Special Article

# Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.)

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The American College of Critical Care Medicine (ACCM), which honors individuals for their achievements and contributions to multidisciplinary critical care medicine, is the consultative body of the Society of Critical Care Medicine (SCCM) that possesses recognized expertise in the practice of critical care. The College has developed administrative guidelines and clinical practice parameters for the critical care practitioner. New

guidelines and practice parameters are continually developed, and current ones are systematically reviewed and revised.

These guidelines are being copublished by the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) in the *Journal of Parenteral and Enteral Nutrition* (*JPEN*), 2016: 40(2):159–211.

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## PRELIMINARY REMARKS (INTENT OF GUIDELINES)

A.S.P.E.N. and SCCM are both nonprofit organizations composed of multidisciplinary healthcare professionals. The mission of A.S.P.E.N. is to improve patient care by advancing the science and practice of clinical nutrition and metabolism. The mission of SCCM is to secure the highest quality care for all critically ill and injured patients.

***Guideline Limitations***: These A.S.P.E.N.–SCCM Clinical Guidelines are based on general conclusions of health professionals who, in developing such guidelines, have balanced potential benefits to be derived from a particular mode of medical therapy against certain risks inherent with such therapy. However, practice guidelines are not intended as absolute requirements. The use of these practice guidelines does not in any way project or guarantee any specific benefit in outcome or survival.

**The judgment of the healthcare professional based on individual circumstances of the patient must always take precedence over the recommendations in these guidelines.**

The guidelines offer basic recommendations that are supported by review and analysis of the current literature, other national and international guidelines, and a blend of expert opinion and clinical practicality. The population of critically ill patients in an intensive care unit (ICU) is not homogeneous. Many of the studies on which the guidelines are based are limited by sample size, patient heterogeneity, variability in disease severity, lack of baseline nutritional status, and insufficient statistical power for analysis.

***Periodic Guideline Review and Update:*** This particular report is an update and expansion of guidelines published by A.S.P.E.N. and SCCM in 2009 (1). Governing bodies of both A.S.P.E.N. and SCCM have mandated that these guidelines be updated every three to five years. The database of randomized controlled trials (RCTs) that served as the platform for the analysis of the literature was assembled in a joint "harmonization process" with the Canadian Clinical Guidelines group. Once completed, each group operated separately in their interpretation of the studies and derivation of guideline recommendations (2). The current A.S.P.E.N. and SCCM guidelines included in this paper were derived from data obtained via literature searches by the authors through December 31, 2013. Although the committee was aware of landmark studies published after this date, these data were not included in this manuscript. The process by which the literature was evaluated necessitated a common end date for the search review. Adding a last-minute landmark trial would have introduced bias unless a formalized literature search was re-conducted for all sections of the manuscript.

***Target Patient Population for Guideline:*** The target of these guidelines is intended to be the adult (≥ 18 years) critically ill patient expected to require a length of stay (LOS) greater than 2 or 3 days in a medical ICU (MICU) or surgical ICU (SICU). The current guidelines were expanded to include a number of additional subsets of patients who met the above criteria, but were not included in the previous 2009 guidelines. Specific patient populations addressed by these expanded and updated guidelines include organ failure (pulmonary, renal, and liver), acute pancreatitis, surgical subsets (trauma, traumatic brain injury [TBI], open abdomen [OA], and burns), sepsis, postoperative major surgery, chronic critically ill, and critically ill obese. These guidelines are directed toward generalized patient populations but, like any other management strategy in the ICU, nutrition therapy should be tailored to the individual patient.

***Target Audience***: The intended use of these guidelines is for all healthcare providers involved in nutrition therapy of the critically ill, primarily physicians, nurses, dietitians, and pharmacists.

***Methodology:*** The authors compiled clinical questions reflecting key management issues in nutrition therapy. A committee of multidisciplinary experts in clinical nutrition composed of physicians, nurses, pharmacists, and dietitians was jointly convened by the two societies. Literature searches were then performed using key words (critically ill, critical care, intensive care, nutrition, enteral, parenteral, tube feeding, and those related to assigned topics such as pancreatitis, sepsis, etc.) to evaluate the quality of evidence supporting a response to those questions, which were then used to derive a subsequent treatment recommendation. The literature search included MEDLINE, PubMed, Cochrane Database of Systemic Reviews, the National Guidelines Clearing House and an Internet search using the Google search engine for scholarly articles through an end date of December 31, 2013 (including ePub publications).

While preference was given to RCTs, other forms of resource material were used to support the response, including nonrandomized cohort trials, prospective observational studies, and retrospective case series. Use of publications was limited to full-text articles available in English on adult humans. For all included RCTs, two readers completed data abstraction forms (DAFs) examining the data and assessing the quality of the research methodology to produce a shared evaluation achieved by consensus for each study (example of DAF provided in the **supplemental data**, Supplemental Digital Content 1, http://links.lww.com/CCM/B571). DAFs were constructed only for RCTs. When the strongest available evidence was a published meta-analysis, the studies from the meta-analysis were used to determine the quality of the evidence and assessed by two evidence assessors. The data from included trials were entered into Review Manager 5.2 software to create forest plots aggregating the effect size for each intervention and outcome (3). The key forest plots supporting the recommendation are included throughout the text and in the supplement data (Supplemental Digital Content 1, http://links.lww.com/CCM/B571). No new forest plots were created when a meta-analysis was evaluated.

Since release of the 2009 A.S.P.E.N. and SCCM Clinical Guidelines, the concepts of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group have been adopted (4–7). A full description of the methodology has been previously published (4). The data from the Review Manager analysis was uploaded to GRADEPro software (8), where the body of evidence for a given intervention and outcome was evaluated for overall quality. One analyst created each GRADE table that was then independently confirmed by a second analyst. The GRADE tables are provided in the supplement data (Supplemental Digital Content 1, http://links.lww.com/CCM/B571). Due to the inordinately large number of RCTs evaluated, observational studies were critically reviewed, but not utilized to construct the GRADE tables. However, in the few cases where observational studies were the only available evidence in a population, their quality of evidence was reviewed, using GRADE (**Table 1**). When no RCT or observational study was available to answer a question directly, consensus of the author group on the best clinical practice approach was used, and the recommendation was designated "based on expert consensus."

A recommendation for clinical practice was based on both the best available evidence and the risks and benefits to patients. While small author teams developed each recommendation and provided the supporting rationale, a full discussion by the entire author group followed, and every committee member was polled anonymously for their agreement with the recommendation. Achievement of consensus was arbitrarily set at 70% agreement of authors with a particular recommendation. Only one recommendation (H3a) did not meet this level of agreement, with a final consensus of 64%. All other consensus-based recommendations reached a level of agreement of 80% or higher. As with all A.S.P.E.N. and SCCM clinical guidelines, this manuscript was subjected to rigorous peer review by clinical content experts from all the practice disciplines that would use the guidelines, both internal and external to the organizations. A summary of the guidelines is presented in the supplement data (Supplemental Digital Content 1, http://links.lww.com/CCM/B571). A nutrition bundle based on the top guidelines (as voted on by the committee) for the bedside practitioner is presented in **Table 2**.

## CONFLICT OF INTEREST

All authors completed both an A.S.P.E.N. and SCCM conflict of interest form for copyright assignment and financial disclosure. There was no input or funding from industry, nor were any industry representatives present at any of the committee meetings.

## DEFINITIONS

**Nutrition Therapy** refers specifically to the provision of either enteral nutrition (EN) by enteral access device and/or parenteral nutrition (PN) by central venous access. **Standard therapy (STD)** refers to provision of IV fluids, no EN or PN, and advancement to oral diet as tolerated.

## INTRODUCTION

The significance of nutrition in the hospital setting (and especially the ICU) cannot be overstated. Critical illness is typically associated with a catabolic stress state in which patients demonstrate a systemic inflammatory response coupled with complications of increased infectious morbidity, multiple organ dysfunction, prolonged hospitalization, and disproportionate mortality. Over the past three decades, exponential advances have been made in the understanding of the molecular and biological effects of nutrients in maintaining homeostasis in the critically ill population. Traditionally, *nutrition support* in the critically ill population was regarded as adjunctive care designed to provide exogenous fuels to preserve lean body mass and support the patient throughout the stress response. Recently this strategy has evolved to represent *nutrition therapy,* in which the feeding is thought to help attenuate the metabolic response to stress, prevent oxidative cellular injury, and favorably modulate immune responses. Improvement in the clinical course of critical illness may be achieved by early EN, appropriate macro- and micronutrient delivery, and meticulous glycemic control. Delivering early nutrition support therapy, primarily by the enteral route, is seen as a proactive therapeutic strategy that may reduce disease severity, diminish complications, decrease LOS in the ICU, and favorably impact patient outcomes.

## A. NUTRITION ASSESSMENT

**Question:** Does the use of a nutrition risk indicator identify patients who will most likely benefit from nutrition therapy?

**A1. Based on expert consensus, we suggest a determination of nutrition risk (for example, Nutritional Risk Score [NRS-2002], NUTRIC score) be performed on all patients admitted to the ICU for whom volitional intake is anticipated to be insufficient. High nutrition risk identifies those patients most likely to benefit from early EN therapy.**

**Rationale:** Poor outcomes have been associated with inflammation generated by critical illness that leads to deterioration of nutrition status and malnutrition (9). However, malnutrition in the critically ill has always been difficult to define. An international consensus group modified definitions to recognize the impact of inflammation. Objective measures of baseline nutrition status have been described by A.S.P.E.N. and the Academy of Nutrition and Dietetics (10, 11). On the other hand, nutrition risk is easily defined and more readily determined by evaluation of baseline nutrition status and assessment of disease severity. All hospitalized patients are required to undergo an initial nutrition screen within 48 hours of admission. However, patients at higher nutrition risk in an ICU setting require a full nutrition assessment. Many screening and assessment tools are used to evaluate nutrition status, such as the Mini Nutritional Assessment (MNA), the Malnutrition Universal Screening Tool (MUST), the Short Nutritional Assessment Questionnaire (SNAQ),

**TABLE 1. Type of Evidence**

| Type of Evidence | Initial GRADE | Criteria to Decrease GRADE | Criteria to Increase Grade | Final Quality GRADE (confidence in the estimate of effect |
|---|---|---|---|---|
| Randomized Control Trial (RCT) | High | **Study Limitations**<br>**Risk of Bias** Serious (−1) or very serious (−2) limitation to study quality (inadequate randomization or blinding, no use of intent to treat analysis) | | High |
| | | **Consistency** Important inconsistency (heterogeneity across studies, as $I^2 > 0.5$ or some say yes but other say no) (−1) | | Moderate |
| | | **Directness** Some (−1) or major (−2) uncertainty about directness (outcome variable is not a direct measure of the process, ie nitrogen balance to represent protein catabolism) | | Low |
| | | **Precision** Imprecise or sparse data (−1) (combined effect size is not significant, small number of subjects) | | Very Low |
| | | **Publication bias** High probability of reporting bias (−1) | | |
| Observational Study (Cohort, Case Series, Case Study) | Low | | **Strong Association**<br>Significant relative risk of > 2 (< 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1) | Low |
| | | | Significant relative risk of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2) | Very Low |
| | | | Evidence of a dose response gradient (+1) | |
| | | | **Unmeasured Confounders**<br>All plausible confounders would have reduced the effect (+1) | |
| Good Practice Statement | | | | Ungraded |

