0148-6071/03/2705-0355$03.00/0
JOURNAL OF PARENTERAL AND ENTERAL NUTRITION
Vol. 27, No. 5
*Printed in U.S.A.*


# *Special Interest*

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# Canadian Clinical Practice Guidelines for Nutrition Support in Mechanically Ventilated, Critically Ill Adult Patients*

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**ABSTRACT.** *Objective:* This study was conducted to develop evidence-based clinical practice guidelines for nutrition support (ie, enteral and parenteral nutrition) in mechanically ventilated critically ill adults. *Options:* The following interventions were systematically reviewed for inclusion in the guidelines: enteral nutrition (EN) *versus* parenteral nutrition (PN), early *versus* late EN, dose of EN, composition of EN (protein, carbohydrates, lipids, immune-enhancing additives), strategies to optimize delivery of EN and minimize risks (ie, rate of advancement, checking residuals, use of bedside algorithms, motility agents, small bowel *versus* gastric feedings, elevation of the head of the bed, closed delivery systems, probiotics, bolus administration), enteral nutrition in combination with supplemental PN, use of PN *versus* standard care in patients with an intact gastrointestinal tract, dose of PN and composition of PN (protein, carbohydrates, IV lipids, additives, vitamins, trace elements, immune enhancing substances), and the use of intensive insulin therapy. *Outcomes:* The outcomes considered were mortality (intensive care unit [ICU], hospital, and long-term), length of stay (ICU and hospital), quality of life, and specific complications. *Evidence:* We systematically searched MEDLINE and CINAHL (cumulative index to nursing and allied health), EMBASE, and the Cochrane Library for randomized controlled trials and meta-analyses of randomized controlled trials that evaluated any form of nutrition support in critically ill adults. We also searched reference lists and personal files, considering all articles published or unpublished available by August 2002. Each included study was critically appraised in duplicate using a standard scoring system. *Values:* For each intervention, we considered the validity of the randomized trials or meta-analyses, the effect size and its associated confidence intervals, the homogeneity of trial results, safety, feasibility, and the economic consequences. The context for discussion was mechanically ventilated patients in Canadian ICUs. *Benefits, Harms, and Costs:* The major potential benefit from implementing these guidelines is improved clinical outcomes of critically ill patients (reduced mortality and ICU stay). Potential harms of implementing these guidelines include increased complications and costs related to the suggested interventions. *Summaries of Evidence and Recommendations:* When considering nutrition support in critically ill patients, we strongly recommend that EN be used in preference to PN. We recommend the use of a standard, polymeric enteral formula that is initiated within 24 to 48 hours after admission to ICU, that patients be cared for in the semirecumbent position, and that arginine-containing enteral products not be used. Strategies to optimize delivery of EN (starting at the target rate, use of a feeding protocol using a higher threshold of gastric residuals volumes, use of motility agents, and use of small bowel feeding) and minimize the risks of EN (elevation of the head of the bed) should be considered. Use of products with fish oils, borage oils, and

Received for publication January 31, 2003.
Accepted for publication May 28, 2003.
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†This guideline was funded by unrestricted grants from the Canadian Institute of Health Research, The Canadian Critical Care Society, and The Canadian Society for Clinical Nutrition.
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*This study was the work of the Canadian Critical Care Practice Guidelines Committee, a broadly representative committee of Canadian physicians and nutritional authorities with representation from United States and Canadian nutritional organizations, and external advisors from the nutritional industry. The membership of the Committee is listed in Appendix I. **The recommendations contained in this report do not represent official policy of A.S.P.E.N., nor has there been any explicit endorsement by A.S.P.E.N., nor is there an endorsement implied by the publication of this report in the *Journal of Parenteral and Enteral Nutrition.*** The findings and recommendations contained in this report are to be used to assist in the care of patients only as the result of the professional judgment of the attending health professional.

antioxidants should be considered for patients with acute respiratory distress syndrome. A glutamine-enriched formula should be considered for patients with severe burns and trauma. When initiating EN, we strongly recommend that PN not be used in combination with EN. When PN is used, we recommend that it be supplemented with glutamine, where available. Strategies that maximize the benefit and minimize the risks of PN (hypocaloric dose, withholding lipids, and the use of intensive insulin therapy to achieve tight glycemic control) should be considered. There are insufficient data to generate recommendations in the following areas: use of indirect calorimetry; optimal pH of EN; supplementation with trace elements, antioxidants, or fiber; optimal mix of fats and carbohydrates; use of closed feeding systems; continuous *versus* bolus feedings; use of probiotics; type of lipids; and mode of lipid delivery. *Validation:* This guideline was peer-reviewed and endorsed by official representatives of the Canadian Critical Care Society, Canadian Critical Care Trials Group, Dietitians of Canada, Canadian Association of Critical Care Nurses, and the Canadian Society for Clinical Nutrition. *Sponsors:* This guideline is a joint venture of the Canadian Critical Care Society, the Canadian Critical Trials Group, the Canadian Society for Clinical Nutrition, and Dietitians of Canada. The Canadian Critical Care Society and the Institute of Nutrition, Metabolism, and Diabetes of the Canadian Institutes of Health Research provided funding for development of this guideline. (*Journal of Parenteral and Enteral Nutrition* **27:**355–373, 2003)

In critically ill patients, malnutrition is associated with impaired immune function, impaired ventilatory drive, and weakened respiratory muscles, leading to prolonged ventilatory dependence and increased infectious morbidity and mortality.[1] Malnutrition is prevalent in intensive care unit (ICU) patients, has been reported as being as high as 40%, and is associated with increased morbidity and mortality.[2]

The benefits of nutrition support in the critically ill include improved wound healing, a decreased catabolic response to injury, improved gastrointestinal (GI) structure and function, and improved clinical outcomes, including a reduction in complication rates and length of stay, with accompanying cost savings.[3] However, nutrition support is not without adverse effects or risks. Early enteral nutrition (EN) can be associated with high gastric residual volumes, bacterial colonization of the stomach, and an increased risk of aspiration pneumonia.[4,5] Parenteral nutrition (PN) has been associated with gut mucosal atrophy, overfeeding, hyperglycemia, an increased risk of infectious complications, and increased mortality in critically ill patients.[6] Both forms of nutrition support can increase health care costs and workloads of care providers.

Despite the widespread use of nutrition support, many areas in clinical practice remain controversial. Variation in nutrition support practices in ICUs throughout the world is widely reported. The use of nutrition support in ICUs has been shown to vary from 14% to 67% of all patients in the ICU.[7–11] Recent surveys report the use of PN ranging from 12% to 71% and the use of EN ranging between 33% and 92% of patients receiving nutrition support in the ICU.[7–11]

Recent review papers have documented that nutrition support *does* influence morbidity and mortality in critically ill patients.[3,6,12] Therefore, strategies to improve the delivery of nutrition support are relevant and may result in decreased morbidity and mortality. Systematically developed practice guidelines that focus on these strategies will allow practitioners to make decisions about appropriate nutrition support care and will aim at improving the quality of patient care and maximizing the efficiency with which resources are used.

Published data on clinical practice guidelines for nutrition support in the critically ill are limited. Two existing documents[13,14] were appraised using a validated instrument for evaluation of clinical practice guidelines.[15] Neither was acceptable, according to the criteria in this instrument. The American Society of Parenteral and Enteral Nutrition (A.S.P.E.N.) document[13] was not intended to establish practice guidelines for nutrition support, but rather to review published literature and to make recommendations for future research directions. It lacks representation from key disciplines, it only addresses specific disease states in critically ill patients, and it does not address the more basic issues related to optimizing delivery of nutrition support in the ICU setting. The American College of Chest Physicians consensus statement[14] fails to describe a valid method to identify and interpret the evidence, is based mostly on expert opinion, and does not mention a source of external funding. It also lacks broad representation and external validation from other disciplines. Recently, A.S.P.E.N. guidelines were updated to reflect a more current, evidence-based approach to the practice of nutrition support.[16] Pertaining to critical illness, the panel concluded that "specialized nutrition support should be initiated when it is anticipated that critically ill patients will be unable to meet their nutrients orally for a period of 5 to 10 days" and "enteral nutrition is the preferred route of feeding." There were no guidelines put forward to assist practitioners in how to best optimize the benefits and minimize the risks of specialized nutrition support in critical illness.

The development of detailed, original, evidence-based guidelines is needed to facilitate more effective, efficient, and consistent delivery of nutrition support that can lead to improved patient outcomes in the adult critical care setting. This paper describes the systematic approach that was used to develop these guidelines and the recommendations that emerged.

## MATERIALS AND METHODS

In October 2001, a workshop was held that brought together various stakeholders interested in nutrition support in the critical care setting. In attendance were representatives of the Canadian Critical Care Society, Canadian Critical Care Trials Group, Dietitians of Canada, Canadian Association of Critical Care Nurses, Canadian Society for Clinical Nutrition, the Institute of Nutrition, Metabolism, and Diabetes of the Canadian Institute of Health Research, Nestle Canada, and Abbott Laboratories. The attendees were ICU physicians, surgeons, gastroenterologists, dietitians, nurses, pharmacists, nutrition scientists, invited international experts, and representatives from the nutrition industry.

In small group sessions, a process to develop evidence-based nutrition support guidelines for the ICU setting was developed. Several areas of nutrition practice were identified as important components that needed to be systematically reviewed.

A panel to develop clinical practice guidelines was appointed and consisted of representatives from key disciplines, ie, epidemiologists, intensivists, surgeons, gastroenterologists, dietitians, nurses, and pharmacists from across Canada. External reviewers included international experts and industry representatives (Appendix I).

*Search Strategy*

To locate relevant articles to be included in these practice guidelines, 4 bibliographic databases (MEDLINE, EMBASE, CINAHL, and the Cochrane Library) were searched. Search terms included *nutrition support* or *dietary supplementation* or *enteral nutrition* or *parenteral nutrition* or *peripheral parenteral nutrition* or *total parenteral nutrition* (TPN) or *nutrition support team* or *nutritional requirements* or *nutrition assessment* or *parenteral nutrition solutions* and *critical care* or *critical illness* or *ICUs*. These searches spanned from 1980 to August 2002. In addition, personal files and relevant review articles were searched for additional studies. There were no language restrictions on included papers. Unpublished manuscripts were included in the review process. Data reported in abstract only were excluded.

