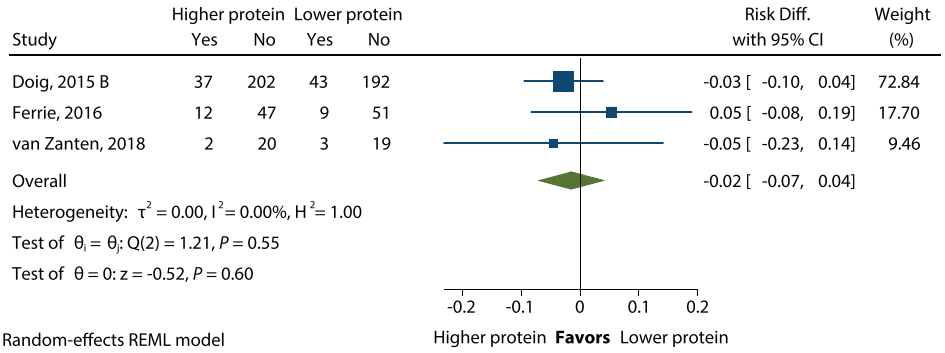

FIGURE 13 Mean difference in hospital mortality in patients with higher vs lower protein dose. Diff., difference; REML, restricted maximum likelihood

critical illness. As PN was not found to be superior to EN and no differences in harm were identified, we recommend that either PN or EN is acceptable.

Quality of evidence: High

Strength of recommendation: Strong

To be included in the analysis for this question, trials needed to randomize patients who were candidates for EN to EN or PN within the first 3 days of ICU admission. Two large, multicenter trials comparing early PN with EN, using data from 4798 critically ill medical ICU patients, met our inclusion criteria (Table 5).[22,23]

The quality of research for this question was high (Figures S73–S74). Both trials were designed to answer our question directly. They were randomized to PN or EN within 36 h of admission[22] or 24 h after intubation.[23] The interventions were only 5–7 days. However, reported outcomes occurred from randomization to hospital discharge; mortality was reported to 90 days post discharge. Nutrition intake information outside of the short intervention interval was not provided. The energy and protein delivery were very similar in these trials, suggesting that differences observed were not likely because of variations in their exposure. Blinding in studies comparing EN and PN is difficult; however, the impact of this lack of blinding is likely small for the objective outcome measures (mortality or culture-proven infection) used as the primary end points.[22,23] The high sample size and low-bias study designs in these two large trials, together with their consistent findings, support the quality of evidence as high. It is unlikely that future large trials will be undertaken to answer this question. The recommendation grade is strong, as there do not appear to be any harms or benefits concerning the choice of using EN vs PN. Given these data, the cost and convenience of providing EN vs PN may be larger determinants of route of feeding early in critical illness than differences in clinical outcomes.

Comparison of data in forest plots to evaluate effect size was not possible because there were only two trials. The individual trial outcomes are summarized in Table 5. No significant differences in any clinical outcome were reported. Adverse events such as infection were not significantly different, and enteral feeding intolerance was, as expected, more common in the EN treatment group.

Superiority between modalities was not found, and the short course of PN delivered early in critical illness was not found to increase infections or other adverse events.

This recommendation differs from that of the previous guideline.[1,24] Based on expert consensus, the 2016 ASPEN-SCCM guideline suggested to withhold PN for 7 days in patients with low nutrition risk who are unable to tolerate EN but to use PN in patients at high nutrition risk or those with malnutrition. The current guideline is based

TABLE 5 Summary data for question 3: In adult critically ill patients who are candidates for EN, does early PN vs EN in the first week of critical illness impact clinical outcomes?

First author, year	Population	Comparison (sample size *n*) of PN vs EN	Intake provided	Infections, *n* (%)	Time on mechanical ventilation, median (IQR) or mean ± SD, days	Length of stay, median (IQR) or mean ± SD, days	Mortality, *n* (%)
Harvey, 2014[22]	Critically ill adults with unplanned admission to 33 med/surg ICUs Median BMI: 27.7 vs 28.2	PN (*n* = 1191) vs EN (*n* = 1197)	Energy (kcal/kg/day): 21.3 (7.7) vs 18.5(7.7) Total protein (g/kg/day) through 5 days: 3 ± 2 vs 3 ± 2	NR	NR	ICU: 8.1 (4–15.8) vs 7.3 (3.9–14.3) Hospital: 17(8–34) vs 16(8–33)	30-day: 393 (33) vs 409 (34) ICU: 317 (27) vs 352 (29) Hospital: 431(36) vs 450(38) 90-day: 442(37) vs 464(39)
Reignier, 2017[23]	Ventilated adults with shock requiring PN in 44 med/surg ICUs Mean BMI: 27.7 vs 28	PN (*n* = 1208) vs EN (*n* = 1202)	Total energy (kcal/kg/day): 19.6 ± 5.3 vs 17.8 ± 5.5 vs Protein (g/kg/day): 0.8(0.2) vs 0.7(0.2)	Bacteremia: 55(5%) vs 38(3%) Pneumonia: 118(10%) vs 113(9%) Any infection: 194(16%) vs 173(14%)	NR	ICU: 10(5–17) vs 9(5–16) Hospital: 18(9–33) vs 17(8–32)	ICU: 405(31) vs 429(33) Hospital: 479(34) vs 498(36) 28-day: 422(35) vs 443(37) 90-day: 507(43) vs 530(45)

Abbreviations: BMI, body mass index (kg/m^2); EN, enteral nutrition; ICU, intensive care unit; med, medical; NR, not reported; PN, parenteral nutrition; surg, surgical.

on more recent (2001–2020), higher-quality data from large, multicenter trials. More modern nutrition support practices in critically ill patients, including improved catheter care, glycemic control, and avoidance of overfeeding energy, may have reduced the risk of bacteremia and hyperglycemia commonly seen with the early years of PN administration. The current trials also began feedings in most cases within 24–36 h of ICU admission and continued them for a few days and not for weeks or longer. Because the evidence on which this recommendation was predominantly based started PN within the first 3 days of ICU admission and continued therapy for only 5–7 days, this recommendation is directed to the first week of ICU therapy and in patients who may be candidates for EN. Given the limited enrollment of patients unable to tolerate EN in these studies, the results may not be generalizable to populations of patients with decreased EN tolerance, such as complex surgical populations.

Question 4. In adult critically ill patients receiving early EN, does provision of SPN to meet energy targets vs no SPN during the first week of critical illness impact clinical outcomes?

Recommendation: There was no significant difference in clinical outcomes. Based on findings of no clinically important benefit in providing SPN early in the ICU admission, we recommend not initiating SPN prior to day 7 of ICU admission.

Quality of evidence: High

Strength of recommendation: Strong

To be included in the analysis for this question, trials needed to report on differences in outcomes in response to SPN vs no SPN or standard care. Six RCTs[17,25–29] with data from 6731 critically ill patients met our inclusion criteria (Table 6).