Adapted from GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004, 328 (7454): 1490–1494
Guyatt et al, J Clin Epidemiol 2015. (8)

the Malnutrition Screening Tool (MST), and the Subjective Global Assessment (SGA) (12). However, only the NRS-2002 and the NUTRIC score determine both nutrition status and disease severity. Although both scoring systems were based on retrospective analysis, they have been used to define nutrition risk in RCTs in critically ill patients (13–16). Patients at "risk" are defined by an NRS-2002 > 3 and those at "high risk" with a score ≥ 5; or a NUTRIC score ≥ 5 (if interleukin-6 is not included, otherwise ≥ 6) (13, 18). Interleukin-6 is rarely available as a component for the NUTRIC score; therefore, Heyland et al has shown a NUTRIC score ≥ 5 still indicates high nutrition risk (19). Two prospective nonrandomized studies show that patients at high nutrition risk are more likely to benefit from early EN with improved outcome

**TABLE 2. Bundle Statements**

| |
|---|
| • Assess patients on admission to the ICU for nutrition risk, and calculate both energy and protein requirements to determine goals of nutrition therapy. |
| • Initiate enteral nutrition (EN) within 24–48 hours following the onset of critical illness and admission to the ICU and increase to goals over the first week of ICU stay. |
| • Take steps as needed to reduce risk of aspiration or improve tolerance to gastric feeding (use prokinetic agent, continuous infusion, chlorhexidine mouthwash, elevate the head of bed, and divert level of feeding in the gastrointestinal tract). |
| • Implement enteral feeding protocols with institution-specific strategies to promote delivery of EN. |
| • Do not use gastric residual volumes as part of routine care to monitor ICU patients on EN. |
| • Start parenteral nutrition early when EN is not feasible or sufficient in high-risk or poorly nourished patients. |

(reduced nosocomial infection, total complications, and mortality) than patients at low nutrition risk (13, 18). While widespread use and supportive evidence is somewhat lacking to date, improvement in these scoring systems may increase their applicability in the future by providing guidance as to the role of EN and PN in the ICU.

**Question:** What additional tools, components or surrogate markers provide useful information when performing nutrition assessments in critically ill adult patients?

**A2. Based on expert consensus, we suggest that nutritional assessment include an evaluation of comorbid conditions, function of the gastrointestinal (GI) tract, and risk of aspiration. We suggest not using traditional nutrition indicators or surrogate markers, as they are not validated in critical care.**

**Rationale:** In the critical care setting, the traditional serum protein markers (albumin, prealbumin, transferrin, retinol-binding protein) are a reflection of the acute phase response (increases in vascular permeability and reprioritization of hepatic protein synthesis) and do not accurately represent nutrition status in the ICU setting (20). Anthropometrics are not reliable in assessment of nutrition status or adequacy of nutrition therapy (21). Individual levels of calcitonin, C-reactive protein (CRP), IL-1, tumor necrosis factor (TNF), IL-6, and citrulline are still investigational and should not be used as surrogate markers. Ultrasound is emerging as a tool to expediently measure muscle mass and determine changes in muscle tissue at bedside in the ICU, given its ease of use and availability (22, 23). A CT scan provides a precise quantification of skeletal muscle and adipose tissue depots; however it is quite costly unless a scan taken for other purposes is used to determine body composition (24, 25). Both may be valuable future tools to incorporate into nutrition assessment; however, validation and reliability studies in ICU patients are still pending. Assessment of muscle function is still in its infancy. Its measurement, reproducibility, and applicability are still being validated for use in critically ill patients, and may be of value in the future.

**Question:** What is the best method for determining energy needs in the critically ill adult patient?

**A3a. We suggest that indirect calorimetry (IC) be used to determine energy requirements, when available and in the absence of variables that affect the accuracy of measurement.**

[**Quality of Evidence: Very Low**]

**A3b. Based on expert consensus, in the absence of IC, we suggest that a published predictive equation or a simplistic weight-based equation (25–30 kcal/kg/day) be used to determine energy requirements. (See section Q for obesity recommendations.)**

**Rationale:** Clinicians should determine energy requirements in order to establish the goals of nutrition therapy. Energy requirements may be calculated either through simplistic formulas (25–30 kcal/kg/day), published predictive equations, or IC. The applicability of IC may be limited at most institutions by availability and cost. Variables in the ICU that affect the timing and accuracy of IC measurements include the presence of air leaks or chest tubes, supplemental oxygen (e.g., nasal cannula, bilevel positive airway pressure), ventilator settings (fractional inspiratory oxygen and positive end-expiratory pressure), continuous renal replacement therapy (CRRT), anesthesia, physical therapy, and excessive movement (26). More than 200 predictive equations have been published in the literature, with accuracy rates ranging from 40–75% when compared to IC, and no single equation emerges as being more accurate in an ICU (27–32). Predictive equations are less accurate in obese and underweight patients (33–36). Equations derived from testing hospital patients (Penn State, Ireton-Jones, Swinamer) are no more accurate than equations derived from testing normal volunteers (Harris-Benedict, Mifflin St. Jeor) (37). The poor accuracy of predictive equations is related to many non-static variables affecting energy expenditure in the critically ill patient, such as weight, medications, treatments, and body temperature. The only advantage of using weight-based equations over other predictive equations is simplicity. However, in critically ill patients following aggressive volume resuscitation or in the presence of edema or anasarca, clinicians should use dry or usual body weight in these equations.

Additional energy provided by dextrose-containing fluids and lipid-based medications such as propofol should be accounted for when deriving nutrition therapy regimens to meet target energy goals. Achieving energy balance as guided

by IC measurements compared to predictive equations may lead to more appropriate nutrition intake.

While two RCTs (38, 39) that met our inclusion criteria (with data from 161 patients) showed that higher mean intake of energy and protein were provided in IC-directed study patients compared to controls whose nutrition therapy was directed by predictive equations, issues with study design prevent a stronger recommendation for use of IC. In a study of burn patients, use of IC-directed nutrition therapy helped provide the minimal effective intake, avoiding the excesses of overfeeding seen in controls whose therapy was directed by the Curreri formula. Complications between groups (diarrhea and hyperglycemia) were no different, but traditional outcome parameters were not evaluated (38). A second study in general ICU patients used both EN and PN to meet target energy goals determined by IC measurement or a weight-based predictive equation (25 kcal/kg/day) (39). While the IC-directed energy goal was no different than the value obtained by predictive equation (1976 ± 468 vs 1838 ± 468 kcal/day, respectively, $p = 0.60$), only study patients were monitored vigilantly by an ICU dietitian, while controls were managed by standard of care (less frequent ICU dietitian monitoring), which led to significantly more energy and protein per day in the study patients. The trend toward reduced mortality in study patients compared to controls (RR = 0.63; 95% CI, 0.39–1.02; $p = 0.06$) is difficult to reconcile in light of their increased morbidity with regard to ICU LOS (17.2 + 14.6 vs 11.7 + 8.4 days, $p = 0.04$) and duration of mechanical ventilation (16.1 + 14.7 vs 10.5 + 8.3 days, $p = 0.03$) (38, 39).

Whether measured by IC or estimated by predictive equations, energy expenditure should be reevaluated more than once per week, and strategies to optimize energy and protein intake should be used (39, 40).

**Question:** Should protein provision be monitored independently from energy provision in critically ill adult patients?

### A4. Based on expert consensus, we suggest an ongoing evaluation of adequacy of protein provision be perforMed

**Rationale:** In the critical care setting, protein appears to be the most important macronutrient for healing wounds, supporting immune function, and maintaining lean body mass. For most critically ill patients, protein requirements are proportionately higher than energy requirements and thus are not easily met by provision of routine enteral formulations (which have a high nonprotein calorie-to-nitrogen ratio [NPC:N]). Patients with suboptimal EN due to frequent interruptions may benefit from protein supplementation. The decision to add protein modules should be based on an ongoing assessment of adequacy of protein intake. Weight-based equations (e.g., 1.2–2.0 g/kg/day) may be used to monitor adequacy of protein provision by comparing the amount of protein delivered to that prescribed, especially when nitrogen balance studies are not available to assess needs (see section C4) (41, 42). Serum protein markers (albumin, prealbumin, transferrin, CRP) are not validated for determining adequacy of protein provision and should not be used in the critical care setting in this manner (20, 43).

## B. INITIATE EN

**Question:** What is the benefit of early EN in critically ill adult patients compared to withholding or delaying this therapy?

### B1. We recommend that nutrition support therapy in the form of early EN be initiated within 24–48 hours in the critically ill patient who is unable to maintain volitional intake.

**[Quality of Evidence: Very Low]**

**Rationale:** EN supports the functional integrity of the gut by maintaining tight junctions between the intraepithelial cells, stimulating blood flow, and inducing the release of trophic endogenous agents (such as cholecystokinin, gastrin, bombesin, and bile salts). EN maintains structural integrity by maintaining villous height and supporting the mass of secretory IgA-producing immunocytes (B cells and plasma cells) that comprise the gut-associated lymphoid tissue (GALT), and in turn contribute to mucosal-associated lymphoid tissue (MALT) at distant sites such as the lungs, liver, and kidneys (44–46).

Adverse change in gut permeability from loss of functional integrity is a dynamic phenomenon that is time dependent (channels opening within hours of the major insult or injury). The consequences of the permeability changes include increased bacterial challenge (engagement of GALT with enteric organisms), risk for systemic infection, and greater likelihood of multiple organ dysfunction syndrome (MODS) (45, 46). As disease severity worsens, increases in gut permeability are amplified and the enteral route of feeding is more likely to favorably impact outcome parameters of infection, organ failure, and hospital LOS (47).

The specific reasons for providing EN are to maintain gut integrity, modulate stress and the systemic immune response, and attenuate disease severity (44, 47, 48). Additional endpoints of EN therapy may include use of the gut as a conduit for the delivery of immune-modulating agents and use of enteral formulations as an effective means for stress ulcer prophylaxis.

Three previous meta-analyses aggregated data from RCTs comparing early versus delayed EN. One meta-analysis of eight trials by Heyland showed a trend toward reduced mortality (RR = 0.52; 95% CI, 0.25–1.08; $p = 0.08$) (49), when EN was started within 48 hours compared to delayed initiation of EN started after that point. A second meta-analysis of 12 trials by Marik showed significant reductions in infectious morbidity (RR = 0.45; 95% CI, 0.30–0.66; $p = 0.00006$) and hospital LOS (mean 2.2 days; 95% CI, 0.81–3.63 days; $p = 0.001$) when early EN was started on average within 36 hours of ICU admission (50). A third meta-analysis of six trials by Doig showed a significant reduction in pneumonia (OR = 0.31; 95% CI, 0.12–0.78; $p = 0.01$) and mortality (OR = 0.34; 95% CI, 0.14–0.85; $p = 0.02$), but no difference in multiple organ failure (MOF) when early EN was started within 24 hours of admission to the ICU, compared to EN started after that point (51).