*Study Selection Criteria*

Studies were selected for inclusion in the review process if they met the following criteria:

Study design: Randomized clinical trials or meta-analysis of randomized controlled trials (pseudorandomized trials were excluded)

Population: Mechanically ventilated, critically ill adult patients (elective surgery patients were excluded)

Intervention: Any Form of EN or PN

Outcome: mortality (ICU, hospital, long-term), length of stay, quality of life, complications and cost. Studies with only surrogate outcomes were excluded.

For the purpose of this review process, we defined a critically ill patient as a patient cared for in an ICU environment who had an urgent or life-threatening complication (high baseline mortality rate) to distinguish them from patients with elective surgery who also are cared for in some ICUs but have a low baseline mortality rate (<5%).

According to the above search and study selection criteria, the included articles covered the range of topics listed in Appendix II. Additional topics including checking gastric residuals, methods of detecting aspiration, timing of initiation of PN, protein sparing therapy, use of nutrition support teams, peripheral PN *versus* central line PN were considered of interest, but no randomized controlled trials on these topics evaluating clinically important outcomes were available for inclusion in the review process. In addition, practical aspects of tube placement and management for EN and catheter placement for PN are beyond the scope of this paper.

The panel agreed to review all randomized controlled trials and the most recent meta-analyses for all topics. Each randomized trial was critically appraised independently by each member of a pair of reviewers according to an explicit procedure. Appraisers were given instructions on how to appraise studies, and for each trial the following descriptors were abstracted: intervention, study population, nature of allocation, co-interventions, exclusions after randomization, double-blinding, event rates, relative risk, and other outcomes. Authors of primary studies were contacted for supplementary information or clarification if necessary. Clinical trials were assigned "level 1" if randomization was concealed, outcome adjudication was blinded, and an intention-to-treat analysis was performed. Trials were assigned "level 2" if any 1 of the above characteristics was unfulfilled. For each intervention that had >2 similar studies, where possible, we combined data from all studies to estimate the common risk ratio and associated 95% confidence intervals (CIs) for death and infectious complications. The common risk ratios and their CIs were estimated using the random effects model of DerSimonian and Laird[17] as implemented in RevMan 4.1.[18] We considered $p < .25$ to be supportive of a trend and $p < .05$ to be statistically significant.

For each meta-analysis included in the review process, the following descriptors were abstracted: intervention, number of trials, population selection criteria, search strategy, independent validity assessment, method of pooling results, assessment of homogeneity, pooled event rates, and other outcomes. Patients' perspectives could not be elicited, because of the inability of most critically ill patients to engage in discussions about their nutrition.

In advance of the panel meeting, each pair of reviewers achieved consensus on the data abstracted from the included studies, and written summaries were prepared and circulated to all panel members. The panel then met to translate the summaries of evidence into clinical recommendations. The context for discussion was mechanically ventilated adult patients in Canadian ICUs. At the meeting, we considered the validity of the randomized trials, the effect size of each intervention and its associated CIs, the homogeneity of trial results, safety, feasibility of implementing the new intervention, including impact on workload, and the cost related to each intervention. We did not conduct a formal economic evaluation of any of the interventions. For every intervention, each of these items was scored using a semiquantitative scale (0 to 3+) by the guideline panel. These scores made transparent the weights used to derive the summary recommendations. The language of the recommendations was linked to the semiquantitative scores and the strength of the evidence as shown in Table I. Where possible, recommendations were generated for specific subpopulations of critically ill patients (trauma, burns, malnourished, etc). Otherwise, the guidelines were developed to apply to the average mechanically ventilated patient or the general situation. We recognize that these recommen-

TABLE I
*Language of summary recommendations*

| Conditions | Language of recommendation |
|---|---|
| If there were no reservations about endorsing an intervention | "Strongly recommended" |
| If evidence was supportive but there were minor uncertainties about the safety, feasibility, or costs of the intervention | "Recommended" |
| If the supportive evidence was weak and/or there were major uncertainties about the safety, feasibility, or costs of an intervention | "Should be considered" |
| If there was either inadequate or conflicting evidence | No recommendation, ie, "insufficient data" |

dations may not apply in all situations, and individual patient or site characteristics will need to be considered. These guidelines should not be used as a substitute for a physician's, dietitian's, or other health practitioner's informed clinical judgment with respect to the appropriate manner to treat an individual, mechanically ventilated, critically ill patient.

After the panel meeting, the draft guidelines were written and circulated to panel members for approval. Revisions were made before submitting the guidelines for structured external review (see Appendix 1 for list of reviewers). The external reviewers were asked to provide feedback on whether there were additional studies pertinent to the topic, whether the guideline was logical, clear, and practical, and to critique the guideline development process. Members of the panel considered the comments of all reviewers and revised the guidelines according to this feedback. The final guideline was returned to panel members for final approval and then to official sponsors for their respective endorsements.

## RESULTS

A review of the evidence, a summary of the committee discussion, and the final summary recommendation for each topic are presented below and summarized in Appendix 2. There were insufficient data to generate treatment recommendations in the following areas: use of indirect calorimetry, optimal pH of EN, optimal mix of fats and carbohydrates, use of closed feeding systems, continuous *versus* other methods of EN administration, use of probiotics, type of lipids and mode of lipid delivery, and supplementation with trace elements, antioxidants, or fiber.

### 1. Does EN compared with PN result in better outcomes in the critically ill adult patient?

There were 12 level 2 studies[19–30] and 1 level 1 study[31] that compared EN to PN in critically ill patients with an intact GI tract. When the results of these studies were aggregated statistically, there was no apparent difference in mortality rates across groups receiving EN or PN (relative risk [RR], 1.08; 95% CI, 0.70, 1.65; $p = .7$; Fig. 1). Compared with PN, EN was associated with a significant reduction in infectious complications (RR, 0.61; 95% CI, 0.44, 0.84; $p = .003$; Fig. 2).

The committee noted that the aggregated effect of PN on infectious complications across several studies was homogeneous and resulted in a large effect size with narrow CIs. Safety, cost, and feasibility considerations favored the use of EN over PN. The committee noted that the results of the subgroup analysis of the studies, in which the PN group received more calories and had higher blood sugars than the EN group, could not explain the higher rates of infections.

*Recommendation*

According to 1 level 1 and 12 level 2 studies, when considering nutrition support for critically ill patients, we strongly recommend the use of EN over PN.

### 2. Does early EN compared with delayed nutrient intake result in better outcomes in the critically ill adult patient?

There were 8 randomized controlled trials (level 2 studies) comparing early EN *versus* delayed nutrient

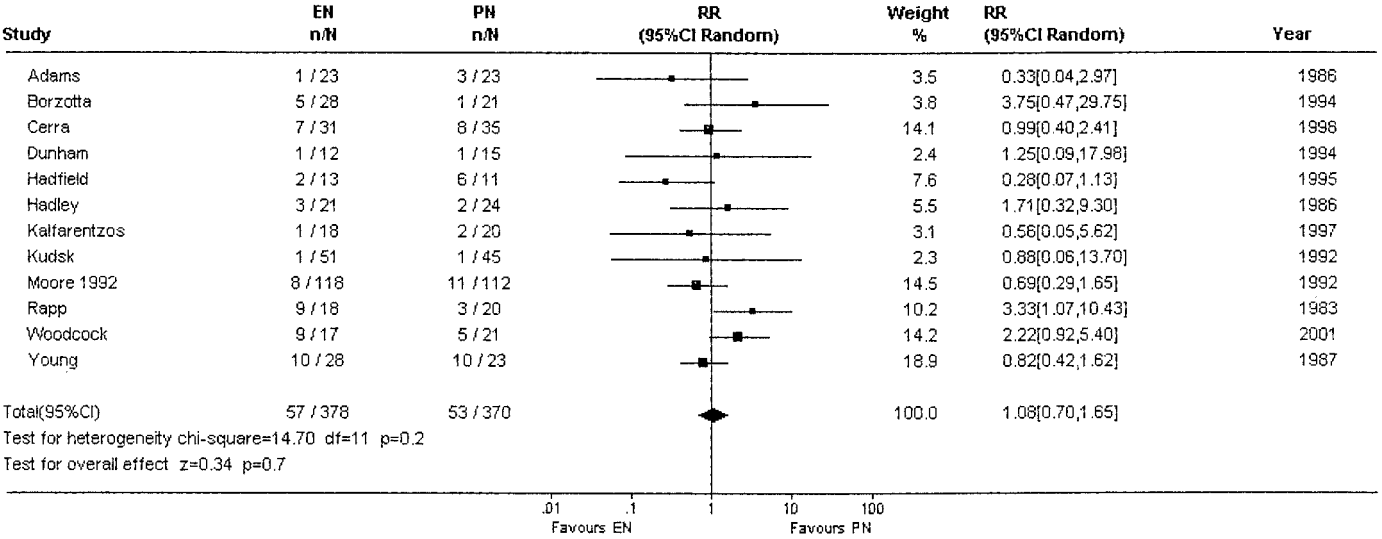


FIG. 1. Studies comparing PN *versus* EN: Effect on mortality. RR, risk ratio; CI Random, random effects model.