The quality of evidence was varied. All trials used randomization concealment at the point of study enrollment, objective primary outcomes, and blinded outcome adjudicators. However, two trials[27,28] had protein or energy delivery as the primary outcome, and one[26] focused on quality of life. Most reported acute ICU admissions, but the largest trial[30] enrolled only 40% acute admissions. Three trials[17,28,29] did not report the amount of energy or protein delivered, whereas the others documented greater energy and protein intake in the SPN group. The discrepant approaches to presentation of findings on ICU and hospital LOS and ventilator days precluded our determination of an effect size for these outcomes, and reported outcomes varied. Most trials reported null findings for days on mechanical ventilation and both ICU and hospital LOS. An exception to this was the large EPaNIC study[29] (*n* = 4640) that reported increased ICU LOS and increased percentage of patients requiring >2 days of mechanical ventilation. The evidence quality for the group of trials was high, based upon our critical outcome, hospital mortality. The recommendation strength for this question is strong.

TABLE 6 Data summary for question 4: In adult critically ill patients receiving early EN, does provision of SPN to meet energy targets vs no SPN during the first week of critical illness impact clinical outcomes?

First author, year	Population	Comparison (sample size *n*) of SPN vs control	Intake provided	Infections, *n* (%)	Time on mechanical ventilation, median (IQR), days	Length of stay, median (IQR) or mean ± SD, days	Mortality, *n* (%)
Allingstrup, 2017[26]	Acutely admitted adult ICU patients Median BMI: 22 vs 22	EN plus PN dosed by indirect calorimetry (*n* = 100) vs 25 kcal/kg EN (*n* = 99) over ICU stay	Energy (kcal/day): 1877 (1567–2254) vs 1061 (745–1470) Protein (g/kg/day): 1.5(1.1–1.7) vs 0.5(0.3–0.7)	Bacteremia: 5(5) vs 4(4) Pneumonia: 4(4) vs 4(4) Any infection: 19(19) vs 12(12)	NR	ICU: 7(5–22) vs 7(4–11) Hospital: 30(12–53) vs 34(14–53)	28-day: 20(20) vs 21(21) 90-day: 30(30) vs 32(32) 6-month: 37(37) vs 34(34)
Casaer, 2011[29]	Patients with nutrition risk score ≥3 out of 7; 40% emergency admission BMI ≥ 25, 57.3% vs 55.7%	Early PN (*n* = 2312) vs delayed PN (*n* = 2328) (both groups also received EN)	NR	Bacteremia: 174(7.5) vs 142(6.1) Pneumonia: 447(19.3) vs 381(16.4) Any infection: 605(26.2) vs 531(22.8)	2(1–5) vs 2(1–5)	ICU: 4(2–9) vs 3(2–7) Hospital: NR	ICU: 146(6) vs 141(6) Hospital: 251(11) vs 242(10) 90-day: 255(11) vs 257(11)
Doig, 2013[17]	Critically ill patients with short-term contraindication to EN in 31 med/surg ICUs Mean BMI: 27.9 vs 28.5	Early PN (*n* = 681) vs standard care (*n* = 682) (both groups also received EN)	NR	Bacteremia: 39(6) vs 33(5) Pneumonia: 43(6) vs 45(7) Any infection: 74(11) vs 78(11)	NR	ICU: [a]8.6(8.2–9) vs 9.3(8.9–9.7) Hospital: [a]25.4(24.4–26.6) vs 24.7(23.7–25.8)	ICU: 81(12) vs 100(15) Hospital: 140(21) vs 151(22) 60-day: 146(22) vs 155(23)
Heidegger, 2013[25]	Patients in med/surg ICUs Mean BMI: 25.4 vs 26.4	EN + SPN to meet needs (*n* = 153) vs EN alone (*n* = 152)	Energy (kcal/kg/day), day 4–8: 28 ± 5 vs 20 ± 7 Protein (g/kg/day), day 4–8: 1.2 ± 0.2 vs 0.8 ± 0.3	Bacteremia: 10(19) vs 6(14) Pneumonia: 35(67) vs 28(65)	6.4 ± 6.8 vs 6.9 ± 6.7	ICU: 13 ± 10 vs 13 ± 11 Hospital: 31 ± 23 vs 32 ± 23	ICU: 8(5) vs 12(7) Hospital: 20(13) vs 28(18)
Ridley, 2018[27]	Critically ill adults Mean BMI: 29 vs 30	EN + SPN by day 3 ICU admit (*n* = 51) vs EN alone (*n* = 48)	Energy (kcal/kg/day): 24.9 ± 6.4 vs 16.8 ± 8.2 Protein (g/kg/day): 1.0 ± 0.3 vs 0.6 ± 0.3	Any infection: 18(35) vs 16(33)	10(6–15) vs 8(5–18)	ICU: 11(5–17) vs 11(6–17) Hospital: 22 ± 21 vs 23 ± 17	ICU: 15(29) vs 11(23) Hospital: 16(31) vs 11(23) 90-day: 19(37) vs 13(27) 180-day: 19(37) vs 13(27)
Wischmeyer, 2017[28]	Underweight and obese critically ill adults Mean BMI: 33.5 vs 33.2	EN + SPN (*n* = 52) vs EN (*n* = 73)	NR	Bacteremia: 0 vs 1(2.2) Pneumonia: 12(31.6) vs 18(39.1) Any infection: 14(26.9) vs 23(31.5)	6.5(3.9–14.1) vs 8.3 (3.8–13.3)	ICU: 12.8 (7.9–17.8) vs 12.6 (8.1–18.7) Hospital: 23.5 (17.5–34.7) vs 24 (16.6–38.9)	ICU: 7(14) vs 13(18) Hospital: 8(15) vs 17(23)

Abbreviations: BMI, body mass index (kg/m^2); EN, enteral nutrition; ICU, intensive care unit; med, medical; NR, not reported; PN, parenteral nutrition; SPN, supplemental PN; surg, surgical.

[a]Mean (95% CI).

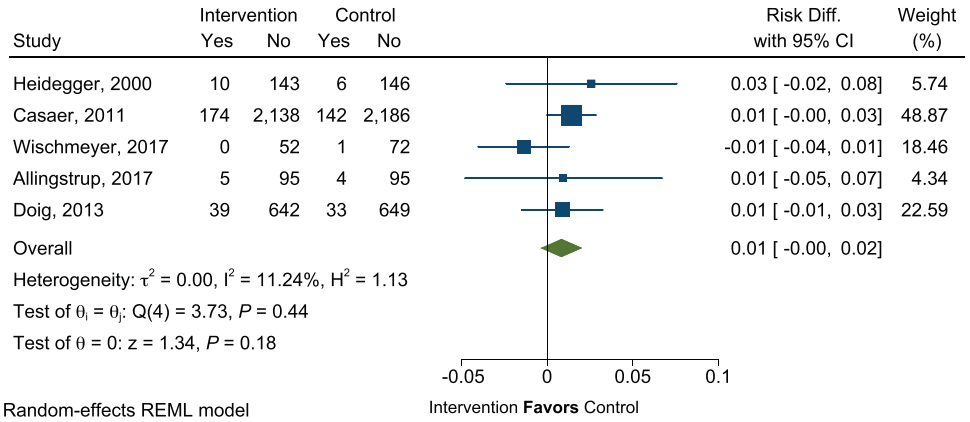

FIGURE 14 Mean difference in bacteremia incidence in critically ill patients with supplemental parenteral nutrition (PN) vs no supplemental PN. Diff., difference; REML, restricted maximum likelihood