Of an updated meta-analysis of 21 RCTs that met our inclusion criteria comparing the provision of early EN versus delayed EN, all

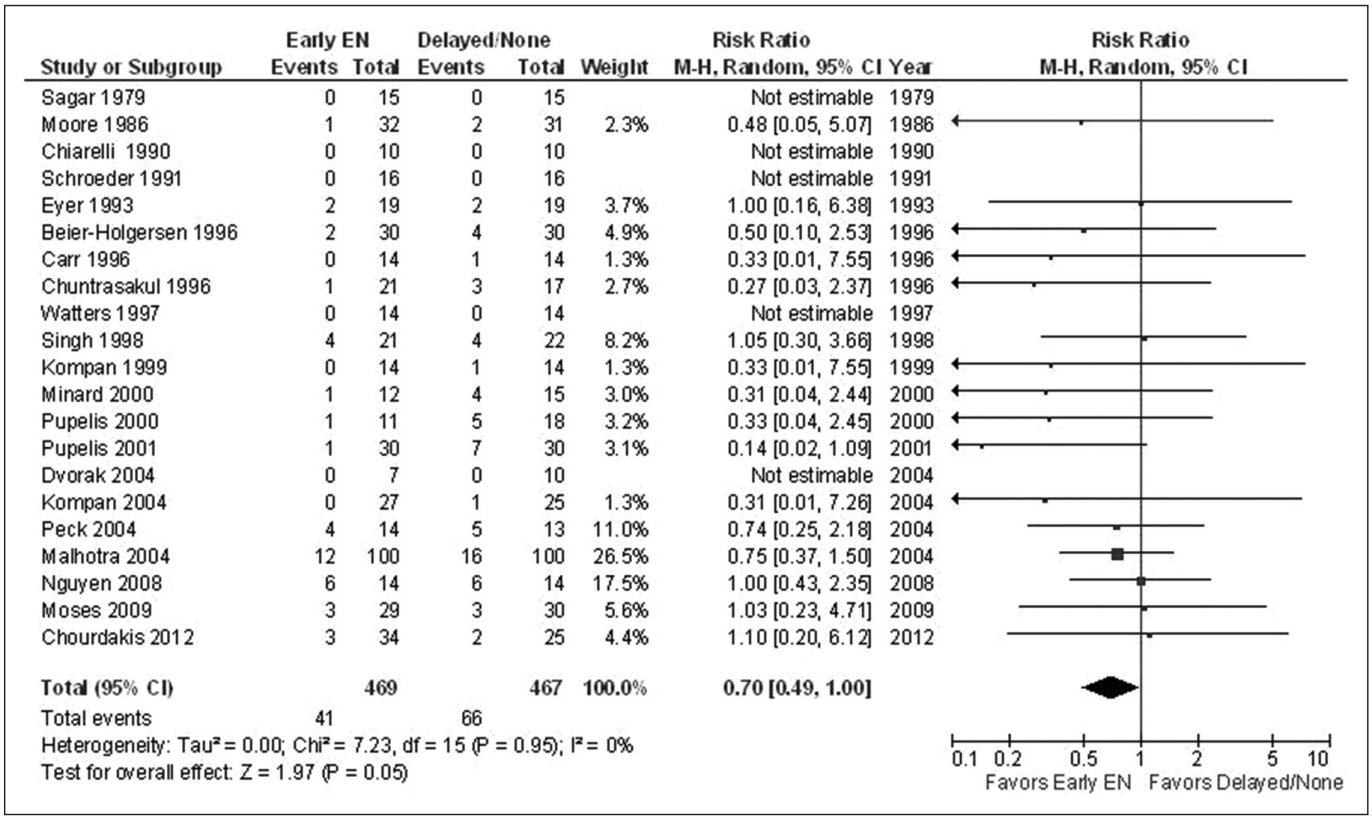


**Figure 1.** Early enteral nutrition (EN) vs delayed EN, mortality.

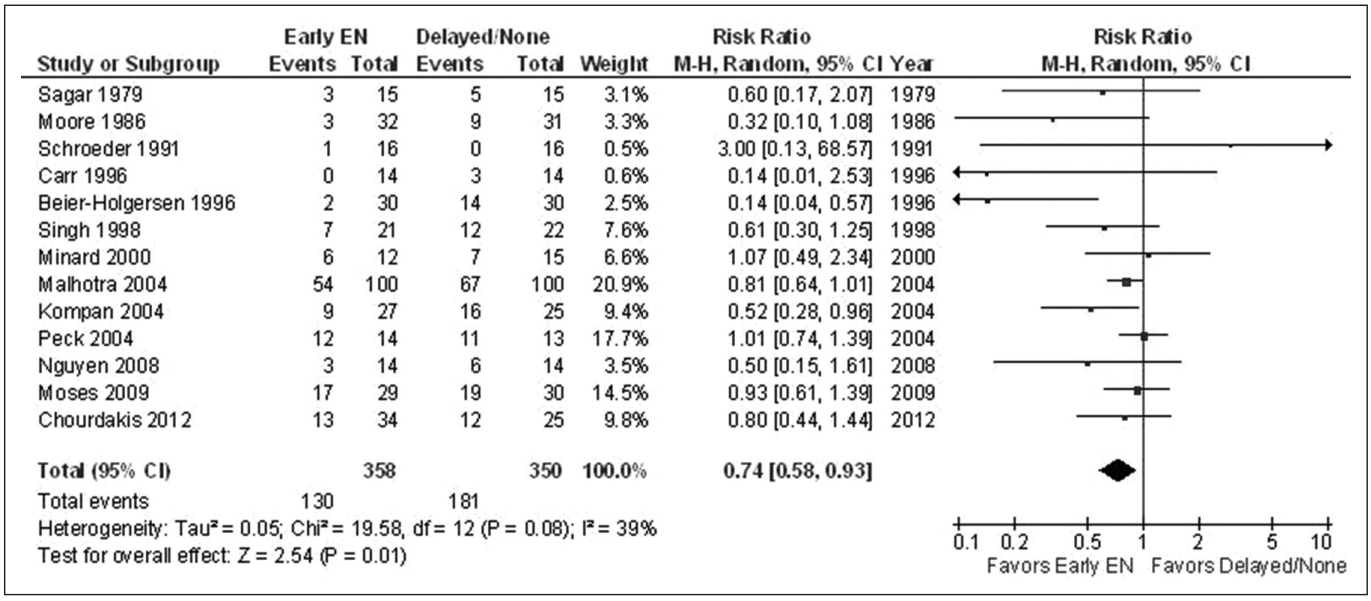


**Figure 2.** Early enteral nutrition (EN) vs delayed EN, infectious complications.

reported on mortality (**Figure 1**), with 13 reporting on infection (**Figure 2**). Provision of early EN was associated with a significant reduction in mortality (RR = 0.70; 95% CI, 0.49–1.00; $p = 0.05$) and infectious morbidity (RR = 0.74; 95% CI, 0.58–0.93, $p = 0.01$), compared to withholding early EN (delayed EN or STD).

**Question:** Is there a difference in outcome between the use of EN or PN for adult critically ill patients?

### B2. We suggest the use of EN over PN in critically ill patients who require nutrition support therapy.

[**Quality of Evidence: Low to Very Low**]

**Rationale:** In the majority of critically ill patients it is practical and safe to use EN instead of PN. The beneficial effects of EN compared to PN are well documented in numerous RCTs involving a variety of patient populations in critical illness, including trauma, burns, head injury, major surgery, and acute pancreatitis

(47, 49, 52–54). While few studies have shown a differential effect on mortality, the most consistent outcome effect from EN is a reduction in infectious morbidity (generally, pneumonia and central line infections in most patient populations, and specifically, abdominal abscess in trauma patients) and ICU LOS.

Six previous meta-analyses comparing EN to PN showed significant reductions in infectious morbidity with use of EN (49, 55–59). Non-infective complications (risk difference = 4.9; 95% CI, 0.3–9.5; $p = 0.04$) and reduced hospital LOS (weighted mean difference [WMD] = 1.20 days; 95% CI, 0.38–2.03; $p = 0.004$) were seen with use of EN compared to PN in one of the meta-analyses by Peter (57). Five of the meta-analyses showed no difference in mortality between the two routes of nutrition support therapy (49, 55–59). One meta-analysis by Simpson showed a significantly lower mortality (RR = 0.51; 95% CI, 0.27–0.97; $p = 0.04$) despite a significantly higher incidence of infectious complications (RR = 1.66; 95% CI, 1.09–2.51; $p = 0.02$) with use of PN compared to EN (59).

In 12 studies (53, 58, 60–69) representing 618 patients that met our inclusion criteria, 9 reported on infection (**Figure 3**), which was shown to be significantly less with EN than PN (RR = 0.56; 95% CI, 0.39–0.79; $p < .00001$). ICU LOS also was shorter with EN compared to PN by nearly one full day (MD = –0.82; 95% CI, –1.29 to –0.34, $p = 0.0007$). Hospital LOS and mortality were not significantly different. These differences in outcome from the separate routes of feeding largely reflect findings from older studies and may diminish in the future with improvements in glycemic control, protocolized medical management and new lipid emulsions.

**Question:** Is the clinical evidence of contractility (bowel sounds, flatus) required prior to initiating EN in critically ill adult patients?

**B3. Based on expert consensus, we suggest that, in the majority of MICU and SICU patient populations, while GI contractility factors should be evaluated when initiating EN, overt signs of contractility should not be required prior to initiation of EN.**

**Rationale:** The literature supports the concept that bowel sounds and evidence of bowel function, i.e., passing flatus or stool, are not required for initiation of EN. GI dysfunction in the ICU setting occurs in 30–70% of patients, depending on the diagnosis, premorbid condition, ventilation mode, medications, and metabolic state (70). Proposed mechanisms of ICU and postoperative GI dysfunction are related to mucosal barrier disruption, altered motility, atrophy of the mucosa, and reduced mass of GALT. GI intolerance has been variably defined (e.g., absence or abnormal bowel sounds, vomiting, bowel dilatation, diarrhea, GI bleeding, high gastric residual volumes [GRVs], etc.) and appears to occur in up to 50% of patients on mechanical ventilation. Bowel sounds are indicative only of contractility and do not necessarily relate to mucosal integrity, barrier function, or absorptive capacity.

The argument for initiating EN regardless of the extent of audible bowel sounds is based on studies (most of which involve critically ill surgical patients) reporting the feasibility and safety of EN within the initial 36–48 hours of admission to the ICU.

Nonetheless, reduced or absent bowel sounds may reflect greater disease severity and worsened prognosis. Patients with normal bowel sounds have been shown to have lower ICU mortality than those with hypoactive or absent bowel sounds (11.3% vs 22.6% vs 36.0%, respectively) (71). ICU LOS has been shown to increase with greater number of symptoms of GI intolerance (2.9 days when asymptomatic versus up to 16.8 days with four symptoms of intolerance) (72). Not surprisingly, success of EN delivery is reduced with a greater number of symptoms of GI intolerance. A greater number of signs of intolerance may warrant increased vigilance as EN is started, and may necessitate further clinical evaluation.