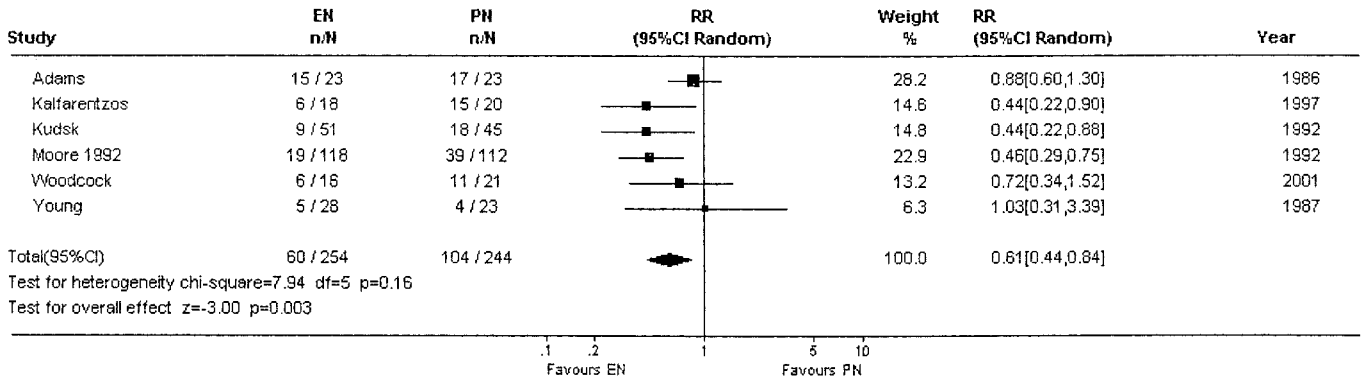


FIG. 2. Studies comparing PN *versus* EN: Effect on infectious complications. RR, risk ratio; CI Random, random effects model.

intake (ie, delayed EN, PN, or oral diet).[32–39] In all the trials, EN was started within 24 to 48 hours of resuscitation. When these studies were aggregated, early EN was associated with a trend toward a reduction in mortality (RR, 0.52; 95% CI, 0.25, 1.08; $p = .08$) when compared with delayed nutrient intake (Fig. 3). Three studies reported infectious complications.[32,36,38] When these were aggregated, early EN was associated with a trend toward a reduction in infectious complications (RR, 0.66; 95% CI, 0.36, 1.22; $p = .19$) when compared with delayed nutrient intake (Fig. 4). No differences in length of stay were observed between groups. All 7 studies that reported nutritional endpoints showed a significant improvement in the groups receiving early EN (calorie intake, protein intake, percentage goal achieved, better nitrogen balance achieved). There were no differences in other complications between the groups.

The committee noted the inconsistent and variable definitions of early EN and delayed nutrition and the considerable heterogeneity in trial designs. Concerns were expressed about the safety of early intragastric EN, given recent reports from nonrandomized trials of increased harm experienced by patients fed aggressive, early EN.[5,40] However, given the potentially large treatment effect with respect to reduced mortality and infections, improved nutritional intake, and the minimal cost and feasibility concerns of early EN, the committee decided to recommend its use. Early EN, like other interventions (use of small bowel feeding and motility agents) can be used as a strategy to optimize delivery of EN. According to the studies reviewed, the committee agreed that early EN could be defined as "within 24 to 48 hours after admission to ICU" and that it be applied to all mechanically ventilated patients (medical, surgical, trauma, etc), presuming patients were adequately resuscitated and hemodynamically stable.

*Recommendation*

According to 8 level 2 studies, we recommend early EN (within 24–48 hours after admission to ICU) in critically ill patients.

**3. Does achieving target dose of EN result in better outcomes in the critically ill adult patient?**

There was only 1 level 2 study that compared the use of early aggressive EN (ie, starting at goal rate on day 1, 34% of patients went on to small bowel feeding) to standard early EN intragastrically starting at 15 mL/hour on day 1 and increasing gradually.[41] In this randomized trial of severely head-injured patients, those patients fed aggressively, compared with standard provision of EN, received significantly more calories and protein, had fewer infectious complications, and experienced a more rapid recovery from their illness. There was no difference in mortality.

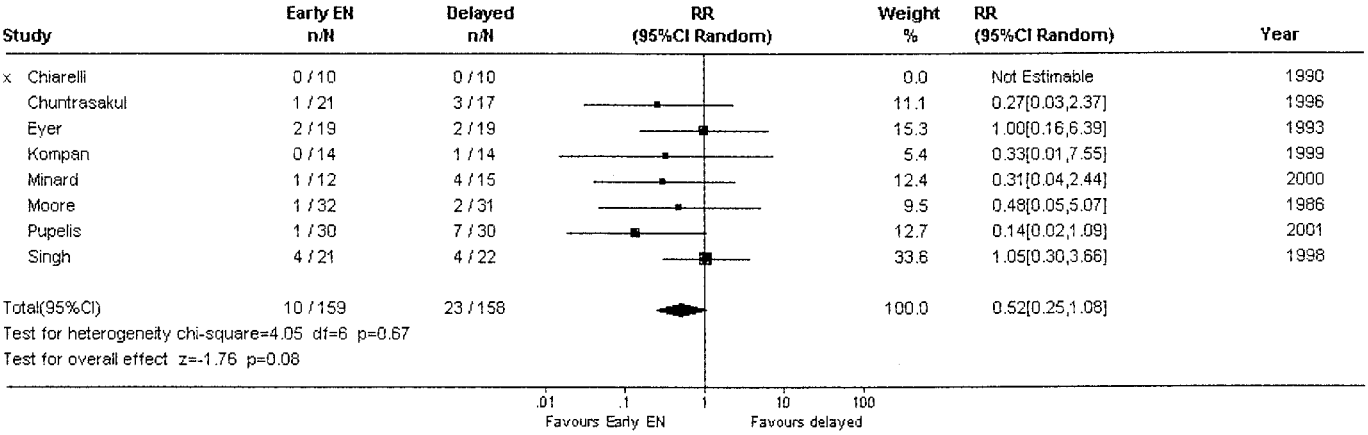


FIG. 3. Studies comparing early *versus* delayed nutrient intake: Effect on mortality. "×" signifies that the study did not contribute to the analysis of overall treatment as 0 events occurred in the study. RR, risk ratio; CI Random, random effects model.

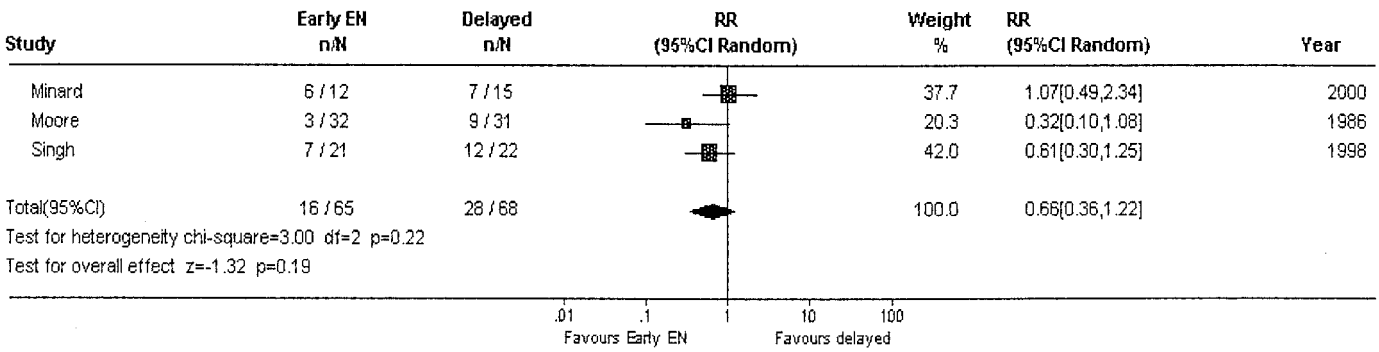


FIG. 4. Studies comparing early *versus* delayed nutrient intake: Effect on infectious complications. RR, risk ratio; CI Random, random effects model.

The committee noted the modest treatment effect associated with aggressive EN in the 1 study of head-injured patients that had high internal validity. Cost and feasibility concerns were favorable and the improved calorie and protein intake with aggressive EN was also noted. Two other studies, although related to PN, showed that higher energy intake also resulted in better outcomes in head-injured patients.[29,30] However, the committee was concerned about the probability of harm associated with aggressive EN, as illustrated by recent nonrandomized studies.[5,40]

*Recommendation*

According to 1 level 2 study, when initiating EN in head-injured patients, strategies to optimize delivery of nutrients (starting at target rate, higher threshold of gastric residual volumes and use of small bowel feedings) should be considered. In other critically ill patients, there are insufficient data to make a recommendation.

**4. Compared with standard enteral feeds, do diets supplemented with arginine and other nutrients result in improved clinical outcomes in critically ill patients?**

There were 14 studies reviewed, 2 level 1 studies[43,46] and 12 level 2 studies.[42,44,45,47–55] All 14 studies reported on mortality, and when these were aggregated, there was no effect on mortality (RR, 1.05; 95% CI, 0.79, 1.38; $p = .8$; Fig. 5). A subgroup analysis of high-quality studies (score >8) *versus* low-quality studies (score ≤8) showed that in the higher-quality studies, diets supplemented with arginine and other nutrients had no effect on mortality (RR, 1.1; 95% CI, 0.82, 1.64; $p = .4$), whereas in lower-quality studies, diets supplemented with arginine and other nutrients were associated with a trend toward a reduction in mortality (RR, 0.74; 95% CI, 0.48, 1.15; $p = .18$). The difference between these 2 subgroups was borderline significant ($p = .07$). When studies of trauma *versus* nontrauma patients were compared, there were no differences in mortality ($p$ value for test of heterogeneity across subgroups was .61).

According to 10 studies that reported on infectious complications, there was no difference in the rate of

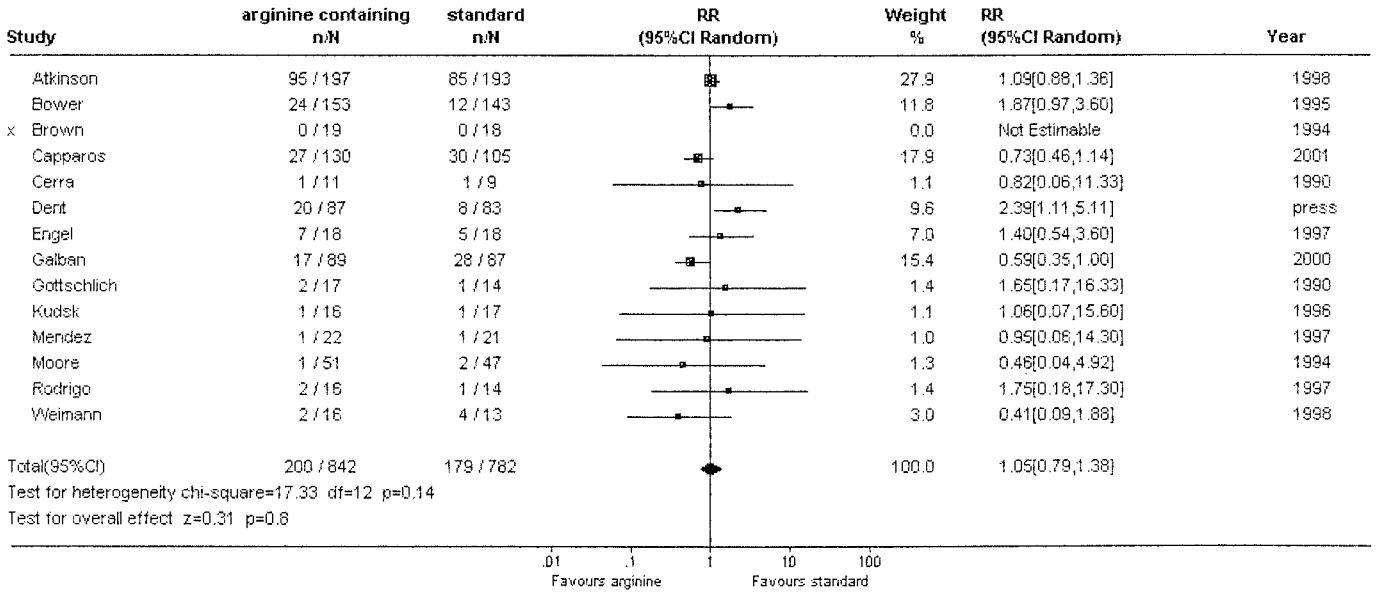


FIG. 5. Studies comparing arginine-containing immune-enhancing diets *versus* standard formulas: Effect on mortality. "×" signifies that the study did not contribute to the analysis of overall treatment as 0 events occurred in the study. RR, risk ratio; CI Random, random effects model.