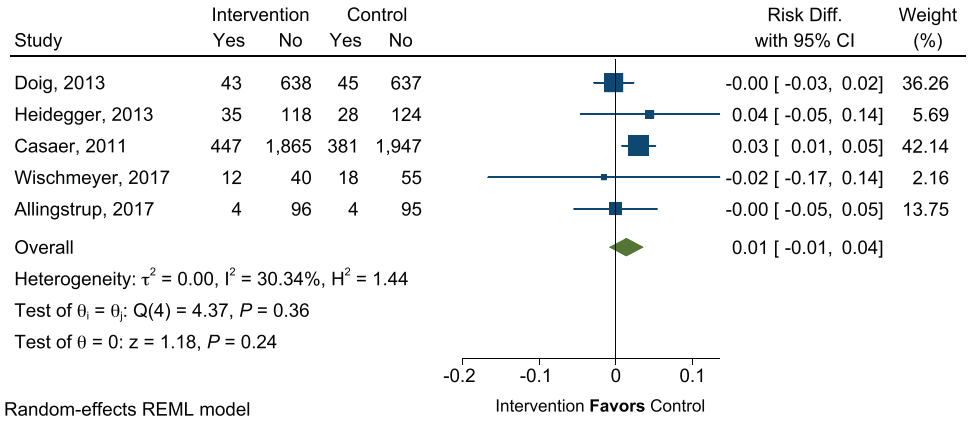

FIGURE 15 Mean difference in pneumonia incidence in critically ill patients with supplemental parenteral nutrition (PN) vs no supplemental PN. Diff., difference; REML, restricted maximum likelihood

Outcomes during the ICU stay were not significantly improved with the addition of SPN. The risk of bacteremia was not significantly different (RD = 0.01; 95% CI, −0.00 to 0.02; *P* = 0.18), with a risk of bacteremia of 6% in the standard-care group (Figure 14).

The incidence of pneumonia was not different with the addition of SPN (RD = 0.01; 95% CI, −0.01 to 0.04; *P* = 0.36), with a risk of pneumonia in the control group of 17% (Figure 15).

Any type of infection was not different with the addition of SPN (RD = 0.02; 95% CI, −0.01 to 0.05; *P* = 0.25), with a 20% rate of any infection in the control group (Figure 16).

ICU mortality was not different with the addition of SPN in five trials including data from 6532 patients (RD = −0.01; 95% CI, −0.03 to 0.01; *P* = 0.42), with 8% ICU mortality in the control group (Figure 17).

Hospital mortality was not different with the addition of SPN in five trials with data from 6532 patients (RD = −0.00; 95% CI, −0.03 to 0.02; *P* = 0.69), with 14% hospital mortality in the control group (Figure 18).

Ninety-day mortality was not different with the addition of SPN (RD = 0.00; 95% CI, −0.02 to 0.02; *P* = 0.96), with a 12% 90-day mortality rate in the control group (Figure 19).

The previous guideline recommended the use of SPN after 7–10 days in patients unable to tolerate >60% of goal protein and energy requirements.[1,24] Whereas the 2016 guideline suggested waiting 7–10 days to add SPN, the trials included here began SPN by day 3, and most continued the therapy for 6–8 days. However, no difference in infectious complications or mortality was noted in the combined data. Based on findings of no clinically important benefit in providing SPN early in the ICU admission, we suggest not initiating SPN prior to day 7 of ICU admission.

Question 5A. In adult critically ill patients receiving PN, does provision of mixed-oil ILEs (ie, medium-chain triglycerides, olive oil, FO, mixtures of oils), as compared with 100% SO ILE, impact clinical outcomes?

Recommendation: Owing to limited statistically or clinically significant differences in key outcomes, we suggest that either mixed-oil ILE or 100% SO ILE be provided to critically ill patients who are appropriate candidates for initiation of PN, including within the first week of ICU admission.

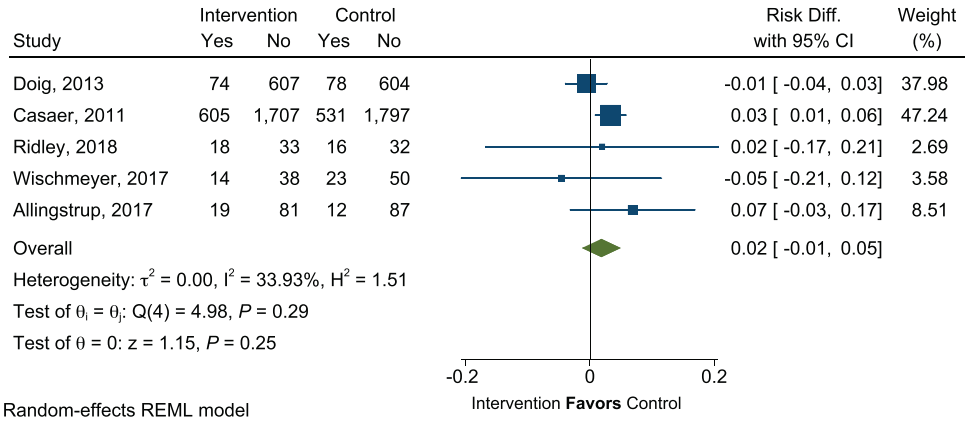

FIGURE 16 Mean difference in any infection in critically ill patients with supplemental parenteral nutrition (PN) vs no supplemental PN. Diff., difference; REML, restricted maximum likelihood

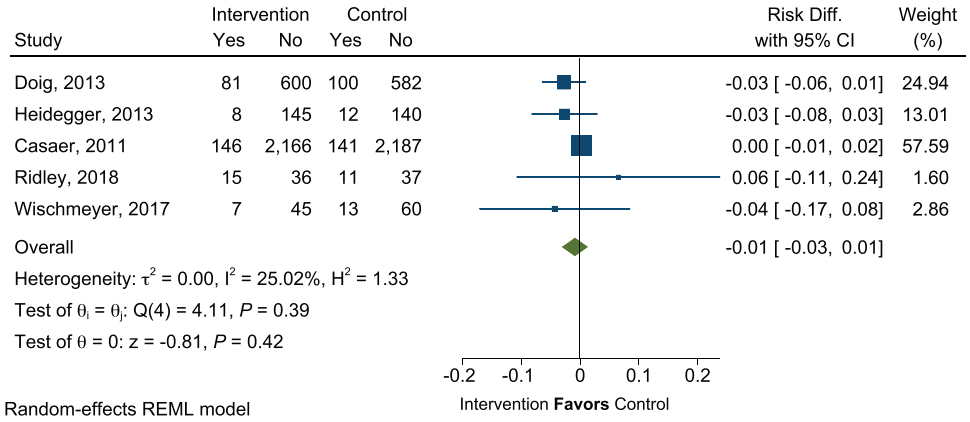

FIGURE 17 Mean difference in intensive care unit mortality in critically ill patients with supplemental parenteral nutrition (PN) vs no supplemental PN. Diff., difference; REML, restricted maximum likelihood

Quality of evidence: Low

Strength of recommendation: Weak

To be included in the analysis for this question, RCTs needed to (1) compare initiation of PN with mixed-oil ILE against 100% SO ILE as a component of PN and (2) report clinical outcomes. Seven trials[31–37] met these criteria, with data from 624 patients (Table 7).