**Question:** What is the preferred level of infusion of EN within the GI tract for critically ill patients? How does the level of infusion of EN affect patient outcomes?

**B4a. We recommend that the level of infusion be diverted lower in the GI tract in those critically ill patients at high risk for aspiration (see section D4) or those who have shown intolerance to gastric EN.**

[**Quality of Evidence: Moderate to High**]

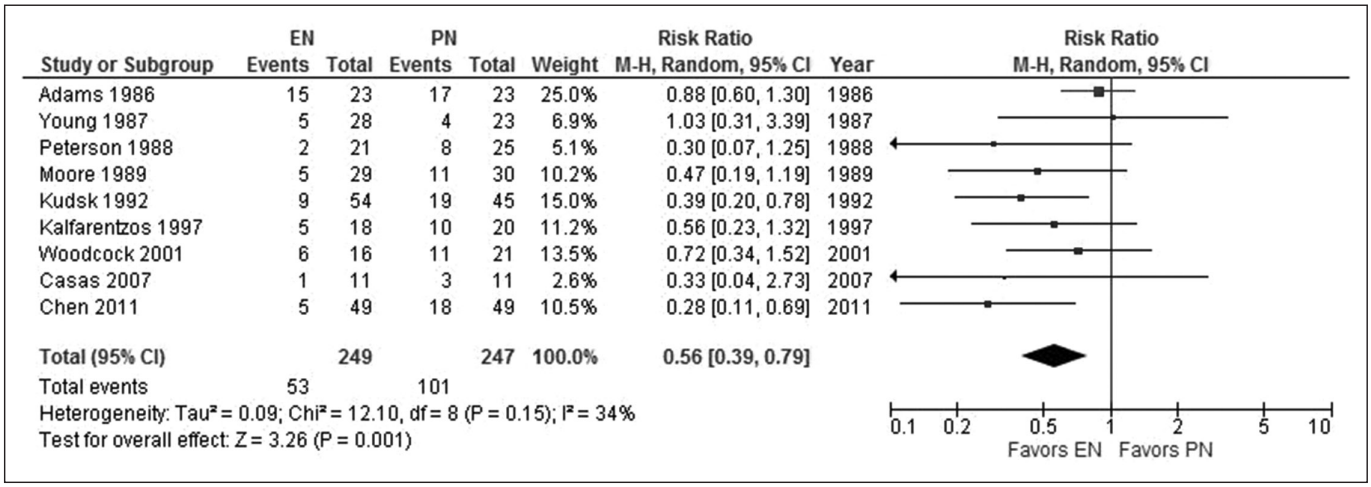


**Figure 3.** Enteral nutrition (EN) vs parenteral nutrition (PN), infectious complications.

**B4b. Based on expert consensus we suggest that, in most critically ill patients, it is acceptable to initiate EN in the stomach.**

**Rationale:** Initiating EN therapy in the stomach is technically easier and may decrease the time to initiation of EN. The choice of level of infusion (i.e., whether the tip of the feeding tube is in the stomach, different segments of the duodenum [D1, D2, D3 or D4], or the jejunum) within the GI tract may be determined by patient selection within ICU practitioners' institutional framework (ease and feasibility of placing small bowel enteral access devices, institutional policies, and protocols).

In the largest multicenter RCT to compare gastric versus small bowel EN in critically ill patients, Davies et al found no difference in clinical outcomes between groups, including LOS, mortality, nutrient delivery, and incidence of pneumonia (73). Aggregating the data from the RCTs that met our inclusion criteria, six trials reported on improved nutrient delivery with small bowel feedings (WMD = 11.06%; 95% CI, 5.82–16.30%; $p < 0.00001$) (**Figure 4**) (73–78), and 12 trials demonstrated a reduced risk of pneumonia compared to gastric EN (RR = 0.75; 95% CI, 0.60–0.93, $p = 0.01$) (**Figure 5**) (73–84). Although small bowel EN decreases the risk of pneumonia, there is no difference in mortality or LOS between small bowel and gastric EN. Therefore, if timely obtainment of small bowel enteral access device is not feasible, early EN via the gastric route may provide more benefit than delaying feeding initiation while awaiting small bowel access (73).

**Question:** Is EN safe during periods of hemodynamic instability in adult critically ill patients?

**B5. Based on expert consensus, we suggest that in the setting of hemodynamic compromise or instability, EN should be withheld until the patient is fully resuscitated and/or stable. Initiation/re-initiation of EN may be considered with caution in patients undergoing withdrawal of vasopressor support.**

**Rationale:** At the height of critical illness, EN is being provided to patients who are prone to GI dysmotility, sepsis,

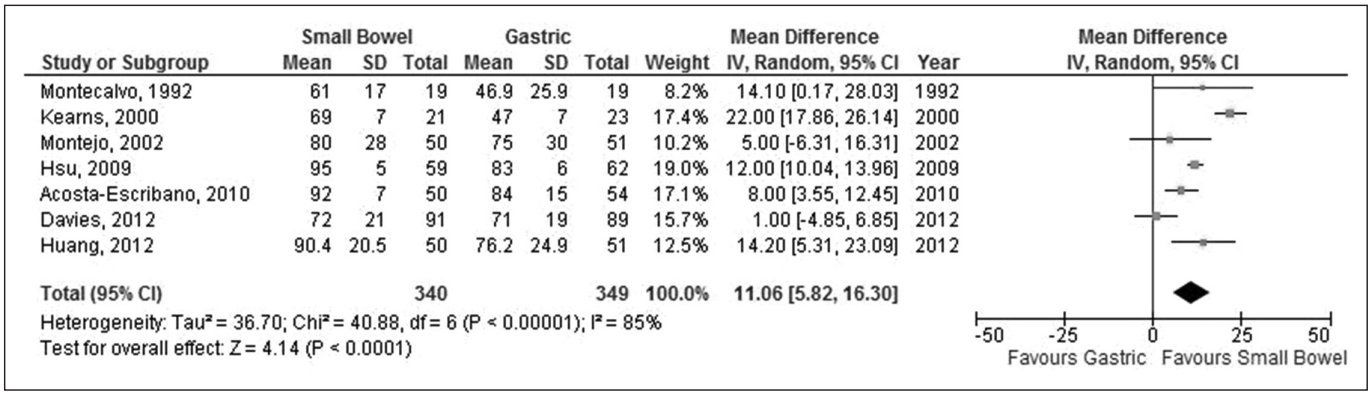


**Figure 4.** Gastric vs small bowel feedings, nutritional efficiency.

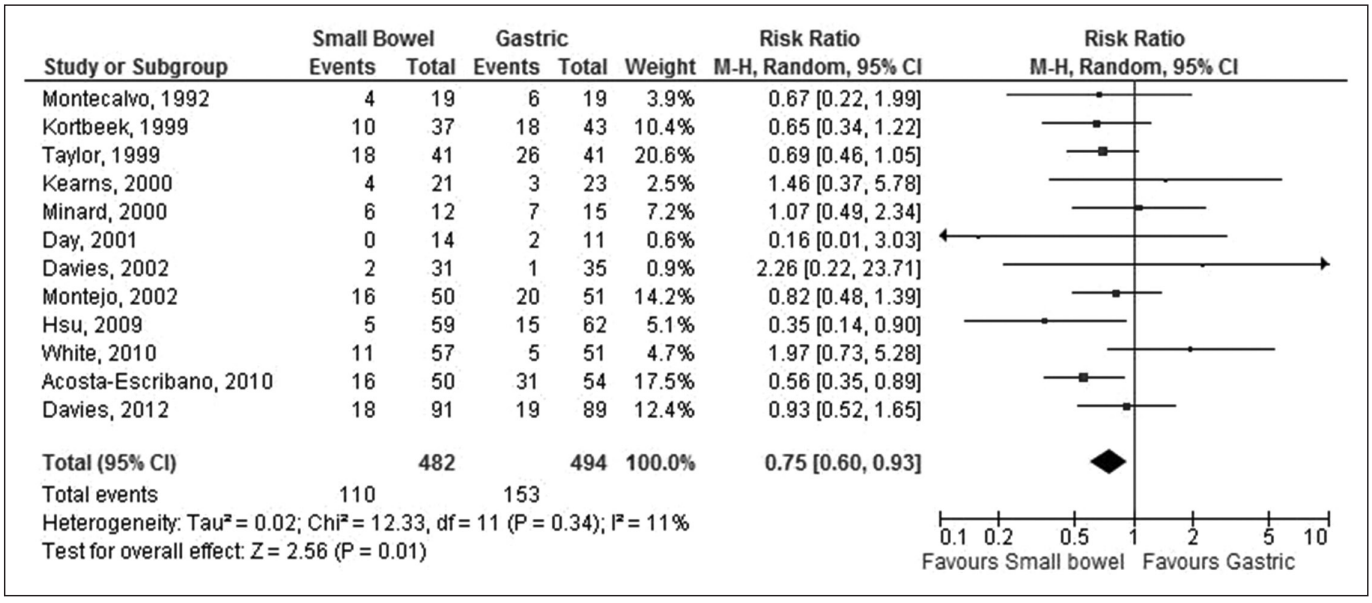


**Figure 5.** Gastric vs small bowel feedings, pneumonia.

and hypotension, and thus are at increased risk for subclinical ischemia/reperfusion injuries involving the intestinal microcirculation. Ischemic bowel is a very rare complication associated with EN (85). In a retrospective review of patients requiring stable low doses of vasopressors, those patients receiving early delivery of EN had lower ICU mortality (22.5% vs 28.3%, $p = .03$) and hospital mortality (34% vs 44%, $p < 0.001$) than those receiving late EN, respectively. The beneficial effect of early EN was more evident in patients treated with multiple vasopressors (odds ratio 0.36; 95% CI, 0.15–0.85). When adjustments were made for confounding by matching for propensity score, early EN was associated with decreased hospital mortality (86).

While EN may be provided with caution to patients on chronic, stable low doses of vasopressors (76), EN should be withheld in patients who are hypotensive (mean arterial blood pressure < 50 mm Hg), in patients for whom catecholamine agents (e.g., norepinephrine, phenylephrine, epinephrine, dopamine) are being initiated, or in patients for whom escalating doses are required to maintain hemodynamic stability.

For patients on vasopressor therapy receiving EN, any signs of intolerance (abdominal distention, increasing nasogastric [NG] tube output or GRVs, decreased passage of stool and flatus, hypoactive bowel sounds, increasing metabolic acidosis and/or base deficit) should be closely scrutinized as possible early signs of gut ischemia and EN should be held until symptoms and interventions stabilize.

## C. DOSING OF EN

**Question:** What population of patients in the ICU setting does not require nutrition support therapy over the first week of hospitalization?