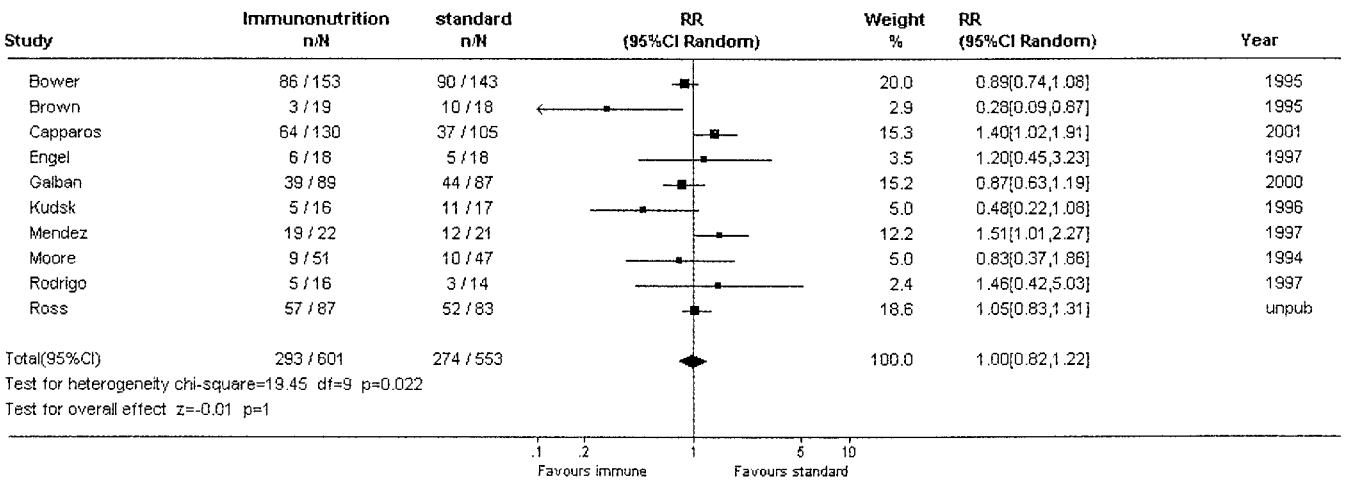


FIG. 6. Studies comparing arginine-containing immune-enhancing diets *versus* standard formulas: Effect on infectious complications. RR, risk ratio; CI Random, random effects model.

infectious complications (RR, 1.00; 95% CI, 0.82, 1.22; $p = 1.0$; Fig. 6). Subgroup analysis also showed no differences in infectious complications when high-quality studies were compared with lower-quality studies and when studies of trauma patients were compared with studies of nontrauma patients. Diets supplemented with arginine and other nutrients were associated with a reduction in hospital length of stay (standardized mean difference [SMD], −.45; 95% CI, −0.90, 0.00; $p = .05$), a trend toward a reduction in ICU length of stay (SMD −0.36, -0.76, 0.04, $p = .08$), and a trend toward a reduction of mechanical ventilation (SMD, −0.36, −0.75, 0.04; $p = .07$). However, these latter findings were confounded by the presence of significant statistical heterogeneity.

The committee noted the lack of a treatment effect with respect to mortality and infections. These results differ from a recent meta-analysis[12] on immune-enhancing diets which included elective surgery patients and did not include a recent study.[46] The committee noted the results of the subgroup analysis, which shows that in higher-quality studies, diets supplemented with arginine and other nutrients had no effect on mortality, whereas in lower-quality studies, there was a trend toward a reduction in mortality. Given the potential harm (increased mortality) associated with the use of diets supplemented with arginine and other nutrients in septic patients[56] and the increased costs, the committee decided to recommend against their use in critically ill patients.

*Recommendation*

According to 2 level 1 studies and 12 level 2 studies, we recommend that diets supplemented with arginine and other select nutrients not be used for critically ill patients.

**5. Does the use of enteral formula with fish oils result in improved clinical outcomes in the critically ill adult patient?**

There was 1 level 1 study in critically ill patients with acute respiratory distress syndrome (ARDS) addressing this question.[57] When compared with a high-fat formula, the use of Oxepa (enteral formula with fish oil or borage oil and antioxidants, ie, vitamin E, vitamin C, β-carotene, taurine, L-carnitine) was associated with a reduction in days receiving supplemental oxygen (13.6 *versus* 17.1; $p = .078$), fewer days of ventilatory support (9.6 *versus* 13.2; $p = .027$), fewer days in ICU (11.0 *versus* 14.8; $p = .016$), and fewer new organ failures (10% *versus* 25%; $p = .018$). There was also a trend toward a reduction in mortality associated with the experimental diet (16% *versus* 25%; $p = .17$).

Although the effect size was modest, it was noted that the results came from 1 study. Although this study had high internal validity, the choice of the control feed (high-fat formula) and need for bronchoscopy to meet the inclusion criteria limit the application of study findings. The committee noted that the acquisition costs of this specialty formula are much higher than standard formula. The committee agreed that because the effects of fish oils cannot be distinguished from the effects of borage oil or antioxidants, this recommendation pertains to products with fish oils, borage oils, and antioxidants, and not to fish oils in general.

*Recommendation*

According to 1 level 1 study, the use of products with fish oils, borage oils, and antioxidants should be considered in patients with ARDS.

**6. Compared with standard care, does glutamine-supplemented EN result in improved clinical outcomes in critically ill patients?**

There were 1 level 1 study (Garrel et al, unpublished observations) and 4 level 2 (Hall et al, unpublished observations)[58–60] studies that demonstrated no statistical difference in mortality between the groups receiving glutamine-supplemented EN or not (RR, 0.80; 95% CI, 0.45, 1.43; $p = .5$). In 1 unpublished study of burn patients (Garrel et al, unpublished observations), a significant reduction in mortality was observed (RR, 0.19; 95% CI, 0.57, 0.76). There were 2 level 2 studies (Hall et al, unpublished observations)[59] that demonstrated a trend toward a reduction in infectious complications with glutamine-supplemented EN (RR, 0.86;

95% CI, 0.66, 1.11; $p = .2$). In 1 study of trauma patients,[59] glutamine-supplemented EN was associated with a significant reduction in infectious complications. There were 2 level 2 studies[58,59] that demonstrated no effect on ICU length of stay with glutamine-supplemented EN.

In examining the results of the meta-analysis of enteral glutamine supplementation, the committee noted the modest treatment effect with wide CIs and the presence of heterogeneity across the studies. The largest effect on mortality was attributable to 1 unpublished study in burn patients with high internal validity (Garrel et al, unpublished observations). On the other hand, a large well-designed trial in a heterogeneous group of ICU patients showed no beneficial effect with glutamine-enriched EN (Hall et al, unpublished observations). With respect to infectious complications, the committee noted that the largest treatment effect was attributed to 1 large study in trauma patients.[59] The safety and cost considerations were favorable despite potential limitations in acquiring the product (ie, lack of product standardization and access may not be easy for all institutions).

*Recommendation*

According to 4 level 2 studies and 1 level 1 study, enteral glutamine should be considered in burn and trauma patients. There are insufficient data to support the routine use of enteral glutamine in other critically ill patients.

**7. Does the use of peptide-based enteral formula, compared with a whole-protein formula, result in better outcomes in the critically ill adult patient?**

There were 4 level 2 studies that compared a peptide-based enteral formula to one with intact proteins.[61–64] Only 2 studies reported mortality and found no difference (RR, 0.42; 95% CI, 0.06, 2.88; $p = .4$).[61,63] According to the 2 studies that reported on infections, there were no differences between the groups (RR, 0.85; 95% CI, 0.64, 1.13; $p = .3$).[62,64] A trend toward an increase in diarrhea with the use of peptides was seen in 1 study,[62] whereas another study showed a decrease in the incidence of diarrhea in the peptide group.[63] A third study found no differences in diarrhea between the 2 groups.[64] A meta-analysis showed no difference in diarrhea between the peptide-based and standard groups (RR, 0.76; 95% CI, 0.25, 2.33; $p = .6$). There were no differences in calorie or protein intake between the groups.

The committee noted that despite no safety concerns and the ease of implementation of peptide-based enteral formulas, there were no studies demonstrating any favorable clinically important treatment effects associated with their use. The higher cost of peptide-based formulas compared with standard was noted. The committee also noted that patients with GI complications (short bowel syndrome, pancreatitis, etc) may benefit from peptide-based formulas, but there are insufficient data to put forward a recommendation.

*Recommendation*

According to 4 level 2 studies, when initiating enteral feeds, we recommend the use of whole-protein formulas (polymeric).