All formulations compared outcomes against a 100% SO ILE; however, the intervention groups varied considerably. The intervention was 30% SO/30% medium-chain triglyceride (MCT)/25% olive oil (OO)/15% FO ILE in two trials[31,33]; 10% FO/50% MCT/40% SO ILE in two trials[34,37]; 50 g SO/10 g FO ILE in two trials[32,36]; and 80% OO/20% SO ILE in one trial.[35] The length of the intervention varied from 12 h[34] to 28 days.[35] These studies included ILE as part of the PN regimen at the time of initiation, rather than withholding for the first week as recommended based on very low-quality evidence in the 2016 guideline.[1] Variability in the mixed-oil ILEs studied precluded comparisons in forest plots to determine effect sizes.

There were no differences in any clinical outcome reported, and the quality of evidence between trials was generally low. No trial was planned with the primary aim to examine the clinical outcomes selected for this guideline. Two trials[31,33] did not use ITT analysis or analyze differences between trial completers and noncompleters. Most trials[31,32,34,36,37] had unclear reporting of energy or the intervention delivered. No trial was powered for mortality outcomes. Only two trials[31,33] reported days of mechanical ventilation. The number of events was limited for each outcome (pneumonia, 22 events; bacteremia, 31 events; ICU mortality, 18 events; hospital mortality, 21 events; and 28-day/30-day mortality, 19 events). Low event rates may have left many studies underpowered to detect an effect. Serious risk of bias and lack of power for our critical outcomes resulted in a low evidence quality grade for this question. The recommendation strength for this question is weak because of a lack of quality evidence that would permit certainty of the harms and benefits.

Mixed-oil ILE products were not available in time for inclusion in the 2016 ASPEN-SCCM guideline.[1] Current RCTs in critically ill patients

TABLE 7 Data summary for question 5A: In adult critically ill patients receiving PN, does provision of mixed-oil ILEs (ie, MCTs, OO, FO, mixtures of oils), as compared with 100% SO ILE, impact clinical outcomes?

First author, year	Population	Comparison (sample size *n*) of mixed oil vs control	Intake provided	Infections, *n* (%)	Ventilator days, mean ± SD	Length of stay, median (IQR), days	Mortality, *n* (%)
Chen, 2017[32]	SIRS patients in 1 ICU BMI: NR	PN providing 20 kcal/kg/day with 10 g FO/50 g SO ILE (*n* = 24) vs PN with SO ILE (*n* = 24)	Energy (kcal/kg/day): NR Protein (g/kg/day): NR	NR	NR	ICU: 13.8 ± 9.9 vs 24.4 ± 23.2	28-day: 3(13) vs 10 (42)
Donoghue, 2019[31]	ARDS or SIRS in surg ICU Mean BMI: 29.2 vs 27.6	PN with 30% SO/30% MCT/25% OO/15% FO ILE (*n* = 35) vs 100% SO ILE (*n* = 33)	Energy (kcal/kg/day): NR Protein (g/kg/day): NR Four-oil ILE: 0.09–0.22 g/kg/day	NR	1.24 ± 0.83 vs 0.88 ± 1.63	ICU: 9.5 ± 7.1 vs 10.7 ± 7.6	NR
Metry, 2014[33]	Postoperative patients in surg ICU Mean BMI: 27.9 vs 28.1	PN with 30% SO/30% MCT/25% OO/15% FO ILE (*n* = 41) vs PN with 100% SO ILE (*n* = 42)	Energy (kcal/kg/day): 35 vs 35 Protein (g/kg/day): 1.2 vs 1.2 ILE (g/kg/day): 1.2+0.3 FO vs 1.5	NR	6.5 ± 5.1 vs 7.2 ± 4.3	ICU: 10.4 ± 6.2 vs 11.7 ± 7.2 Hospital: 15.7 ± 11.4 vs 19.4 ± 12.6	30-day: 3(7) vs 3(7)
Sabater, 2011[34]	ARDS BMI: NR	10%FO/50%MCT/40%SO ILE (*n* = 8) vs 100% SO ILE (*n* = 8)	Energy (kcal/kg/day): NR Protein (g/kg/day): NR ILE (g/kg/day): NR	NR	NR	NR	Hospital: 4(50) vs 2(25)
Umpierrez, 2012[35]	Adult med surg ICU patients Mean BMI: 27.4 vs 27.3	PN with 80%OO/20%SO ILE (*n* = 49) vs PN with 100% SO ILE (*n* = 51)	Energy (kcal/kg/day): 22 ± 6 vs 22 ± 5 Protein (g/kg/day): 1.2 ± 0.3 vs 1.2 ± 0.3 ILE (g/kg/day): 0.6 ± 0.2 vs 0.6 ± 0.2	Bacteremia: 11(22) vs 11(22) Pneumonia: 7(14) vs 5(10) Any infection: 29(57) vs 21(43)	NR	ICU: 17 ± 18 vs 15.2 ± 14 Hospital: 40.8 ± 36 vs 46.7 ± 48	ICU: 4 (8) vs 5(10) Hospital: 5(10) vs 8(16)
Weiss, 2002[36]	Adult surg ICU patients BMI: NR	PN up to 1400 kcal with 10 g FO/50 g SO (*n* = 12) vs 50 g SO (*n* = 11)	NR	Pneumonia: 1(8) vs 3(27)	NR	ICU: 4.1 vs 9.1 Hospital: 17.8 vs 23.5	Hospital: 1(8) vs 1(9)
Wichmann, 2007[37]	Major abdominal surgery Mean BMI: 25 vs 25	PN with 10%FO/50%MCT/40%SO ILE (*n* = 127) vs 100% SO ILE (*n* = 129)	NR	Bacteremia: 4(3%) vs 5 (4%) Pneumonia: 1(0.8) vs 5(4)	NR	ICU: 4.1 vs 6.3 Hospital: 17.2 vs 21.9	ICU: 6(5) vs 3(2)

Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index (kg/m^2); FO, fish oil; ICU, intensive care unit; ILE, lipid injectable emulsion; MCT, medium-chain triglycerides; med, medical; NR, not reported; OO, olive oil; PN, parenteral nutrition; SIRS, systemic inflammatory response syndrome; SO, soybean oil; surg, surgical.