**C1. Based on expert consensus, we suggest that patients who are at low nutrition risk with normal baseline nutrition status and low disease severity (for example, NRS -2002 ≤ 3 or NUTRIC score ≤ 5) who cannot maintain volitional intake do NOT require specialized nutrition therapy over the first week of hospitalization in the ICU.**

**Rationale:** Patients admitted to the ICU are a heterogeneous group with varying degrees of nutrition risk and disease severity. Occasionally patients with low nutrition risk, normal baseline nutrition status, and low disease severity (as defined by an NRS-2002 of ≤ 3 or a Nutric score ≤ 5) are in the ICU for more than a few days. When possible, these patients should be offered oral intake to try to maintain nutrition status, appropriate immune responses, and optimal organ function. Clinical trials of nutrition therapy in critically ill patients typically involve inclusion of patients with high severity of injury; thus, the duration of time that a lack of adequate volitional intake can elapse before nutrition status is compromised in low-risk subjects has not been determined. Placement and maintenance of enteral access devices in patients who cannot maintain volitional intake has potential complications. Provision of aggressive EN in the low-risk ICU patient population may provide little if any benefit early in the first week in ICU. However, patients can deteriorate, and their nutrition risk and disease severity can rapidly change. Low-risk patients should be reassessed daily and, if their metabolic state, disease severity, or expected LOS worsens, the risk-to-benefit ratio may then favor initiation of EN therapy.

**Question:** For which population of patients in the ICU setting is it appropriate to provide trophic EN over the first week of hospitalization?

**C2. We recommend that either trophic or full nutrition by EN is appropriate for patients with acute respiratory distress syndrome (ARDS)/acute lung injury (ALI) and those expected to have a duration of mechanical ventilation ≥ 72 hours, as these two strategies of feeding have similar patient outcomes over the first week of hospitalization.**

**[Quality of Evidence: High]**

**Rationale:** In one randomized single-center study of a heterogeneous population of patients with acute respiratory failure and another larger randomized multicenter trial enrolling patients with ARDS/ALI and those expected to have a duration of mechanical ventilation of at least 72 hours, initial trophic EN (defined as 10–20 kcal/hr or up to 500 kcal/day) for up to six days resulted in a lower incidence of GI intolerance over the first week of hospitalization in the ICU than full EN (87, 88). Initial trophic feeds resulted in similar clinical outcomes, including ventilator-free days, ICU-free days, 60-day mortality, and development of nosocomial infections, compared to early advancement to full EN (targeting energy goals based on energy requirements). The larger multicenter trial has been criticized for under-delivery of protein (0.6–0.8 g/kg/day) and the fact that study patients were moderately critically ill and had a shorter LOS in the ICU, potentially indicating lower nutrition risk. There is a lack of data available to determine the benefit of full versus trophic feed of those patients determined to be at high nutrition risk. These patients were intentionally excluded in the reviewed protocols. For these patients, please review section C3.

**Question:** What population of patients in the ICU requires full EN (as close as possible to target nutrition goals) beginning in the first week of hospitalization? How soon should target nutrition goals be reached in these patients?

**C3. Based on expert consensus, we suggest that patients who are at high nutrition risk (for example, NRS-2002 > 5 or NUTRIC score ≥ 5, without interleukin-6) or severely malnourished should be advanced toward goal as quickly as tolerated over 24–48 hours while monitoring for refeeding syndrome. Efforts to provide > 80% of estimated or calculated goal energy and protein within 48–72 hours should be made in order to achieve the clinical benefit of EN over the first week of hospitalization.**

**Rationale:** Trophic feeds (usually defined as 10–20 mL/hr or 10–20 kcal/hr) may be sufficient to prevent mucosal atrophy

and maintain gut integrity in low- to moderate-risk patients, but may be insufficient to achieve the usual endpoints desired for EN therapy in high-risk patients. Studies suggest that > 50–65% of goal energy may be required to prevent increases in intestinal permeability and systemic infection in burn and bone-marrow transplant patients, to promote faster return of cognitive function in head injury patients, and to reduce mortality in high-risk hospitalized patients (13, 46, 80, 89).

In a prospective nonrandomized study, Jie showed that high-risk surgery patients (NRS-2002 ≥ 5) who received sufficient preoperative nutrition therapy (> 10 kcal/kg/day for 7 days) had significant reductions in nosocomial infections and overall complications compared to patients who received insufficient therapy (18). No differences were seen between sufficient and insufficient EN in low-risk patients (18). In a large observational study, Heyland showed that, for high-risk ICU patients with NUTRIC scores ≥ 6, increasing the percent of goal energy delivered (*goal* defined as 100% of energy requirements) correlated significantly with reductions in mortality (90). The lowest mortality was achieved with EN, which provided > 80% goal energy. For low-risk patients, no correlation was seen between percent goal energy delivered and mortality (90).

**Question:** Does the amount of protein provided make a difference in clinical outcomes of adult critically ill patients?

**C4. We suggest that sufficient (high-dose) protein should be provided. Protein requirements are expected to be in the range of 1.2–2.0 g/kg actual body weight per day, and may likely be even higher in burn or multitrauma patients (see sections M and P).**

[**Quality of Evidence: Very Low**]

**Rationale:** Recent studies in critical illness suggest that provision of protein is more closely linked to positive outcomes than provision of total energy (and specifically delivery of the other macronutrients of fat and carbohydrate). Also, the dose of protein required by critically ill patients appears to be higher than previously thought. A prospective observational study in mechanically ventilated patients demonstrated that achievement of both protein (1.3 g/kg protein provided) and energy targets was associated with a 50% decrease in 28-day mortality, whereas no decrease in mortality was noted when energy targets alone were met (0.8 g/kg protein provided) (91). In another prospective observational study in a mixed medical/surgical ICU, a stepwise decrease in 28-day mortality was demonstrated with increased protein provision (Group 1: 0.79 g/kg, 27% mortality; Group 2: 1.06 g/kg, 24% mortality; Group 3: 1.46 g/kg, 16% mortality) (92). Two small RCTs, however, showed no difference in mortality when a higher protein dose was provided (93, 94). Unfortunately, determination of protein requirements in the critical care setting remains difficult, with most clinicians using simplistic weight-based equations (1.2–2.0 g/kg/day). Use of nitrogen balance or NPC:N (70:1 to 100:1) is of limited value in the ICU (95).

## D. MONITORING TOLERANCE AND ADEQUACY OF EN

**Question:** How should tolerance of EN be monitored in the adult critically ill N1. population?

**D1. Based on expert consensus, we suggest that patients should be monitored daily for tolerance of EN. We suggest that inappropriate cessation of EN should be avoided. We suggest that ordering a feeding status of nil per os (NPO) for the patient surrounding the time of diagnostic tests or procedures should be minimized to limit propagation of ileus and to prevent inadequate nutrient delivery.**

**Rationale:** Tolerance may be determined by physical examination, passage of flatus and stool, radiologic evaluations, and absence of patient complaints such as pain or abdominal distention. GI intolerance is usually defined by vomiting, abdominal distention, complaints of discomfort, high NG output, high GRV, diarrhea, reduced passage of flatus and stool, or abnormal abdominal radiographs. Metheny reported that more than 97% of nurses surveyed assessed intolerance solely by measuring GRVs (the most frequently cited threshold levels for interrupting EN listed as 200 mL and 250 mL) (96).

Less than half of patients ever reach their target goal energy intake during their ICU stay. A number of factors impede the delivery of EN in the critical care setting (97–99). Healthcare providers who prescribe EN tend to under-order energy, prescribing only 60–80% of energy requirements. Patients typically receive approximately 80% of what is ordered. This combination of under-ordering and inadequate delivery results in patients receiving on average only 50% of target goal energy from one day to the next. Cessation of EN occurs in over 85% of patients for an average of 8–20% of the infusion time (the reasons for which are avoidable in 23% of planned procedures and 65% of all occasions) (97, 99). While patient intolerance accounts for a third of cessation time, only half of this represents true intolerance. Remaining NPO after midnight for diagnostic tests and procedures affects 25–33% of ICU patients and accounts for up to 25% of cessation time. Technical issues involving the enteral access device, such as maintaining patency or repositioning/replacing the tube, can account for up to 25% of cessation time. In one study, patients randomized to continue EN during frequent surgical procedures (burn wound debridement under general anesthesia) had significantly fewer infections than those patients for whom EN was stopped for each procedure (100). Ileus may be propagated by repeated and prolonged periods for which patients are NPO (101).

**Question:** Should GRVs be used as a marker for aspiration to monitor ICU patients on EN?

**D2a. We suggest that GRVs not be used as part of routine care to monitor ICU patients on EN.**

**D2b. We suggest that, for those ICUs where GRVs are still utilized, holding EN for GRVs < 500 mL in the absence of other signs of intolerance (see section D1) should be avoided.**

[**Quality of Evidence: Low**]

**Rationale:** GRVs do not correlate with incidences of pneumonia (102, 103), regurgitation, or aspiration (104). Although a study showed that cumulative GRV of > 250 mL over 24 hours correlated with gastric emptying using scintigraphy studies and (13)C-octanoate breath tests (105), three other trials using the paracetamol (acetaminophen) test showed poor correlation of GRVs done every 4 hours to gastric emptying (106–108). In a trial using a highly sensitive and specific marker for aspiration, GRVs (over a range of 150–400 mL) were shown to be a poor monitor for aspiration, with a very low sensitivity of 1.5–4.1%, a positive predictive value of 18.2–25%, and a negative predictive value of 77.1–77.4% (109). Results from four RCTs indicate that raising the cutoff value for GRVs (leading to automatic cessation of EN) from a lower number of 50–150 mL to a higher number of 250–500 mL does not increase the incidence of regurgitation, aspiration, or pneumonia (80, 102, 103, 109). Decreasing the cutoff value for GRVs does not protect the patient from these complications. Use of GRVs leads to increased enteral access device clogging, inappropriate cessation of EN, consumption of nursing time and allocation of healthcare resources, and may adversely affect outcome through reduced volume of EN delivered (110).

Three studies have shown that eliminating the practice of using GRVs improves delivery of EN without jeopardizing patient safety (110–112). All three trials, two RCTs (110, 112), and one prospective before/after implementation trial (111) showed no significant difference between groups with regard to pneumonia. Two of the trials showed significantly greater EN delivery, either by increased volume of EN infused (111) or greater reduction in energy deficit (112). One trial showed significantly more vomiting, but significantly better overall GI tolerance when GRVs were eliminated (112), while a second trial showed no difference in vomiting between groups (111).

If the practice of GRVs is eliminated, a number of alternative strategies may be used to monitor critically ill patients on EN: careful daily physical examinations, review of abdominal radiologic films, and evaluation of clinical risk factors for aspiration. EN protocols should be initiated, and efforts to proactively reduce risk of aspiration pneumonia should be made (see sections D3 and D4). For those ICUs reluctant to stop using GRVs, care should be taken in their interpretation. GRVs in the range of 200–500 mL should raise concern and lead to the implementation of measures to reduce risk of aspiration, but automatic cessation of EN should not occur for GRVs < 500 mL in the absence of other signs of intolerance (80, 102–104, 109).