**8. Does the use of a feeding protocol result in better outcomes in the critically ill adult patient?**

There were no randomized trials found that directly addressed this question. One randomized controlled trial was found that compared outcomes of a feeding protocol with a higher gastric residual volume threshold (250 mL) and mandatory prokinetics to a feeding protocol with a lower gastric residual volume threshold (150 mL).[65] There were a lower number of elevated gastric residual aspirations ($p < .005$) and a trend toward less time taken to reach goal rate of feeding in the group that received the protocol with higher residual volume threshold and prokinetics ($p < .09$). There was no difference in the percentage of nutritional needs met nor the incidence of infections between the 2 groups.

The committee noted the paucity of data (no level 1 or level 2 studies) that demonstrate feeding protocols (or checking residual volumes) influence clinical outcomes in critically ill patients. The small treatment effect on surrogate endpoints of the 1 study (gastric residual volumes, time to reach goal rate of EN) that compared a feeding protocol with a higher gastric residual volume threshold and mandatory prokinetics to 1 with a lower gastric residual volume threshold was noted. Given the favorable safety and feasibility considerations and low cost, it was decided that the use of such a feeding protocol be considered as a strategy to optimize nutritional intake.

*Recommendation*

There are insufficient data from randomized trials to recommend the use of a feeding protocol in critically ill patients. If a feeding protocol is to be used, according to 1 level 2 study, a protocol that incorporates prokinetics (metoclopramide) at initiation and tolerates a higher gastric residual volume (250 mL) should be considered as a strategy to optimize delivery of EN in critically ill adult patients.

**9. Compared with standard practice (placebo), does the routine use of motility agents result in better clinical outcomes in critically ill patients?**

A recent systematic review of the literature synthesized randomized trials of cisapride, metoclopramide, and erythromycin and concluded that, as a class of drugs, promotility agents seem to have a physiologic benefit on GI motility and may improve tolerance to EN in critically ill patients.[66] However, only 1 randomized trial of motility agents has evaluated their effect on clinically important endpoints (pneumonia, length of stay, etc), and it did not demonstrate any significant treatment effect.[67]

The committee noted the small treatment effect with wide CIs from heterogenous studies. With one excep-

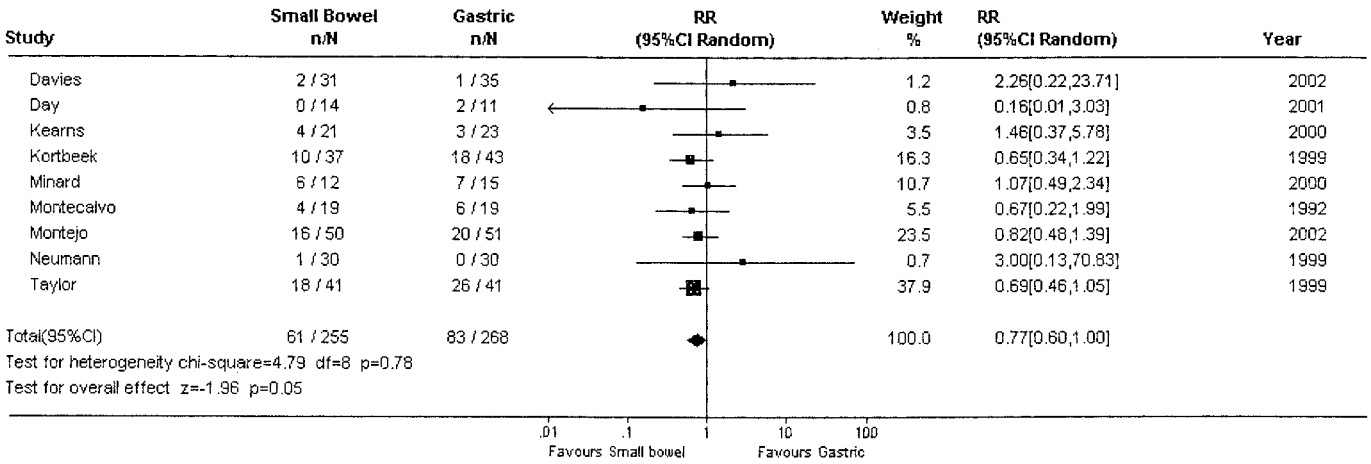


FIG. 7. Studies comparing small bowel *versus* gastric route of feeding: Effect on pneumonia. RR, risk ratio; CI Random, random effects model.

tion,[67] all these studies only measured surrogate endpoints. Given the low probability of harm, favorable feasibility, and cost considerations, it was decided that motility agents may be considered as a strategy to optimize nutritional intake. Because cisapride is no longer available and because of the concerns of bacterial resistance with the use of erythromycin, it was agreed that the recommendation be made for metoclopramide.

*Recommendation*

According to a systematic review of the literature, in critically ill patients who experience feed intolerance (high gastric residuals, emesis), the use of metoclopramide as a motility agent should be considered.

**10. Does enteral feeding via the small bowel compared with gastric feeding result in better outcomes in the critically ill adult patient?**

There were 11 level 2 randomized trials that were included in this meta-analyses.[38,41,68–76] In one study,[41] only 34% of the patients achieved small bowel access (large number of protocol violations), and hence the meta-analysis was done with and without this study. Minard et al[38] compared outcomes in patients receiving early immune-enhanced EN via the small bowel to those receiving delayed immune-enhanced EN via the gastric route. A meta-analysis on the time-dependent variables (such as length of stay) was done with and without the study by Minard et al.[38]

The studies that reported nutritional delivery generally showed better success at meeting goal targets and reaching them sooner in patients fed via the small bowel. According to the 9 studies that reported on infections, the meta-analysis showed that small bowel feeding was associated with a significant reduction in infections (RR, 0.77; 95% confidence interval, 0.60, 1.00; $p = .05$) when compared with gastric feeding (Fig. 7). The study by Taylor et al[41] contributes greatly to the results of this meta-analysis, and when the meta-analysis was done without the Taylor study, the statistical significance of reduction in infections outcomes with small bowel feeding disappeared (RR, 0.83; $p = .3$). With respect to mortality, no significant differences between the groups were found (RR, 0.93; 95% confidence interval, 0.72, 1.20; $p = .6$).

The committee noted an overall modest effect size with respect to pneumonia, with wide CIs among studies that were heterogenous. There were also concerns expressed about implementation of small bowel feeding and the associated costs, which are institution dependent. In other words, the cost-benefit ratio would vary from institution to institution, and the recommendation needed to reflect this fact. The committee also noted that the data on improved nutritional endpoints was favorable, and it was decided that a recommendation be made that incorporated these improvements in nutritional intake.

*Recommendation*

According to 11 level 2 studies, small bowel feeding compared with gastric feeding may be associated with a reduction in pneumonia in critically ill patients. In units where obtaining small bowel access is feasible, we recommend the routine use of small bowel feedings. In units where obtaining access involves more logistical difficulties, small bowel feedings should be considered for patients at high risk for intolerance to EN (on inotropes, continuous infusion of sedatives, or paralytic agents, or patients with high nasogastric drainage) or at high risk for regurgitation and aspiration (cared for in the supine position). Finally, in units where obtaining small bowel access is not feasible (no access to fluoroscopy or endoscopy and blind techniques not reliable), small bowel feedings should be considered for those select patients who repeatedly demonstrate high gastric residual volumes and are not tolerating adequate amounts of EN delivered into the stomach.

**11. Do alterations in body position result in better outcomes in the critically ill adult patient receiving EN?**

There was only 1 level 2 randomized controlled trial that compared the frequency of pneumonia in critically ill patients assigned to semirecumbent or supine position.[77] Caring for patients in the semirecumbent position was associated with a significant reduction in the

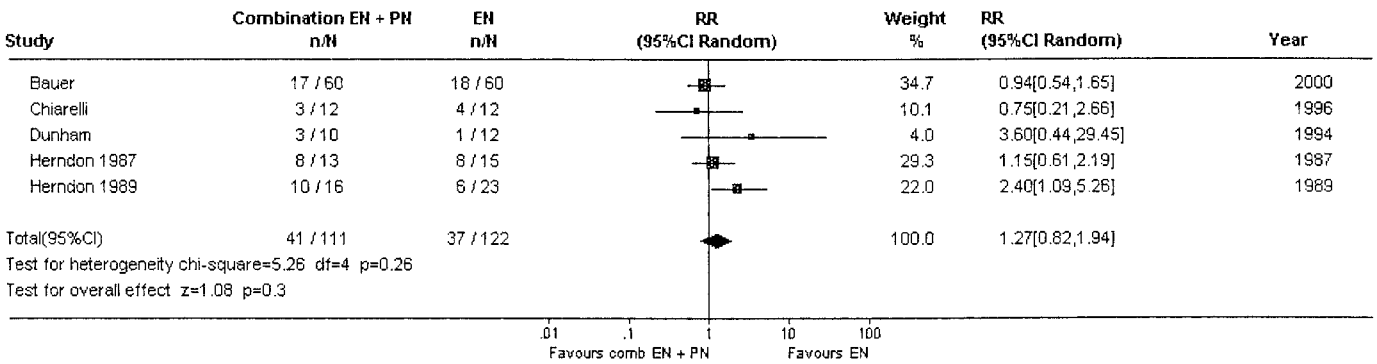


FIG. 8. Studies comparing combined EN and PN to EN alone: Effect on mortality. RR, risk ratio; CI Random, random effects model.

incidence of ventilator-associated pneumonia (5% *versus* 23%; $p < .05$).

The committee noted the large treatment effect with narrow confidence intervals from the 1 level 2 study with high internal validity. It was agreed that the 45 degree position may not be feasible for all patients and the long-term safety concerns of this position are not known (especially skin care). The low cost of this intervention was also noted.

*Recommendation*

According to 1 level 2 study, we recommend that critically ill patients receiving EN have the head of the bed elevated to 45 degrees. Where this is not possible, attempts to raise the head of the bed as much as possible should be considered.

**12. Does the use of PN in combination with EN result in better outcomes in the critically ill adult patient?**

There were 5 level 2 studies[78–82] that compared a strategy of combined EN and PN (started at the same time) to EN alone in critically ill patients. All 5 studies reported on mortality, and the aggregated results demonstrated a trend toward an increased mortality associated with the use of combination EN and PN (RR, 1.27; 95% CI, 0.82, 1.94; $p = .3$; Fig. 8). When a subgroup analysis was done comparing the trials that overfed to those that did not, there was no difference in effect (data not shown). Supplemental PN was not associated with a higher incidence of infections (RR, 1.14; 95% CI, 0.66, 1.96; $p = .6$), had no effect on hospital stay (SMD, 0.12; 95% CI, 0.45, 0.2; $p = .5$), and had no effect on ventilator days.