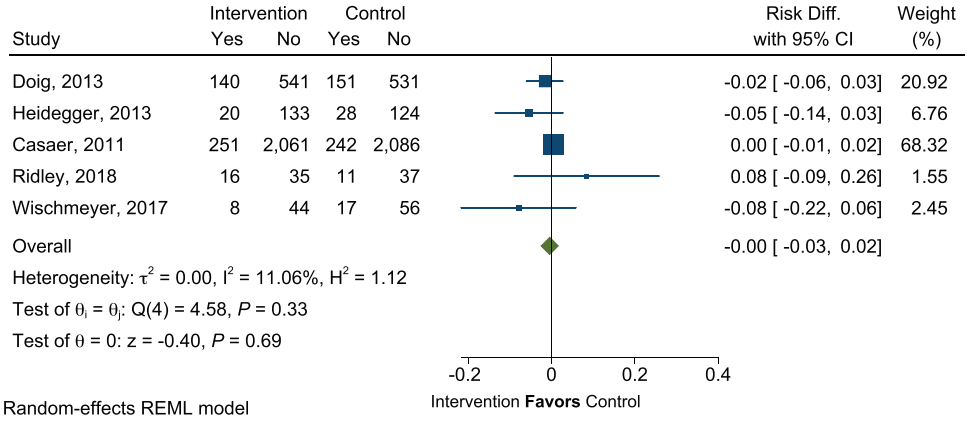

FIGURE 18 Mean difference in hospital mortality in critically ill patients with supplemental parenteral nutrition (PN) vs no supplemental PN. Diff., difference; REML, restricted maximum likelihood

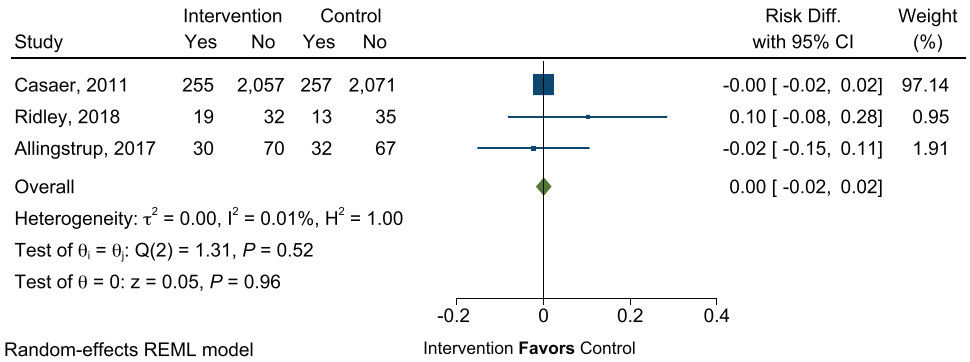

FIGURE 19 Mean difference in 90-day mortality in critically ill patients with supplemental parenteral nutrition (PN) vs no supplemental PN. Diff., difference; REML, restricted maximum likelihood

are limited, and further research is needed to investigate the potential anti-inflammatory and immunomodulatory properties of mixed-oil ILEs. Given that the differences in clinical outcomes were either statistically or clinically insignificant, we suggest at this time that either mixed-oil ILE or 100% SO ILE may be provided to critically ill patients who are appropriate candidates for initiation of PN, including within the first week of ICU admission.

Question 5B. In adult critically ill patients receiving PN, does provision of FO-containing ILE, as compared with non–FO-containing ILE, impact clinical outcomes?

Recommendation: Because there was only one outcome with a significant difference that was not supported by data covering the other key downstream outcomes, we suggest that either FO- or non–FO-containing ILE be provided to critically ill patients who are appropriate candidates for initiation of PN, including within the first week of ICU admission.

Quality of evidence: Low

Strength of recommendation: Weak

To be included in the analysis for this question, RCTs needed to (1) compare FO-containing ILE with non–FO-containing ILE as a component of PN and (2) report pertinent clinical outcomes. Ten trials[31–34,36–41] met these criteria, with data from a total of 919 patients (Table 8). In these studies, ILE was included as part of the PN regimen at the time of initiation.

The quality of evidence of the trials was generally low. Most trials focused primarily on biochemical or inflammatory outcomes. None of the studies had the clinical outcomes considered in this guideline as their primary outcome and a small number of events was reported for all outcomes. Two trials[31,33] did not use ITT analysis. Most trials[31,32,34,36,37,39,40] were unclear in their reporting of energy and/or intervention delivered. All formulations compared outcomes against a non–FO-containing ILE; however, the intervention groups varied considerably. The length of the intervention was generally very short, especially when considered relative to the time frame of the outcomes. As in question 5A, serious risk of bias and lack of power for our critical

TABLE 8 Data summary for question 5B: In adult critically ill patients receiving PN, does provision of FO-containing ILE, as compared with non–FO-containing ILE, impact clinical outcomes?

First author, year	Population	Comparison (sample size *n*) of FO vs control	Intake provided	Infections, *n* (%)	Ventilator days, mean ± SD	Length of stay, median (IQR), days	Mortality, *n* (%)
Barbosa, 2010[38]	Adults with SIRS in single-center study Mean BMI: 28.9 vs 28.5	10% FO/50% MCT/40% SO (*n* = 13) vs 50%MCT/50%SO (*n* = 10)	Energy (kcal/kg/day): 29.3 ± 7.6 vs 25.3 ± 5.6 Protein (g/kg/day): 1.17 ± 0.30 vs 1.22 ± 0.28	NR	10 ± 4 vs 11 ± 4	ICU: 12 ± 4 vs 13 ± 4 Hospital: 22 ± 7 vs 55 ± 16	28-day: 4(31) vs 4(40)
Chen, 2017[32]	SIRS patients in single center BMI: NR	PN providing 20 kcal/kg/day with 10 g FO/50 g SO ILE (*n* = 24) vs PN with SO ILE (*n* = 24)	Energy (kcal/kg/day): NR Protein (g/kg/day): NR	NR	NR	ICU: 13.8 ± 9.9 vs 24.4 ± 23.2	28-day: 3(13) vs 10 (42)
Chen, 2017[39]	Adults with severe sepsis, mechanical ventilation, and acute GI dysfunction BMI: NR	PN providing 10 g/day FO (*n* = 41) vs standard PN (*n* = 37) for 7 days	NR	NR	NR	NR	28-day: 10(24) vs 15(41) 60-day: 11(27) vs 18(49)
Donoghue, 2019[31]	ARDS or SIRS in surg ICU Mean BMI: 29.2 vs 27.6	PN with 30% SO/ 30% MCT/25% OO/15% FO/ ILE (*n* = 35) vs 100% SO ILE (*n* = 33) for 6 days	Energy (kcal/kg/day): NR Protein (g/kg/day): NR Four-oil ILE: 0.09–0.22 g/kg/day	NR	1.2 ± 0.8 vs 0.9 ± 1.6	ICU: 9.5 ± 7.1 vs 10.7 ± 7.6	NR
Friesecke, 2008[41]	Adult med ICU BMI: NR	83% Lipofundin (50% MCT/50% SO) + 17% Omegaven (FO emulsion) (*n* = 83) vs 100% Lipofundin (*n* = 82)	Energy (kcal/kg/day): 22.2 ± 5.5 vs 21.6 ± 5.6 Protein (g/kg/day): 1.1 ± 0.3 vs 1.1 ± 0.3 Lipid (g/kg/day): 0.91 ± 0.26 vs 0.93 ± 0.28	Pneumonia: 4(5) vs 5(6)	22.8 ± 22.9 vs 20.5 ± 19.0	ICU: 28 ± 25 vs 23 ± 20	28-day: 18 (22) vs 22 (27)
Grau-Carmona, 2015[40]	Adults in 17 med/surg ICUs Mean BMI: 26.6 vs 27.1	10% FO/50% MCT/40% SO (*n* = 81) vs 50% MCT/50% SO (*n* = 78) for 5 days	Energy (kcals/day): 1737 vs 1782 Protein (g/kg/day): 1.43 vs 1.41 Lipid (g/kg/day): 1.04 vs 1.05	Bacteremia: 10(12) vs 12(15) Pneumonia: 7(11) vs 14(22)	[a]7(6.0) vs 8(8.5)	ICU: [a] 12(18.5) vs 18(13.25) Hospital: [a] 25(34.5) vs 36.5 (34.0)	ICU: 26(33) vs 16(21) Hospital: 32(44) vs 22(31) 6-month: 34(42) vs 24(31)
Metry, 2014[33]	Postoperative patients in surg ICU Mean BMI: 27.9 vs 28.1	PN with 30% SO/30% MCT/25% OO/15% FO ILE (*n* = 41) vs PN with 100% SO ILE (*n* = 42) for 7 days	Energy (kcal/kg/day): 35 vs 35 Protein (g/kg/day): 1.2 vs 1.2 ILE (g/kg/day): 1.5+0.3 FO vs 1.5	NR	7.2 ± 4.3 vs 6.5 ± 5.1	ICU: 10.4 ± 6.2 vs 11.7 ± 7.2 Hospital: 15.7 ± 11.4 vs 19.4 ± 12.6	30-day: 3(7) vs 3(7)
Sabater, 2011[34]	ARDS BMI: NR	10% FO/50% MCT/40% SO ILE (*n* = 8) vs 100% SO ILE (*n* = 8) for 12 h	NR	NR	NR	NR	Hospital: 4(50) vs 2(25)