**Question:** Should EN feeding protocols be used in the adult ICU setting?

**D3a. We recommend that enteral feeding protocols be designed and implemented to increase the overall percentage of goal calories provided.**

[**Quality of Evidence: Moderate to High**]

**D3b. Based on expert consensus, we suggest that use of a volume-based feeding protocol or a top-down multi-strategy protocol be considered.**

**Rationale:** Use of ICU- or nurse-driven protocols that define goal EN infusion rate, designate more rapid startups, and provide specific orders for handling GRVs, frequency of flushes, and conditions or problems under which EN may be adjusted or stopped, have been shown to be successful in increasing the overall percentage of goal energy provided (80, 113–117). In addition, volume-based feeding protocols, in which 24-hour or daily volumes are targeted instead of hourly rates, have been shown to increase volume of nutrition delivered (116). These protocols empower nurses to increase feeding rates to make up for volume lost while EN is held. Top-down protocols use multiple different strategies simultaneously at the time of initiation of EN to enhance tolerance and increase delivery of EN, removing individual strategies as tolerance improves over the first few days of infusion. Top-down multi-strategy protocols typically use volume-based feeding in conjunction with prokinetic agents and post-pyloric tube placement initially (among other strategies), with prokinetic agents stopped in patients who demonstrate lack of need (116).

Aggregating the data from two studies that met our inclusion criteria (**Figure 6**), use of nurse-driven EN protocols to increase EN delivery positively impacted patient outcome by reducing the incidence of nosocomial infections compared to controls where no protocol was used (RR = 0.58; 95% CI, 0.43–0.81, $p = 0.001$) (80, 116).

**Question:** How can risk of aspiration be assessed in critically ill adults patients receiving EN, and what measures may be taken to reduce the likelihood of aspiration pneumonia?

**D4. Based on expert consensus, we suggest that patients placed on EN should be assessed for risk of aspiration, and that steps to reduce risk of aspiration and aspiration pneumonia should be proactively employed.**

**Rationale:** Aspiration is one of the most feared complications of EN. Patients at increased risk for aspiration may be identified by a number of factors, including inability to protect the airway, presence of a nasoenteric enteral access device, mechanical ventilation, age over 70 years, reduced level of consciousness, poor oral care, inadequate nurse/patient ratio, supine positioning, neurologic deficits, gastroesophageal reflux, transport out of the ICU, and use of bolus intermittent EN (104). Pneumonia and bacterial colonization of the upper respiratory tree is more closely associated with aspiration of contaminated oropharyngeal secretions than regurgitation and aspiration of contaminated gastric contents (118–120).

**D4a. We recommend diverting the level of feeding by post-pyloric enteral access device placement in patients deemed to be at high risk for aspiration (see also section B5)**

[**Quality of Evidence: Moderate to High**]

**Rationale:** Changing the level of infusion of EN from the stomach to the small bowel has been shown to reduce the incidence of regurgitation, aspiration, and pneumonia (121, 122). In 13 RCTs (73–84), pneumonia was significantly lower in patients with small bowel EN (RR = 0.75; 95% CI, 0.6–0.93, $p = 0.01$), including when restricted to studies using evidence of ventilator-associated pneumonia (VAP) (RR = 0.72; 95%, CI, 0.55–0.93, $p = 0.01$), compared to patients on gastric EN.

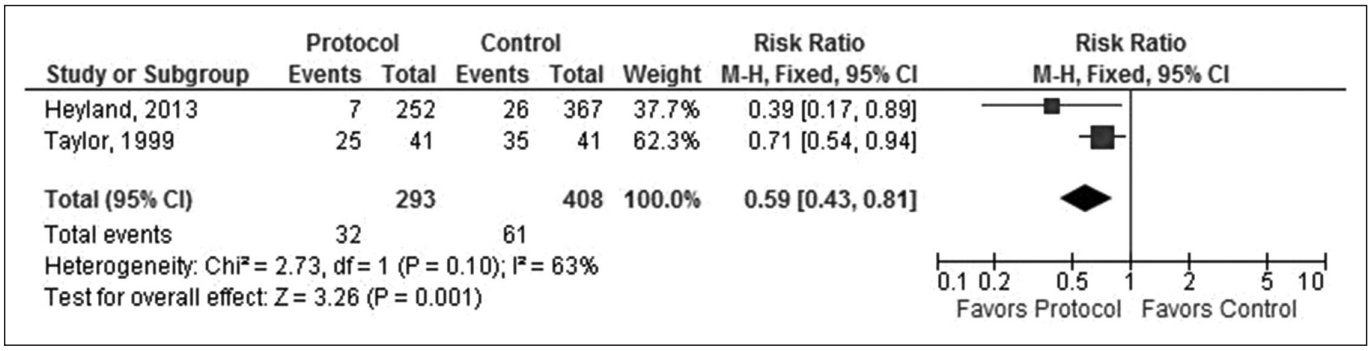


**Figure 6.** Feeding protocol vs control, infections.

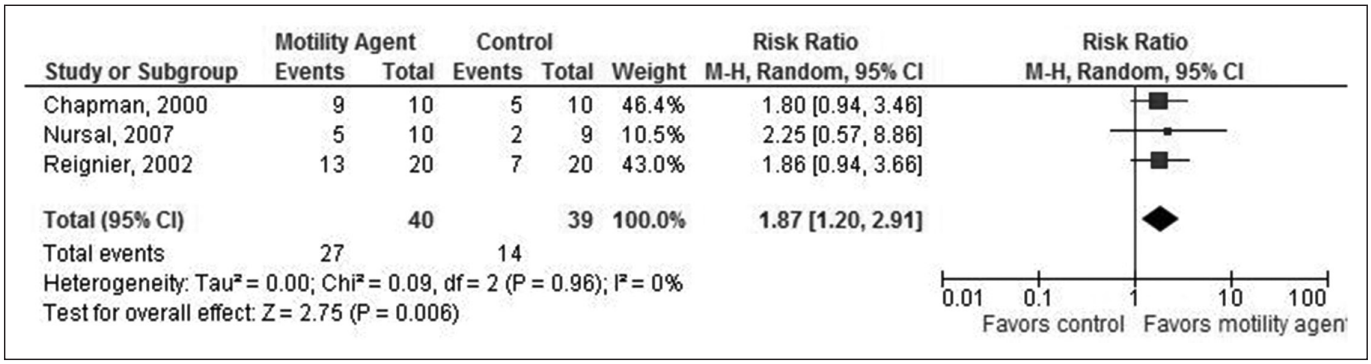


**Figure 7.** Motility agent vs placebo, lower gastric residual volume.

There was no difference in mortality, ICU LOS, hospital LOS, duration of mechanical ventilation, or time to goal EN.

### D4b. Based on expert consensus, we suggest that for high-risk patients or those shown to be intolerant to bolus gastric EN, delivery of EN should be switched to continuous infusion.

**Rationale:** The potential harm from aggressive bolus infusion of EN leading to increased risk of aspiration pneumonia was shown in one study (123). An RCT showed a trend toward decreased mortality with continuous EN (13.9% intermittent vs 7.4% continuous, $p = 0.18$) (124). Five small RCTs comparing bolus to continuous infusion have shown greater volume with fewer interruptions in delivery of EN with continuous EN, but no significant difference between techniques with regard to patient outcome (125–129).

### D4c. We suggest that, in patients at high risk of aspiration, agents to promote motility, such as prokinetic medications (metoclopramide or erythromycin), be initiated where clinically feasible.

[**Quality of Evidence: Low**]

**Rationale:** Adding prokinetic agents such as erythromycin or metoclopramide has been shown to improve gastric emptying and tolerance of EN, but has resulted in little change in clinical outcome for ICU patients. A total of eight RCTs that met our inclusion criteria (130–137) using metoclopramide and one combining erythromycin with metoclopramide were reviewed by meta-analysis. No difference was found in terms of mortality or infection. However, GRVs were lower with prokinetic agents than with control (RR = 1.87; 95% CI, 1.20–2.91, $p = 0.006$) in three RCTs that met our inclusion criteria (**Figure 7**). Erythromycin doses of 3–7 mg/kg per day have been utilized to treat gastric enteral feeding intolerance. Likewise, metoclopramide, 10 mg 4 times a day, has been shown to be efficacious for elevated gastric residuals; however, dosage adjustments to metoclopramide may be necessary in patients with declining renal function. For both pharmaceutical agents, oral and IV routes may be used. Erythromycin has been associated with undesirable effects, including cardiac toxicity, tachyphylaxis, and bacterial resistance, and should be used cautiously with monitoring. Metoclopramide also has associated adverse complications, including tardive dyskinesia, more frequently in the elderly. Both agents have been associated with QT prolongation, predisposing to cardiac arrhythmias (138, 139). Combination therapy with erythromycin and metoclopramide did demonstrate improved GRVs, allowing for greater feeding success; however, neither hospital LOS nor mortality were different. Furthermore, the incidence of watery diarrhea was statistically higher in patients receiving combination therapy (54% vs 26.3%, $p = 0.01$) (133). Studies demonstrating improved clinical outcomes from combination therapy without associated increase in risk of adverse effects are needed before this approach can be recommended. Use of naloxone infused through the enteral access device (to reverse the effects of opioid narcotics at the level of the gut in order to improve intestinal motility) was shown in one study to significantly increase the volume of EN infused, reduce GRVs, and decrease the incidence of VAP (compared to placebo) (132). Peripherally acting mu-opioid receptor antagonists, specifically methylnaltrexone and alvimopan, have

been shown to facilitate recovery of GI function after surgery; however, to date there are no studies investigating their use as prokinetic agents.

**D4d. Based on expert consensus, we suggest that nursing directives to reduce risk of aspiration and VAP be employed. In all intubated ICU patients receiving EN, the head of the bed should be elevated 30–45° and use of chlorhexidine mouthwash twice a day should be considered.**

**Rationale:** Elevating the head of the bed 30–45° was shown in one study to reduce the incidence of pneumonia from 23% to 5%, comparing supine to semi-recumbent position, respectively ($p = 0.018$) (140, 141). Optimizing oral health with chlorhexidine mouthwash twice daily was shown in two studies to reduce respiratory infection and nosocomial pneumonia in patients undergoing heart surgery (142, 143). While studies evaluating the use of chlorhexidine in general ICU populations have shown little outcome effect, two studies in which chlorhexidine oral care was included in bundled interventions showed significant reductions in nosocomial respiratory infections (144, 145). Other steps to decrease aspiration risk would include reducing the level of sedation/analgesia when possible and minimizing transport out of the ICU for diagnostic tests and procedures (104, 146).

**Question:** Are surrogate markers useful in determining aspiration in the critical care setting?

**D5. Based on expert consensus, we suggest that neither blue food coloring nor any coloring agent be used as a marker for aspiration of EN. Based on expert consensus, we also suggest that glucose oxidase strips not be used as surrogate markers for aspiration in the critical care setting.**

**Rationale:** Traditional monitors for aspiration are ineffective. Any use of a color monitor (e.g., methylene blue, blue food coloring) interferes with other colorimetric tests such as hemocult, gastrocult, and pH testing (147, 148). High-dose methylene blue may have effects similar to blue food coloring regarding mitochondrial toxicity and interference with oxidative phosphorylation (147). Blue food coloring, an insensitive marker for aspiration, was shown to be associated with mitochondrial toxicity and patient death (147, 149). The U.S. Food and Drug Administration (FDA), through a Health Advisory Bulletin (September 2003) issued a mandate against the use of blue food coloring as a monitor for aspiration in patients on EN (150). The basic premise for the use of glucose oxidase (that glucose content in tracheal secretions is solely related to aspiration of glucose-containing formulation) has been shown to be invalid, and its use is thwarted by poor sensitivity/specificity characteristics (151).