The committee noted that these data pertain to patients with an intact GI tract, not to those who have an absolute indication for PN. When aggregated statistically, these studies that initiated PN at the same time as starting EN suggest a trend toward harm. The committee noted that the study results were homogenous and that when the studies that overfed were excluded, there was still a trend toward harm. The increase in mortality seen in the patients receiving combination EN and PN could not be explained by overfeeding. Given the probability of harm and excess costs associated with the addition of PN when initiating EN, a recommendation against its use was put forward. However, the committee noted the absence of data from randomized trials related to patients not tolerating adequate amounts of EN and when PN should be used in combination in this scenario.

*Recommendation*

According to 5 level 2 studies, for critically ill patients starting on EN, we recommend that PN not be started at the same time as EN. In the patient who is not tolerating adequate EN, there are insufficient data to put forward a recommendation about when PN should be initiated. Practitioners will have to weigh the safety and benefits of initiating PN in patients not tolerating EN on an individual case-by-case basis. We recommend that PN not be started in critically ill patients until all strategies to maximize EN delivery (such as the use of small bowel feeding tubes and motility agents) have been attempted.

**13. Compared with standard care (IV fluids, oral diet, etc), does PN result in better outcomes in critically ill patients who have an intact GI tract?**

In a recent meta-analysis of PN *versus* standard care in critically ill and surgical patients,[6] 6 of 26 studies included patients who would routinely be admitted to the ICU as part of their management. Two of these trials evaluated the use of combination EN and PN and hence were excluded from this section and incorporated into the previous section (combination EN and PN).[78,79] There were 4 level 2 studies of patients with pancreatitis, or after major trauma or surgery, that were reviewed[83–86] When these 4 studies were aggregated, PN had no effect on mortality (RR, 1.16; 95% CI, 0.60, 2.24; $p = .7$). In the only study[86] that reported the number of patients with infectious complications, PN was associated with an increase in infectious complications (4.0% *versus* 14.0%; $p = .36$). According to 3 studies[84–86] that reported hospital length of stay, the use of PN was associated with a trend toward an increase in hospital stay (SMD, 0.78; 95% confidence interval, −0.03, 1.59; $p = .06$).

The committee noted that the differences in these aggregated results compared with the previous meta-analysis were largely because of different studies included in each analysis. In critically ill patients, the current aggregated results suggest no effect on mortal-

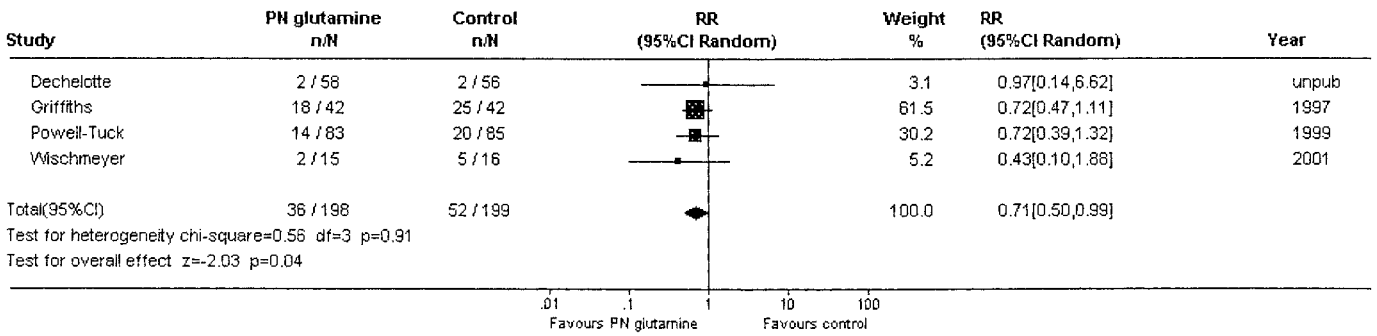


FIG. 9. Studies evaluating PN supplemented with glutamine: Effect on mortality. RR, risk ratio; CI Random, random effects model.

ity but that PN may be associated with an increase in complications and length of stay. Given the concerns about the possibility of harm and higher cost associated with PN when compared with standard treatment, the committee decided to put forward a recommendation against its use in patients with an intact GI tract. An intact GI tract excludes patients in whom PN would be life-sustaining, such as patients with short bowel syndrome, perforated gut, or a high output fistula.

*Recommendation*

In critically ill patients with an intact GI tract, we recommend that PN not be used routinely.

**14. Compared with standard PN, does glutamine-supplemented PN result in better outcomes in critically ill patients?**

There are 2 level 1[87,88] and 3 level 2 studies[89–91] that demonstrate a significant reduction in mortality associated with glutamine-supplemented PN in critically ill patients (RR, 0.71; 95% confidence interval, 0.50, 0.99; $p = .04$; Fig. 9). There was 1 level 1 study[87] and 2 level 2 studies[89,90] that, overall, demonstrated no effect on infectious complications or length of stay in ICU with glutamine-supplemented PN.

The committee noted that in patients receiving PN, there was a modest reduction in mortality associated with parenteral glutamine. The high cost and lack of availability of parenteral glutamine limit the applicability of this intervention. Whether parenteral glutamine has an effect in patients fed enterally is unknown.

*Recommendation*

According to 2 level 1 studies and 3 level 2 studies, when PN is prescribed to critically ill patients, parenteral supplementation with glutamine, where available, is recommended. There are insufficient data to generate recommendations for IV glutamine in critically ill patients receiving EN.

**15. Does hypocaloric PN influence the outcome of critically ill patients?**

Only 2 small level 2 studies have evaluated the effect of hypocaloric feeding in critically ill patients. To achieve a hypocaloric dose of PN, Choban et al[92] reduced both carbohydrates and lipids in obese critically ill patients, whereas McCowen et al[93] withheld lipids in a heterogenous group of patients, including critically ill patients. Only 1 study reported infectious complications, and in that study,[93] hypocaloric feeding was associated with a trend toward a reduction in infectious complications ($p = .2$). There were no significant differences in mortality or length of stay between groups in either study.

The committee's discussion and recommendation related to hypocaloric PN is in the context of an earlier recommendation that EN be used preferentially to PN and that strategies to maximize EN be used before initiating PN. The issue of hypocaloric PN is only relevant to those patients tolerating some (inadequate) EN where practitioners, on a case-by-case basis, are deliberating about adding PN (see section on EN *versus* PN and combination EN and PN). Given the inconsistencies in the definition of hypocaloric PN among the studies included, the committee could not agree upon a specific definition. It was agreed that hypocaloric PN could be achieved by either withholding lipids or reducing carbohydrate load. With respect to the effect on infectious complications, the committee noted the potentially large treatment effect in 1 of the 2 studies, but the wide CIs weaken this estimate. Hypocaloric PN may be equivalent to standard PN with respect to cost and feasibility. However, given that all the other signals related to PN suggest that PN is associated with no benefit or harm in critically ill patients, despite the weak evidence available and equivocal cost considerations, the committee took the position that minimizing the dose of PN should be the norm, and stronger evidence to justify increased dosing of PN is needed. One of the studies excluded malnourished patients,[93] and the committee was concerned about the paucity of data in this population and also about the safety and unknown effects of long-term hypocaloric PN. The committee decided that, although the concerns regarding hypocaloric nutrition and essential fatty acid deficiency were probably minimal for those patients tolerating some EN and requiring PN for short term (<10 days), this cannot be extrapolated to those who have an absolute contraindication to EN and need PN for a longer duration.

*Recommendations*

According to 2 level 2 studies, in critically ill patients who are not malnourished, are tolerating some EN, or when PN is indicated for short-term use (<10 days), hypocaloric PN should be considered. There are insufficient data to make recommendations about the use of

hypocaloric PN in the following patients: those requiring PN for long term (>10 days), obese critically ill patients, and malnourished critically ill patients. Practitioners will have to weigh the safety and benefits of hypocaloric PN on an individual case-by-case basis in these latter patient populations.

**16. Does the presence of lipids in PN influence outcomes in the critically ill adult patient?**

There were 2 level 2 studies reviewed that compared the use of lipids to no lipids in PN.[93,94] These studies demonstrated no effect of withholding lipids on mortality (RR, 1.29; CI, 0.16, 10.7; $p = .8$). A significant reduction in pneumonia (48% *versus* 73%; $p = .05$), catheter-related sepsis (19% *versus* 43%; $p = .04$), and a significantly shorter stay in both ICU (18 *versus* 29 days; $p = .02$) and hospital (27 *versus* 39 days; $p = .03$) was observed in trauma patients not receiving lipids compared with those receiving lipids.[94] In the study by McCowen et al,[93] the group that received no lipids (hypocaloric group) showed a trend toward a reduction in infections (29% *versus* 53%; $p = .2$). No difference in length of stay was seen in that study[93] (did not report on ventilator days). Combining these 2 studies, the meta-analysis done showed a significant reduction in infections in the group that received no lipids (RR, 0.63; 95% CI, 0.42, 0.93; $p = .02$).

The committee noted a large reduction in infectious complications associated with withholding lipids, albeit this effect may be influenced by the reduction in calories. However, the small reduction in calories is unlikely to explain such a large reduction in infectious complications, particularly when there are such supportive experimental data that lipids cause immune dysfunction. The feasibility and cost considerations favored withholding lipids. One of the studies excluded malnourished patients,[93] whereas the other excluded patients with essential fatty acid deficiency.[94] The committee expressed concerns over the effects of long-term fat-free PN and the paucity of data in malnourished patients. The committee decided that, although the concerns regarding withholding lipids (ie, hypocaloric nutrition and essential fatty acid deficiency) were probably minimal for those patients tolerating some EN and requiring PN for short term (<10 days), this cannot be extrapolated to those who have an absolute contraindication to EN and need PN for a longer duration.