(Continues)

TABLE 8 (Continued)

First author, year	Population	Comparison (sample size *n*) of FO vs control	Intake provided	Infections, *n* (%)	Ventilator days, mean ± SD	Length of stay, median (IQR), days	Mortality, *n* (%)
Weiss, 2002[36]	Adult surg ICU patients BMI: NR	PN up to 1400 kcal with 10 g FO/50 g SO ($n = 12$) vs 50 g SO ($n = 11$)	NR	Pneumonia: 1(10) vs 3(14)	NR	ICU: 4.1 vs 9.1 Hospital: 17.5 vs 23.5	Hospital: 1(8) vs 1(9)
Wichmann, 2007[37]	Major abdominal surgery Mean BMI: 25 vs 25	PN with 10% FO/50% MCT/40% SO ILE ($n = 127$) vs 100% SO ILE ($n = 129$)	NR	Bacteremia: 4(3) vs 5 (4) Pneumonia: 1(0.8) vs 5(4)	NR	ICU: 4.1 vs 6.3 Hospital: 17.2 vs 21.9	ICU: 6(5) vs 3(2)

Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index (kg/m^2); FO, fish oil; GI, gastrointestinal; ICU, intensive care unit; ILE, lipid injectable emulsion; med, medical; MCT, medium-chain triglyceride; NR, not reported; PN, parenteral nutrition; SIRS, systemic inflammatory response syndrome; SO, soybean oil; surg, surgical.
[a]Median (IQR).

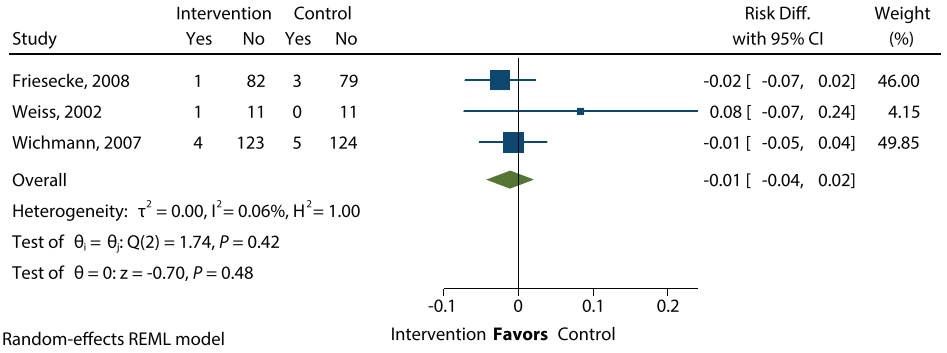

FIGURE 20 Mean difference in catheter-related infection incidence in critically ill patients receiving fish oil (FO)–containing lipid injectable emulsion (ILE) vs non–FO-containing ILE. Diff., difference; REML, restricted maximum likelihood

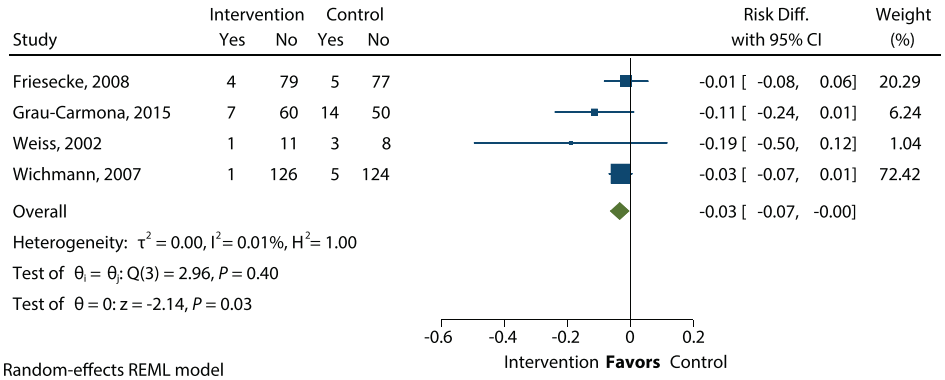

FIGURE 21 Mean difference in pneumonia incidence in critically ill patients receiving fish oil (FO)–containing lipid injectable emulsion (ILE) vs non–FO-containing ILE. Diff., difference; REML, restricted maximum likelihood

outcomes resulted in an evidence quality grade of low for this question. The recommendation strength for this question is weak because of a lack of quality evidence that would permit certainty of the harms and benefits.

Figures 20–25 represent the studies with data reported in a comparable manner. No significant differences in effect were found for any clinical outcomes between FO- or non–FO-containing ILE with the exception of pneumonia. Patients receiving FO ILE had

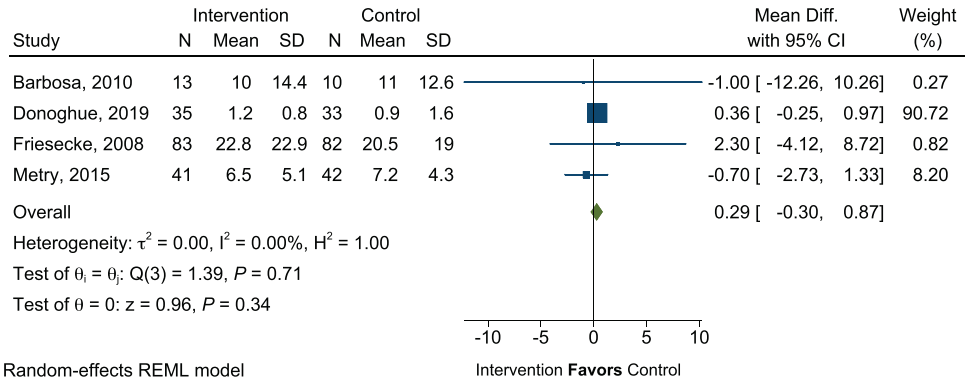

FIGURE 22 Mean difference in days of mechanical ventilation in critically ill patients receiving fish oil (FO)–containing lipid injectable emulsion (ILE) vs non–FO-containing ILE. Diff., difference; REML, restricted maximum likelihood