**Question:** How should diarrhea associated with EN be assessed in the adult critically ill population?

**D6. Based on expert consensus, we suggest that EN NOT be automatically interrupted for diarrhea but rather that feeds be continued while evaluating the etiology of diarrhea in an ICU patient to determine appropriate treatment.**

**Rationale:** Diarrhea in ICU patients receiving EN is common but may be serious, as the incidence ranges from 2–95% and often results in electrolyte imbalance, dehydration, perianal skin breakdown, and wound contamination (152). If unable to control the diarrhea, clinicians often stop EN, with resulting inadequate nutrition intake. Differences in definition, stool collection, and sampling techniques account for the wide range of incidence in clinical studies; the definitions most commonly used are 2–3 liquid stools per day or > 250 g of liquid stool per day (153, 154).

The following factors may contribute to acute diarrhea: type and amount of fiber in formula, osmolality of formula, delivery mode, EN contamination, medications (antibiotics, proton-pump inhibitors, prokinetics, glucose lowering agents, nonsteroidal antiinflammatory drugs, selective serotonin reuptake inhibitors, laxatives, and sorbitol-containing preparations, in particular), and infectious etiologies, including *Clostridium difficile* (152). Studies have shown an association between short-chain carbohydrates, fermentable oligosaccharides, disaccharides and monosaccharides, and polyols (FODMAPS) and diarrhea, as they are highly osmotic and rapidly fermented by gut bacteria. Formulas with a high content of FODMAPS may play a role in diarrhea, especially if the patient is also receiving antibiotics that have a detrimental effect on intestinal microbiota (155). Most episodes of nosocomial diarrhea are mild and self limiting (156).

Assessment of diarrhea should include an abdominal examination, quantification of stool, stool culture for *Clostridia difficile* (and/or toxin assay), serum electrolyte panel (to evaluate for excessive electrolyte losses or dehydration), and review of medications. An attempt should be made to distinguish infectious diarrhea from osmotic diarrhea (157).

## E. SELECTION OF APPROPRIATE ENTERAL FORMULATION

**Question:** Which formula should be used when initiating EN in the critically ill patient?

**E1. Based on expert consensus, we suggest using a standard polymeric formula when initiating EN in the ICU setting. We suggest avoiding the routine use of all specialty formulas in critically ill patients in a MICU and disease-specific formulas in the SICU.**

**Rationale:** For the majority of patients in an ICU setting, a standard polymeric isotonic or near isotonic 1 kcal to 1.5 kcal/mL formula is appropriate and will be well tolerated. This recommendation is one of exclusion, in that no clear benefit to patient outcome has been shown in the literature for the routine use of specialty formulas in a general ICU setting, including those that are designed to be disease specific (diabetes), organ specific (pulmonary, renal, hepatic), semi-elemental, elemental or immune-modulating. One exception would be the use of an immune-modulating formula in the postoperative patient in a SICU setting (see section O3). Use

of immune-modulating formulas has shown no outcome benefits over standard EN formulas in a MICU setting (see section E2). The rationale for pulmonary formulas (high fat to carbohydrate to reduce respiratory quotient) has been shown to be erroneous (effect seen only with overfeeding), and their high content of omega-6 fatty acid may drive inflammatory processes (158). Disease-specific and severe fluid-restricted formulas may be used rarely in a small percent of patients on a case-by-case basis due more to physiologic benefits such as electrolyte profile and volume restriction (renal).

**Question:** Do immune-modulating enteral formulations have an impact on clinical outcomes for the critically ill patient regardless of the ICU setting?

**E2. We suggest immune-modulating enteral formulations (arginine with other agents, including eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA], glutamine, and nucleic acid) should not be used routinely in the MICU. Consideration for these formulations should be reserved for patients with TBI and perioperative patients in the SICU (see sections O and M).**

[**Quality of Evidence: Very Low**]

**Rationale:** In selecting immune-modulating enteral formulations (supplemented with arginine, EPA, DHA, glutamine, and nucleic acid) for the critically ill patient, the clinician must first decide if the patient is a candidate for a specialty immune-modulating formulation (159).

While early meta-analyses suggested outcome benefits of reduced infection, hospital LOS, and duration of mechanical ventilation with use of such formulas in a general ICU setting (both medical and surgical) (160, 161), Heyland showed only a reduction in hospital LOS (WMD = –0.47; 95% CI, –0.93 to –0.01, $p = 0.047$) specifically in a MICU (162). A meta-analysis of 20 RCTs that met our inclusion criteria suggests that adding pharmaconutrients to the enteral formula may have a role in the critically ill hyperdynamic patient, but the data in the MICU population do not support any recommendation for use in terms of mortality (17 studies, 2160 patients) (52, 160, 163–177), infectious complications (9 studies, 1522 patients) (52, 165, 167, 168, 171–173, 175, 178) or hospital LOS (11 studies, 147 patients) (52, 65, 163, 167–171, 174, 177, 178).

Unfortunately, few studies have addressed the individual pharmaconutrients, their specific effects, or their proper dosing. This body of literature has been criticized for the heterogeneity of studies, performed in a wide range of ICU patient populations, with a variety of experimental and commercial formulations. Multiple enteral formulations are marketed as being immune or metabolic modulating, but vary considerably in their makeup and dosage of individual components, and are more costly. It is not clear whether the data from published studies can be extrapolated to promote use of newer formulations with similar components that have not been formally evaluated. Based on the heterogeneity of the populations studied and the inconsistency in the outcomes, the Guidelines Committee felt that no recommendation of support in the MICU was warranted.

**Question:** Should EN formulas with fish oils (FOs), borage oil and antioxidants be used in patients with ALI or ARDS?

**E3. We cannot make a recommendation at this time regarding the routine use of an enteral formulation characterized by an antiinflammatory lipid profile (e.g., omega-3 FOs, borage oil) and antioxidants, in patients with ARDS and severe ALI, given conflicting data.**

[**Quality of Evidence: Low to Very Low**]

**Rationale:** Six RCTs have evaluated the use of additives or formulas with an antiinflammatory lipid profile (omega-3 FO, borage oil, and antioxidants) in patients with ARDS, ALI, and sepsis. These studies have significant heterogeneity based on the method of infusion (continuous vs bolus). In addition, the placebo formula used in the large, multicenter study by Rice et al contained an extra 16 grams of protein daily compared with study patients (20 vs 4 grams of protein, respectively) (179). Furthermore, comparison to a commercial formula high in omega-6 fatty acids increased the risk for the effect of a negative control in two of the studies (180, 181). Aggregating all trials (179–184) together based on outcomes reported suggests that use of enteral omega-3 fatty acids, borage oil, and antioxidants does not significantly reduce ICU LOS, duration of mechanical ventilation, organ failure, or hospital mortality compared to use of a standard enteral formulation. At this time, in light of the conflicting data, the Guidelines Committee cannot recommend that a formula with an antiinflammatory lipid profile in ARDS/ALI patients be used routinely until further data are available.

**Question:** In adult critically ill patients, what are the indications, if any, for enteral formulations containing soluble fiber or small peptides?

**E4a. We suggest that a commercial mixed fiber formula not be used routinely in the adult critically ill patient prophylactically to promote bowel regularity or prevent diarrhea.**

[**Quality of Evidence: Low**]

**E4b. Based on expert consensus, we suggest considering use of a commercial mixed fiber-containing formulation if there is evidence of persistent diarrhea. We suggest avoiding both soluble and insoluble fiber in patients at high risk for bowel ischemia or severe dysmotility. We suggest considering use of small peptide formulations in the patient with persistent diarrhea, with suspected malabsorption, ischemia, or lack of response to fiber.**

**Rationale:** Those patients with persistent diarrhea (in whom other sources of diarrhea have been excluded, such as medications and *C difficile*) may benefit from use of a mixed fiber-containing formula, a small peptide semi-elemental formula or a soluble fiber supplement added to a standard formula (see section F1).

Commercial fiber-containing formulas are mixed, containing both soluble and insoluble fiber. Routine provision of a

commercially available mixed fiber formulation in a non-ICU patient may be useful in promoting bowel regularity. In a critical care setting, however, there is concern for use of mixed-fiber formulas in patients at high risk for bowel ischemia or severe dysmotility due to reports of bowel obstruction in surgical and trauma patients receiving such formulations containing insoluble fiber (185, 186).

While mixed-fiber formulas have been shown to reduce diarrhea in critically ill patients receiving a broad spectrum of antibiotics (187), results have been inconsistent. One RCT in septic SICU patients found accumulated diarrhea scores over 14 days were significantly lower in the group receiving a mixed-fiber diet (187). In contrast, an RCT in Australia comparing a mixed fiber-containing enteral feed with a non-fiber-containing standard formula in ICU patients found that soy polysaccharide as methylcellulose did not decrease diarrhea in this population (188).

The laboratory data, theoretical concepts, and expert opinion would support the use of small peptide-containing enteral formulas, but current large prospective trials are not available to make this a strong recommendation (154). Use of a soluble fiber supplement added to a standard enteral formula would be a third alternative (see section F1).

## F. ADJUNCTIVE THERAPY

**Question:** Should a fiber additive be used routinely in all hemodynamically stable ICU patients on standard enteral formulas? Should a soluble fiber supplement be provided as adjunctive therapy in the critically ill patient who develops diarrhea and is receiving a standard non-fiber-containing enteral formula?

**F1. Based on expert consensus, we suggest that a fermentable soluble fiber (e.g., fructo-oligosaccharides [FOSs], inulin) additive be considered for routine use in all hemodynamically stable medical and surgical ICU patients placed on a standard enteral formulation. We suggest that 10–20 grams of a fermentable soluble fiber supplement be given in divided doses over 24 hours as adjunctive therapy if there is evidence of diarrhea.**

**Rationale:** Soluble fiber has influential effects on nutrient absorption, sterol metabolism, carbohydrate and fat metabolism, gut motility, and stool characteristics. Prebiotic fibers also have an impact on the gut microbiota and the gut barrier function. FOSs are indigestible carbohydrates fermented in the colon into short-chain fatty acids (SCFAs). SCFAs (especially butyrate) provide nutrition for the colonocyte, increase colonic blood flow, and stimulate pancreatic secretions (189–191). Prebiotics (e.g., FOS, inulin) stimulate the growth of *Bifidobacteria* and *Lactobacillus*, often referred to as the "healthy" bacteria. In an observational study of 63 ICU patients with systemic inflammatory response syndrome (SIRS), a stool analysis showed those with feeding intolerance (14 patients) had significantly lower amounts of anaerobes, including *Bifidobacteria*, and higher amounts of *Staphylococus* than those patients without feeding intolerance (49 patients) ($p \leq 0.05$). Patients with feeding intolerance were shown to have a higher rate of bacteremia (86% vs 18%, $p < 0.05$) and greater mortality (64% vs 20%, $p < 0.05$) (192). Thus, the routine use of a soluble fiber additive should be considered in all ICU patients as a prophylactic measure to help maintain commensal microbiota and promote bowel health. An appropriate dose would be 10–20 grams per day divided over 24 hours (193).