*Recommendation*

According to 2 level 2 studies, in critically ill patients who are not malnourished and are tolerating some EN, or when PN is indicated for short-term use (<10 days), withholding lipids should be considered. There are insufficient data to make a recommendation about withholding lipids in critically ill patients who are malnourished or those requiring PN for long term (>10 days). Practitioners will have to weigh the safety and benefits of withholding lipids on an individual case-by-case basis in these latter patient populations.

**17. Does tight blood glucose control result in better outcomes in the critically ill adult patient receiving nutrition support?**

There was 1 level 2 study reviewed. Van den Berghe et al[95] compared intensive insulin therapy *versus* conventional treatment in critically ill patients receiving nutrition support. Patients were started on a glucose load (200 to 300 g/day) and then advanced to either PN, combined PN/EN, or EN 24 hours after admission. Intensive insulin therapy was associated with a lower incidence of sepsis ($p = .003$), a trend toward a reduction in ventilator days, and a reduced ICU ($p < .04$) and hospital mortality ($p = .01$) compared with conventional insulin therapy.

The committee noted the strong effect size seen with narrow CIs and high internal validity in the 1 large study (n = 1548) of surgical ICU patients (predominantly elective cardiovascular surgery). The safety, cost, and feasibility of intensive insulin therapy were reasonable. The committee noted that in this trial, patients had a relatively low APACHE II score (mean of 9) and received high amounts of IV dextrose within 24 hours, and then a significant proportion received PN (approximately 60%). This limits the applicability of the results from this trial to other ICUs where patients are sicker, do not receive high amounts of parenteral glucose early on, and where the use of PN is not excessive. The committee agreed that the need for good glycemic control in critically ill patients should be emphasized; however, the recommendation for tight control should be specific to surgical critically ill patients (and particularly for cardiovascular surgery).

*Recommendation*

According to 1 level 2 study, in surgical critically ill patients receiving nutrition support, intensive insulin therapy to tightly control blood glucose levels between 4.4 and 6.1 mmol/L should be considered. There are insufficient data to make a recommendation regarding intensive insulin therapy in other critically ill patients.

## DISCUSSION

Working with a multidisciplinary group of practitioners, we have developed practical, evidence-based clinical recommendations for the provision of nutrition support to the mechanically ventilated, critically ill, adult patient. Whereas previous guidelines[13,14] relied heavily on expert opinion as to the relative merits of various nutrition interventions, we conducted current systematic reviews and meta-analyses of randomized trials to establish the evidentiary basis of our guidelines. Consistent with how biomedical guidelines are developed, in a transparent fashion, our committee then weighed the evidence (validity, precision, and homogeneity), and considered safety, feasibility, and cost in order to generate the guideline statements. The specific language of the guidelines provides a transparent link between the level of supporting evidence, the values considered by the committee, and the strength of the recommendation (Table I).

To enhance the validity and generalizability of our guidelines, we enlisted the support of external reviewers who provided critical review of both the process and the outcomes of this guidelines project. All comments by external reviewers were openly discussed by panel

members. The panel was under no obligation to adhere to their comments or suggested changes, and proposed changes were derived by consensus methods among the members of the panel. Concerns have been expressed about the credibility of synthetic research, such as practice guidelines, developed or sponsored by industry stakeholders.[96] Although industry representatives did participate as external reviewers (to ensure that their views were understood and their products properly represented), they provided no financial support to the guideline development process.

Our guidelines differ from previous published guidelines not only in the process of how they were created but also in the quantity of the topics and the nature of the recommendations themselves. Whereas previous guidelines dealt with issues of screening "at-risk" patients, nutrition assessment, and developing the nutrition prescription (how much protein and calories), we did not put forward recommendations in these areas because there were insufficient data from randomized controlled trials to inform the guidelines panel. The starting point for our guidelines is that nutrition support does influence the outcome of critically ill patients. Therefore, our objectives were to develop a list of practical, evidence-based recommendations that would optimize the benefits and minimize the risks of nutrition support provided to adult patients. We were successful in developing 17 affirmative recommendations compared with 5 recommendations from the recent A.S.P.E.N. guidelines.[16]

Limitations of these guidelines are universal to any guidelines according to primary studies and systematic reviews of them. In several content areas, data from randomized trials were sparse. Where several trials were available on a particular topic, these data were systematically reviewed and statistically aggregated (in the form of a meta-analysis) where appropriate. Systematic reviews are advocated as the best method to summarize existing evidence to inform both clinical and policy decisions.[97] However, not all systematic reviews or meta-analyses are created equal. Guidelines on assessing the validity of these tools exist[98] and were used to interpret the strength of evidence and, thus, the clinical inference one can make from the meta-analysis. In some cases, the meta-analysis was considered to be hypothesis-confirming (as in the case of PN or arginine-containing diets), and clinical recommendations were put forward, whereas in other cases, the results were considered to be hypothesis-generating (as in the case of antioxidants), and no clinical recommendations were put forward. Although discrepancies between meta-analysis and large randomized controlled trials have been noted,[99] there are usually "reasons" for these discrepancies, and understanding these reasons often leads to further insights into optimal treatment strategies.[100]

A further limitation of our guidelines is that data on costs, feasibility, and safety were not systematically available or considered in developing the recommendations. We relied heavily on committee members' experience and expertise to evaluate these values that were incorporated into the guidelines. Nevertheless, the evaluation of the values component of the guidelines was conducted in a transparent fashion using semiquantitative scoring. If readers disagree with the guideline, they can trace the source of their disagreement back to a difference in summarizing the evidence or different weighting of the related values (see www.criticalcarenutrition.com for complete, up-to-date information on summaries of evidence and weights used by the guidelines panel).

We believe that dissemination and implementation of these guidelines will lead to improved nutrition support practice in ICUs across Canada (and elsewhere). In turn, this will translate into improved clinical outcomes for critically ill patients and enhanced efficiencies to health care systems. We have recently conducted a survey of nutrition support practice in Canada documenting how nutrition support is currently being provided.[11] The survey documented that a significant number of critically ill patients did not receive any form of nutrition support for the study period. Those that did receive nutrition support did not meet their prescribed energy or protein needs, especially earlier in the course of their illness. Contrasting what is actually being done (survey results) with what should be done (as per the evidence-based guidelines) highlights significant opportunities for improving practice. Areas that need the greatest attention are those with the largest gap between actual practice and best practice and include the use of feeding algorithms, small bowel feeding, head-of-the-bed elevation, and motility agents. Attention to narrowing these "gaps" will lead to improved outcomes in the most efficient manner.

Creating change, or narrowing these "gaps," will require active guidelines dissemination strategies that include the use of opinion leaders,[101] educational outreach visits or academic detailing,[102] and audit and feedback,[103] used independently and in various combinations.[104] Multifaceted implementation strategies (ie, applying multiple strategies together) have been shown to have a higher probability of success compared with a single implementation strategy.[104]

In summary, we have developed an evidence-based practice guideline for the provision of nutrition support to adult ICU patients. The process of development of this guideline has included rigorous attention to systematic search and appraisal of evidence, an explicit approach to translating findings from evidence into recommendations, and external review from a broad sample of stakeholders. According to these features, we would expect that this guideline will be accepted by clinicians and that implementation of this guideline, facilitated by proven strategies, will improve outcomes for critically ill patients who need specialized nutrition support.

ACKNOWLEDGMENTS

We thank Dr Morad Hameed, Nadia Rodych, RD, Chris Arnold, RD, Myrna Laycock, RD, Shirley McGowen, RN, Robert Ralph, RN, Stephanie Thoms, RD, and Karen Wood, RD, for reviewing articles and Michelle Boston, RD, Christine McCleary, RD, CDE, and Michele Port, P.Dt., from Dietitians of Canada for reviewing the guidelines. Finally, we thank Andrew Day for his assistance with the statistical analysis.

APPENDIX I

Canadian Critical Care Clinical Practice Guidelines Committee Panel Members: *Co-chairs:* Daren Heyland, MD, Leah Gramlich, MD (CSCN); *Executive Assistant:* Rupinder Dhaliwal, RD.

*Members:* Carmen Christman, RD (Dietitians of Canada), Voula Christofilos, RD, Deborah Cook, MD (CCCTG), Peter Dodek, MD, John Drover, MD, FACS, FRCSC, Jan Greenwood, RD, Darlene Harrietha, RD, Minto Jain, MD, Brian Jurewitsch, Pharmacist (CSCN), Jaime Pinilla, MD, Shannon Mackenzie, RD, Sabrina Martin, RN (CACCN), Dominique Michaud, RN, Deborah Schroter-Noppe, RD.

*External Advisors:* Dr. David August (A.S.P.E.N.), Dr. Alison Avenell, Anne Dumas (Ross Products Division, Abbott Laboratories), Terri Grad (Nestle Canada), Dr. Khursheed Jeejeebhoy, Dr. Ron Koretz, Dr. Steve McClave, Dr. Ulrich Suchner (Fresenius Kabi), Dr. Gary Zaloga (SCCM).