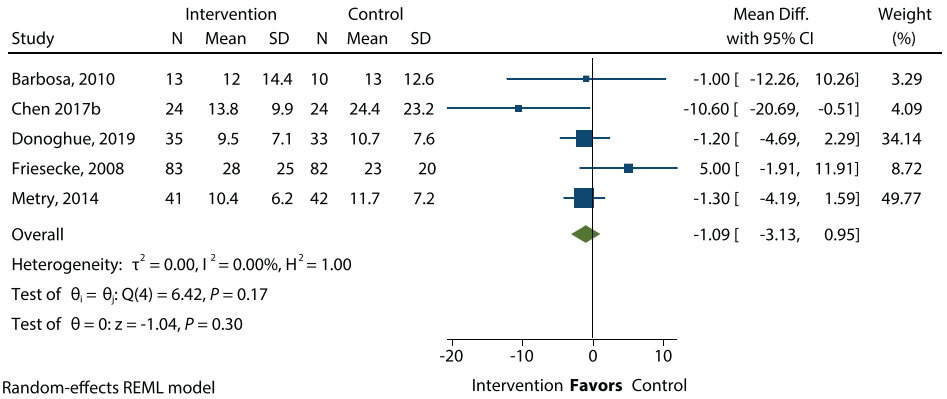

FIGURE 23 Mean difference in intensive care unit length of stay in critically ill patients receiving fish oil (FO)–containing lipid injectable emulsion (ILE) vs non–FO-containing ILE. Diff., difference; REML, restricted maximum likelihood

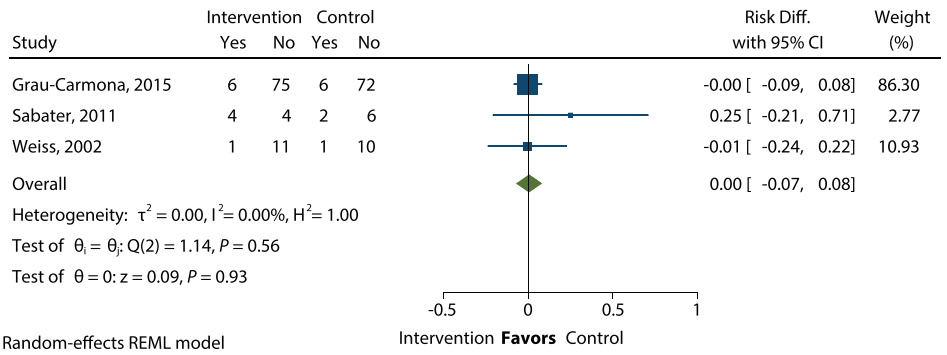

FIGURE 24 Mean difference in hospital mortality in critically ill patients receiving fish oil (FO)–containing lipid injectable emulsion (ILE) vs non–FO-containing ILE. Diff., difference; REML, restricted maximum likelihood

reduced pneumonia. However, this finding was not supported by the null findings for downstream variables such as days of mechanical ventilation or LOS (Figure 21). These findings therefore did not impact the recommendation. Data for other infections, ICU mortality, and hospital LOS were also reported in a manner that precluded the estimation of summary statistics and generation of forest plots.

The incidence of catheter-related infection was not different in patients receiving FO- vs non–FO-containing ILE in three trials including data from 469 patients (RD = −0.01; 95% CI, −0.04 to 0.02 days; $P = 0.48$) when the risk of catheter-related infection in the control group was 3.7% (Figure 20).

The incidence of pneumonia was decreased in patients receiving FO-containing ILE vs non–FO-containing ILE in four trials including

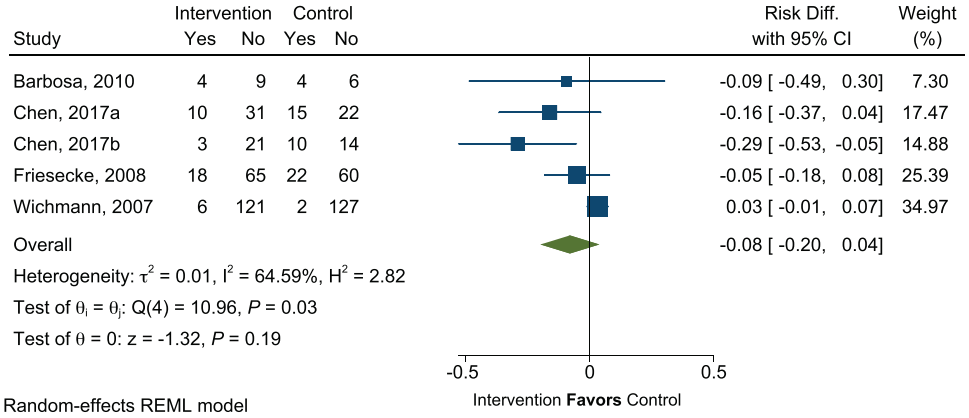

FIGURE 25 Mean difference in 30-day mortality in critically ill patients receiving fish oil (FO)–containing lipid injectable emulsion (ILE) vs non–FO-containing ILE. Diff., difference; REML, restricted maximum likelihood

data from 575 patients with a total of 40 events (RD = −0.03; 95% CI, −0.07 to 0.00 days; $P = 0.03$). The risk of pneumonia in the FO ILE group was ~5% vs ~9% in the non-FO ILE group (Figure 21). This outcome favors the FO intervention and could be considered clinically significant, but confidence in this estimate is somewhat dampened by the low number of studies and the fact that the findings are not supported by the other null outcomes that should be worsened by incident pneumonia, such as days of mechanical ventilation and ICU LOS. For this reason, it was decided that recommendation for FO would be premature. Future studies will reveal whether this preliminary signal of benefit for FO ILE is maintained, and this question will be revisited.

Days of mechanical ventilation were not different in patients receiving FO- vs non–FO-containing ILE in four trials including data from 339 patients (RD = 0.29; 95% CI, −0.30 to 0.87 days; $P = 0.34$) with mean duration of mechanical ventilation of 9.9 days in the control group (Figure 22). Unfortunately, only Friesecke et al[41] reported both pneumonia and time on mechanical ventilation.

ICU LOS was not different in patients receiving FO- vs non–FO-containing ILE in five trials including data from 387 patients (RD = −1.09; 95% CI, −3.13 to 0.95 days; $P = 0.3$) with mean ICU LOS of 16.6 days in the control group (Figure 23).

Hospital mortality was not different in patients receiving FO- vs non–FO-containing ILE in three trials including data from 198 patients (RD = 0.00; 95% CI, −0.07 to 0.08; $P = 0.93$) with 12.5% hospital mortality in the control group (Figure 24).