APPENDIX II
*Summary of topics and recommendations*

| | | | |
|---|---|---|---|
| 1. | EN *vs* PN | Does enteral nutrition compared with parenteral nutrition result in better outcomes in the critically ill adult patient? | According to 1 level 1 study and 12 level 2 studies, when considering nutrition support for critically ill patients, we strongly recommend the use of enteral nutrition over parenteral nutrition. |
| 2. | Early *vs* delayed nutrient intake | Does early enteral nutrition compared with late enteral nutrition result in better outcomes in the critically ill adult patient? | According to 8 level 2 studies, we recommend early enteral nutrition (within 24 to 48 hours following resuscitation) in critically ill patients. |
| 3.1 | Dose of EN: Use of indirect calorimetry *vs* predictive equation for EN | Does the use of indirect calorimetry *vs* a predictive equation for determining energy needs result in better outcomes in the critically ill adult patient? | There are insufficient data to make a recommendation on the use of indirect calorimetry *vs* predictive equations for determining energy needs for enteral nutrition in critically ill patients. |
| 3.2 | Dose of EN: Achieving target dose of EN | Does achieving target dose of enteral nutrition result in better outcomes in the critically ill adult patient? | According to 1 level 2 study, when initiating enteral nutrition in head-injured patients, strategies to optimize delivery of nutrients (starting at target rate, higher threshold of gastric residual volumes and use of small bowel feedings) should be considered. In other critically ill patients, there are insufficient data to make a recommendation. |
| 4.1 (a) | Composition of EN: Immune-enhancing diets: diets supplemented with arginine and other select nutrients | Compared with standard enteral feeds, do diets supplemented with arginine and other select nutrients result in improved clinical outcomes in the critically ill adult patient? | According to 2 level 1 studies and 12 level 2 studies, we recommend that diets supplemented with arginine and other selected nutrients not be used for critically ill patients. |
| 4.1 (b) | Composition of EN: Immune-enhancing diets: fish oils | Does the use of an enteral formula with fish oils, borage oils, and antioxidants result in improved clinical outcomes in the critically ill adult patient? | According to 1 level 1 study, the use of an enteral formula with fish oils, borage oils, and antioxidants should be considered in patients with ARDS. |
| 4.1 (c) | Composition of EN: Immune-enhancing diets: glutamine | Compared with standard care, does glutamine-supplemented EN result in improved clinical outcomes in the critically ill adult patient? | According to 1 level 1 and 4 level 2 studies, enteral glutamine should be considered in burn and trauma patients. There are insufficient data to support the routine use of enteral glutamine in other critically ill patients. |
| 4.2 (a) | Composition of EN: CHO/FAT: high fat, low CHO | Does a high fat/low carbohydrate enteral formula influence outcomes in the critically ill adult patient? | There are insufficient data to recommend high-fat/low carbohydrate diets for critically ill patients. |
| 4.2 (b) | Composition of EN: CHO/FAT: low fat, high CHO | Does a low fat/high carbohydrate enteral formula influence outcomes in the critically ill adult patient? | There are insufficient data to make a recommendation regarding the use of a low-fat formula in critically ill patients. |
| 4.3 | Composition of EN: protein/peptides | Does the use of peptide-based enteral formula, compared with a whole-protein formula, result in better outcomes in the critically ill adult patient? | According to 4 level 2 studies, when initiating enteral feeds, we recommend the use of whole-protein formulas (polymeric) in critically ill patients. |
| 4.4 | Composition of EN: pH | Do acidified feeds (low pH) compared with standard feeds result in better outcomes in the critically ill adult patient? | There are insufficient data to make a recommendation regarding the use of low-pH feeds in critically ill patients. |
| 4.5 | Composition of EN: fiber | Do enteral feeds with fiber, compared with standard feeds result in better outcomes in the critically ill adult patient? | There are insufficient data to support the routine use of fiber in enteral feeding formulas in critically ill patients. |

APPENDIX II
*(continued)*

| | | | |
|---|---|---|---|
| 5.1 | Strategies to optimize delivery and minimize risks of EN: feeding protocols | Does the use of a feeding protocol result in better outcomes in the critically ill adult patient? | There are insufficient data from randomized trials to recommend the use of a feeding protocol in critically ill patients. If a feeding protocol is to be used, according to 1 level 2 study, a protocol that incorporates prokinetics (metoclopramide) at initiation and tolerates a higher gastric residual volume (250 mL) should be considered as a strategy to optimize delivery of enteral nutrition in critically ill adult patients. |
| 5.2 | Strategies to optimize delivery and minimize risks of EN: motility agents | Compared with standard practice (placebo), does the routine use of motility agents result in better clinical outcomes in the critically ill adult patient? | According to a systematic review, in critically ill patients who experience feed intolerance (high gastric residuals, emesis), the use of metoclopramide as a motility agent should be considered. |
| 5.3 | Strategies to optimize delivery and minimize risks of EN: small bowel feeding | Does enteral feeding via the small bowel compared to gastric feeding result in better outcomes in the critically ill adult patient? | According to 11 level 2 studies, small bowel feeding compared with gastric feeding may be associated with a reduction in pneumonia in critically ill patients. In units where obtaining small bowel access is feasible, we recommend the routine use of small bowel feedings. In units where obtaining access involves more logistical difficulties, small bowel feedings should be considered for patients at high risk for intolerance to EN (receiving inotropes, continuous infusion of sedatives or paralytic agents, or patients with high nasogastric drainage) or at high risk for regurgitation and aspiration (nursed in supine position). Finally, in units where obtaining small bowel access is not feasible (no access to fluoroscopy or endoscopy and blind techniques not reliable), small bowel feedings should be considered for those select patients who repeatedly demonstrate high gastric residual volumes and are not tolerating adequate amounts of EN delivered into the stomach. |
| 5.4 | Strategies to optimize delivery and minimize risks of EN: body position | Do alterations in body position result in better outcomes in the critically ill adult patient? | According to 1 level 2 study, we recommend that critically ill patients receiving enteral nutrition have the head of the bed elevated to 45 degrees. Where this is not possible, attempts to raise the head of the bed as much as possible should be considered. |
| 6.1 | EN other: closed *vs* open system | Does the use of a closed system for enteral feeding result in better outcomes when compared with an open system in the critically ill adult patient? | There are insufficient data to make a recommendation on the administration of EN via a closed *vs* open system in critically ill patients. |
| 6.2 | EN other: probiotics | Does the addition of probiotics to enteral nutrition result in better outcomes in the critically ill adult patient? | There are insufficient data to make a recommendation on the use of probiotics in critically ill patients. |
| 6.3 | EN other: continuous *vs* other methods of administration | Does continuous administration of enteral nutrition compared with other methods of administration result in better outcomes in the critically ill adult patient? | There are insufficient data to make a recommendation on enteral feeds given continuously *vs* other methods of administration in critically ill patients. |
| 7. | EN in combination with PN | Does the use of parenteral nutrition in combination with enteral nutrition result in better outcomes in the critically ill adult patient? | According to 5 level 2 studies, for critically ill patients starting enteral nutrition, we recommend that parenteral nutrition not be started at the same time as enteral nutrition. In the patient who is not tolerating adequate enteral nutrition, there are insufficient data to put forward a recommendation about when parenteral nutrition should be initiated. Practitioners will have to weigh the safety and benefits of initiating PN for patients not tolerating EN on a case-by-case basis. We recommend that PN not be started in critically ill patients until all strategies to maximize EN delivery (such as small bowel feeding tubes, motility agents) have been attempted. |
| 8. | PN: PN *vs* standard care | Compared with standard care (IV fluids, oral diet, etc), does parenteral nutrition result in better outcomes in critically ill patients who have an intact GI tract? | According to a meta-analysis, in critically ill patients with an intact GI tract, we strongly recommend that parenteral nutrition not be used routinely. |

APPENDIX II
*(continued)*

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| 9.1 | Composition of PN: branched chain amino acids | Does the addition of branched chain amino acids to parenteral nutrition influence outcomes in the critically ill adult patient? | There are insufficient data to make a recommendation regarding the use of branched chain amino acids in critically ill patients who are receiving parenteral nutrition. |
| 9.2 | Composition of PN: type of lipids | Does the type of lipids in parenteral nutrition influence outcomes in the critically ill adult patient? | There are insufficient data to make a recommendation on the type of lipids to be used in critically ill patients who are receiving parenteral nutrition. |
| 9.3 | Composition of PN: zinc | Does zinc supplementation (via IV/PN) given either alone or in combination with other nutrients result in better outcomes in the critically ill patient? | There are insufficient data to make a recommendation regarding IV/PN zinc supplementation in critically ill patients. |
| 9.4 | Composition of PN: glutamine | Does glutamine supplementation of parenteral nutrition influence outcomes in the critically ill adult patient? | According to 2 level 1 studies and 3 level 2 studies, when parenteral nutrition is prescribed to critically ill patients, parenteral supplementation with glutamine, where available, is recommended. There are insufficient data to generate recommendations for intravenous glutamine in critically ill patients who are receiving enteral nutrition. |
| 10.1 | Strategies to optimize benefits and minimize risks of PN: hypocaloric PN | Does hypocaloric parenteral nutrition influence outcomes in the critically ill adult patient? | According to 2 level 2 studies, in critically ill patients who are not malnourished, are tolerating some EN, or when parenteral nutrition is indicated for short-term use (<10 days), hypocaloric parenteral nutrition should be considered. There are insufficient data to make recommendations about the use of hypocaloric parenteral nutrition or withholding lipids in the following patients: those requiring PN for long term (>10 days), obese critically ill patients, and malnourished critically ill patients. Practitioners will have to weigh the safety and benefits of hypocaloric PN/withholding lipids on a case-by-case basis in these latter patient populations. |
| 10.2 | Strategies to optimize benefits and minimize risks of PN: use of lipids | Does the presence of lipids in parenteral nutrition influence outcomes in the critically ill adult patient? | According to 2 level 2 studies, in critically ill patients who are not malnourished, are tolerating some EN, or when parenteral nutrition is indicated for short-term use (<10 days), withholding lipids should be considered. There are insufficient data to make a recommendation about withholding lipids in critically ill patients who are malnourished or those requiring PN for long term (>10 days). Practitioners will have to weigh the safety and benefits of withholding lipids on a case-by-case basis in these latter patient populations. |
| 10.3 | Strategies to optimize benefits and minimize risks of PN: mode of lipid delivery | Does the mode of delivery of lipids influence outcomes in the critically ill adult patient? | There are insufficient data to make a recommendation on mode of lipid delivery in critically ill patients who are receiving parenteral nutrition. |
| 10.4 | Strategies to optimize benefits and minimize risks of PN: intensive insulin therapy | Does tight blood glucose control result in better outcomes in the critically ill adult patient? | According to 1 level 2 study, in surgical critically ill patients receiving nutrition support, intensive insulin therapy to tightly control blood glucose between 4.4 and 6.1 should be considered. There are insufficient data to make a recommendation regarding intensive insulin therapy in other critically ill patients. |
| 11.1 | Antioxidant strategies: combined: single and multimodal | Does the addition of antioxidant nutrients (single and combined) result in better outcomes in the critically ill patient? | There are insufficient data to make a recommendation regarding antioxidant nutrients (single or combined) in critically ill patients. |
| 11.2 | Antioxidant strategies: selenium | Does parenteral selenium supplementation (alone or in combination with other antioxidants) result in better outcomes in the critically ill patient? | There are insufficient data to make a recommendation regarding IV/PN selenium supplementation alone or in combination with other antioxidants in critically ill patients. |

CHO, carbohydrate.
The numbering system correlates with the numbering on the website. See www.criticalcarenutrition.com for the most current version of the guidelines.

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