One-month mortality (28-day and 30-day) was not different in patients receiving FO- vs non–FO-containing ILE in five trials including data from 570 patients (RD = −0.08; 95% CI, −0.20 to 0.04; $P = 0.19$) with 18.8% mortality in the control group (Figure 25).

Based on these findings, we suggest that either FO-containing or non–FO-containing ILE may be provided to critically ill patients who are appropriate candidates for initiation of PN, including within the first week of ICU admission. Given the initial signal of benefit seen for pneumonia, additional research is clearly warranted to elucidate the role of FO-containing ILE within PN formulations.

Other questions

Though we initially searched for trials related to eight questions, RCTs meeting inclusion and exclusion criteria were only found to answer the five above questions developed by the authors. Adequate data were not found to address three important critical care nutrition questions identified at the outset by the author team:

1. **In adult critically ill patients, do higher nutrition risk scores predict worse outcomes than BMI alone as the indicator of nutrition risk?** Our searches yielded no RCTs comparing clinical outcomes based on groups of patients randomized according to either the Nutrition Risk in the Critically Ill (NUTRIC) score or the Nutrition Risk Screening 2002 (NRS2002) tool relative to BMI. The evidence supporting each of these approaches to nutrition assessment to date has been based largely on retrospective observational studies, a level of evidence excluded in this current guideline.
2. **In adult critically ill patients, do immune-enhancing nutrients provide better outcomes than standard care?** This broad question encompasses differing numbers of nutrients (glutamine; ω-3 fatty acids; individual vitamins, minerals, and trace elements) that are compared at widely variable doses. Because this current guideline was focused on providing answers to foundational practice questions in the general critically ill population, the decision was made to construct a future author panel to deal with this question as its own guideline.
3. **In adult critically ill patients, do probiotics provide better outcomes than standard care?** The RCTs that were identified by our search strategy reported on a variety of probiotic preparations and doses and did not report consistently on the outcomes included in this guideline.

FUTURE RESEARCH DIRECTIONS

In spite of considering data from many well-designed trials, including one question with strong evidence, most recommendations above are

weak and made on low- to moderate-quality evidence. Mortality (ICU, hospital, or 90-day) was the most comparable outcome in these questions, even though mortality that occurs beyond the first week of therapy may be challenging to tie definitively to early time-limited nutrition support interventions. Outcomes such as LOS and ventilator days might logically be impacted by decisions on feeding. Unfortunately, reporting on these outcomes varied widely, reducing the ability to conflate study findings. Lack of reporting on the nutrition exposure variables of interest (energy received per kilogram per day and grams of protein received per kilogram per day) further limited our ability to answer most questions. The items listed below provide recommendations to improve future research in ICU nutrition support and increase our knowledge for optimal nutrition care:

1. Nutrition status likely impacts ICU outcomes and should be considered in future studies of critical care nutrition. Unfortunately, nutrition status is often not assessed, and when it is included, it is often defined differently between studies. A multitude of tools exist to assess nutrition status. The Global Leadership on Malnutrition (GLIM) criteria were an effort to collect all of these tools into one set of criteria to facilitate comparison between the different tools.[42] The GLIM criteria propose a malnutrition diagnosis should be based upon the presence of at least two of the three phenotypic criteria (nonvolitional weight loss, low BMI, reduced muscle mass) and at least one of the two etiologic criteria (reduced food intake/assimilation or increased disease burden). For research purposes, we recommend that studies include the GLIM criteria data in their tables or supplements to facilitate meta-analyses. For future studies in ICU populations, we recommend (1) validation studies of the GLIM tool against a gold standard of nutrition status, such as radiographic imaging of lean muscle status, and (2) RCTs that both include the GLIM criteria in their baseline data and measure the impact of nutrition interventions on clinical outcomes at different levels of nutrition status. This will go a long way to improve the science surrounding the utility of this tool and will flood the literature with comparable studies that lend themselves to statistical conflation.
2. Nutrition support therapy provides nutrients to patients targeted to energy and protein goals. To assess the impact of nutrition support it is essential that investigators report the amount of all primary exposure variables delivered to the patient (for this clinical guideline, the amount of energy, protein, or ILE). To enable accurate comparisons between trials and to discern optimal feeding practices, these variables should be reported standardized to patient body weight as kilocalories per kilograms, grams of protein per kilogram, or grams of ILE per kilogram of body weight in each group with data as mean ± SD. Further, how body weight was obtained should be explicitly stated.
3. Nutrition intake should be described for the entire period of outcome observation. Overall, most nutrition trials in ICU populations were short (5–7 days or only for the duration of mechanical ventilation), and many outcomes reported included measures that occurred after the RCT interval (eg, hospital LOS, mortality, post-trial infections). These postintervention outcomes reflect the nutrition received while in the trial as well as the post-trial interval when all participants revert to standard nutrition care (ie, all patients are fed similarly to the controls). If nutrition intake does impact post-trial outcomes, longer postintervention duration will attenuate differences between the groups for these outcomes. Further, the relatively short trial duration does not provide any information about the broader, more informative question of how a comprehensive approach, designed to optimize nutrition care throughout hospitalization, affects both short- and long-term hospital outcomes.
4. Many of the outcomes used for this guideline were reported as median (IQR) and thus could not be combined with data reported as mean ± SD. Trials should report their data as both median (IQR) as well as mean ± SD for LOS and ventilator days to enable the comparison across all trials in forest plots to determine effect size based on mean ± SD. These data could be published in online supplementary tables if the preference is for median (IQR) in the main document.
5. To date, no clinical trials have examined the impact of withholding vs providing nonvolitional feedings in critically ill populations. Study designs that include an arm with very low to no nutrition intake are still needed to fully explore the clinical efficacy of nonvolitional feeding.
6. Additional clinical outcomes that may be affected by nutrition support in critically ill populations include readmission to the ICU or hospital, measures of physical strength or performance, hospital discharge disposition (to rehabilitation vs continuing nursing care vs home with assistance vs home with no added therapies), and/or post–intensive care syndrome incidence rates. Standardized methods to assess and report these outcomes should be a priority to enable robust detection of interventions on these outcomes.

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CONFLICT OF INTEREST

Jayshil Patel has received speaker and consultant honoraria from Nestlé and Baxter, respectively, neither of which is specifically related to the work published in this paper. Todd W. Rice has received speaker and consultant honoraria from Nestlé and Baxter and research grants from Nestlé unrelated to the work published in this paper. In addition, Todd W. Rice has received consultant honoraria from Cumberland Pharmaceuticals, Inc, and Avisa Pharma, LLC, in addition to serving as a DSMB member for Sanofi Pharma. Charlene Compher, Angela L. Bingham, Michele McCall, Carol Braunschweig, and Liam McKeever report no conflicts of interest.

FINANCIAL DISCLOSURE

None declared.

AUTHOR CONTRIBUTIONS

All authors contributed to conception/design of the research; all authors contributed to acquisition, analysis, or interpretation of the data; Charlene Compher, Carol Braunschweig, Liam McKeever, and Angela L. Bingham drafted the manuscript; all authors critically revised the manuscript; and Charlene Compher, Liam McKeever, and Carol Braunschweig agree to be fully accountable for ensuring the integrity and accuracy of the work. All authors read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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