For the critically ill patient who develops diarrhea, use of a prebiotic soluble fiber supplement appears to show a more consistent benefit for reducing diarrhea than commercial mixed-fiber formulas. The major antidiarrheal mechanism for such a supplement comes from fermentation of the soluble fiber (such as pectin, FOS, inulin, and guar gum) and the production of SCFAs. The trophic effect of SCFAs on the colonocyte stimulates the uptake of water and electrolytes (191). Use of a soluble fiber additive theoretically may pose lower risk of intestinal obstruction than use of a mixed-fiber formula.

Five small RCTs that met our inclusion criteria evaluated the use of a soluble fiber supplement added to standard enteral formulations (153, 194–197). Of the four trials that included diarrhea as a study endpoint, three showed significant reductions in diarrhea in critically ill patients (153, 195, 196). No differences in duration of mechanical ventilation, ICU LOS, or MOF were reported (188, 195). An older prospective double-blind RCT in patients with severe sepsis and septic shock found that the mean frequency of diarrhea days was significantly lower in patients receiving a soluble fiber supplement than those on standard EN alone (195). The type of enteral formula did not influence sepsis-related mortality or ICU LOS (195).

**Question:** Is there a role for probiotic administration in critically ill patients? Is there any harm in delivering probiotics to critically ill patients?

**F2. We suggest that, while the use of studied probiotics species and strains appear to be safe in general ICU patients, they should be used only for select medical and surgical patient populations for which RCTs have documented safety and outcome benefit. We cannot make a recommendation at this time for the routine use of probiotics across the general population of ICU patients.**

[**Quality of Evidence: Low**]

**Rationale:** Probiotics are defined by the World Health Organization and the Food and Agriculture Organization as "viable microorganisms that, when ingested in adequate amounts, can be beneficial for health." Multiple factors in the ICU induce rapid and persistent changes in the commensal microbiota, including metabolic insult, gut ischemia/reperfusion, administration of broad-spectrum antibiotics, prophylaxis for stress gastropathy, vasoactive pressor agents, alterations in motility, and suboptimal luminal nutrient delivery (198, 199). Probiotic agents have species-specific mechanisms of action, including competitive inhibition of pathogenic bacterial growth and epithelial attachment of invasive pathogens, elimination of pathogenic toxins, enhancement of intestinal epithelial barrier, and favorable modulation of the host inflammatory response (200–202). While probiotic supplementation is theoretically sound, there has not been a consistent outcome benefit demonstrated for the general ICU

patient population. There appears to be some beneficial effect of certain probiotic species (primarily *Lactobacillus* GG) in decreasing the incidence of overall infectious complications and VAP (203) depending on the patient population and probiotic strain studied.

In patients undergoing a pylorus-preserving Whipple procedure, Rayes showed that use of a commercial Synbiotic-Forte 2000 (Medifarm, Sweden) product (consisting of $10^{10}$ CFU of each of *Pediococcus pentoseceus, Leuconostoc mesenteroides, L paracasei* subsp paracasei and *L plantarum,* as well as 2.5 g of inulin, oat bran, pectin and resistant starch), showed a significant reduction of infection when the probiotic preparation was begun one hour postoperatively immediately below the anastomosis with the Roux limb, compared to controls receiving placebo (40.0% vs 12.5%, respectively, $p < 0.05$) (204).

Estimating the effect size is difficult due to heterogeneity of the ICU populations studied, the difference in bacterial strains, and the variability in dosing. In a Cochrane review, none of the probiotics studied had an effect on ICU mortality or incidence of diarrhea (205). Improvements in taxonomic classification and future research focusing on targeted probiotic supplementation for the altered bacterial phyla should eventually lead to stronger recommendations for use in specific populations of critically ill patients. With regard to safety issues of probiotic provision to critically ill patients, cases of fungemia in ICU patients associated with the use of *Saccaromyces boulardii*, as well as worsened clinical outcomes in severe pancreatitis patients have been reported (206, 207). Although no other infection or bacteremia due to probiotic strain has been reported, and no studies have described the occurrence of ischemic bowel disease, their routine use cannot be recommended at this time (208). Studied probiotics may be considered for use in selective patient populations (such as liver transplantation, trauma, pancreatectomy) (209–212) in which RCTs have documented safety and outcome benefits (prevention of VAP, pseudomembranous colitis and antibiotic-associated diarrhea) (203, 205, 213–215).

**Question:** Does the provision of antioxidants and trace minerals affect outcome in critically ill adult patients?

**F3. We suggest that a combination of antioxidant vitamins and trace minerals in doses reported to be safe in critically ill patients be provided to those patients who require specialized nutrition therapy**

[**Quality of Evidence: Low**]

**Rationale:** Antioxidant vitamins (including vitamins E and ascorbic acid) and trace minerals (including selenium, zinc, and copper) may improve patient outcome, especially in burns, trauma, and critical illness requiring mechanical ventilation (216, 217). The aggregated results of 15 trials that met our inclusion criteria (**Figure 8**) demonstrated that antioxidant and trace element supplementation was associated with a significant reduction in overall mortality (RR = 0.8; CI 0.7–0.92; $p = 0.001$) (218–232). Infectious complications, ICU or hospital LOS, and duration of mechanical ventilation were not significantly different between patients placed on such antioxidant multivitamin/trace element supplements and controls receiving placebo. Most issues of administration, such as dosage, frequency, duration and route of therapy, have not been well standardized. Renal function should be considered when supplementing vitamins and trace elements.

**Question:** Should enteral glutamine be provided to any subsets of patients in the adult ICU setting?

**F4. We suggest that supplemental enteral glutamine NOT be added to an EN regimen routinely in critically ill patients.**

[**Quality of Evidence: Moderate**]

**Rationale:** The addition of enteral glutamine to an EN regimen (not already containing supplemental glutamine) was shown to reduce mortality in a small but high-quality study by Garrell in burn patients (233). Aggregating the data from 5 RCTs that met our inclusion criteria (**Figure 9**) involving 558 patients from burn, trauma, and mixed ICU populations showed no significant beneficial effect on mortality, infections, or hospital LOS (233–238). While enteral glutamine exerts a trophic effect in maintaining gut integrity, its failure to generate a sufficient systemic antioxidant effect may partially explain the lack of outcome benefit (239).

## G. WHEN TO USE PN

**Question:** When should PN be initiated in the adult critically ill patient at low nutrition risk?

**G1. We suggest that, in the patient at low nutrition risk (for example, NRS-2002 ≤ 3 or NUTRIC score ≤ 5), exclusive PN be withheld over the first 7 days following ICU admission if the patient cannot maintain volitional intake and if early EN is not feasible.**

[**Quality of Evidence: Very Low**]

**Rationale:** The risk/benefit ratio for use of PN in the ICU setting is much narrower than that for use of EN. In a previously well-nourished patient, use of PN provides little benefit over the first week of hospitalization in the ICU (240). Patients who have a diagnosis that makes them PN-dependent (e.g., short bowel) should continue their PN upon admission to the ICU unless bacteremia is suspected (241). Two trials have addressed the timing of initiation of exclusive PN therapy. In a subset of patients from the EPaNiC study for whom there was an absolute contraindication to the use of EN (such as bowel in discontinuity), Casaer showed that those patients for whom use of PN was started on ICU day 3 had worse infectious morbidity and were less likely to be discharged alive than those patients for whom PN was started instead on day 8 (240). In a large RCT involving critically ill patients with a perceived contraindication to EN, use of PN within 24 hours of admission showed minimal benefit over STD where no nutrition therapy was provided (shorter duration of mechanical ventilation, WMD = –0.47 days; 95% CI, –0.82 to –0.11; $p = 0.01$), with no difference between groups with regard to infection, organ failure, total complications, or mortality (242). Because of the wide variation of nutrition

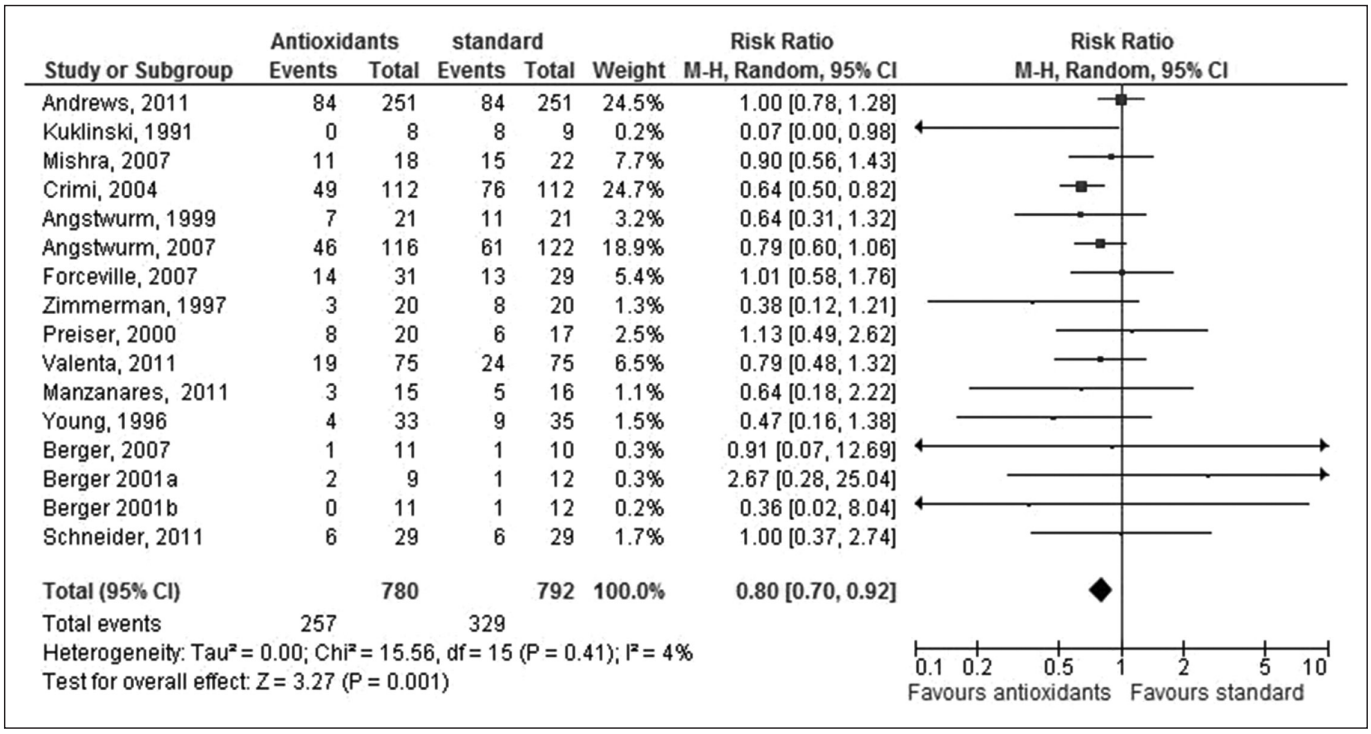


**Figure 8.** Antioxidants vs standard, outcome mortality.

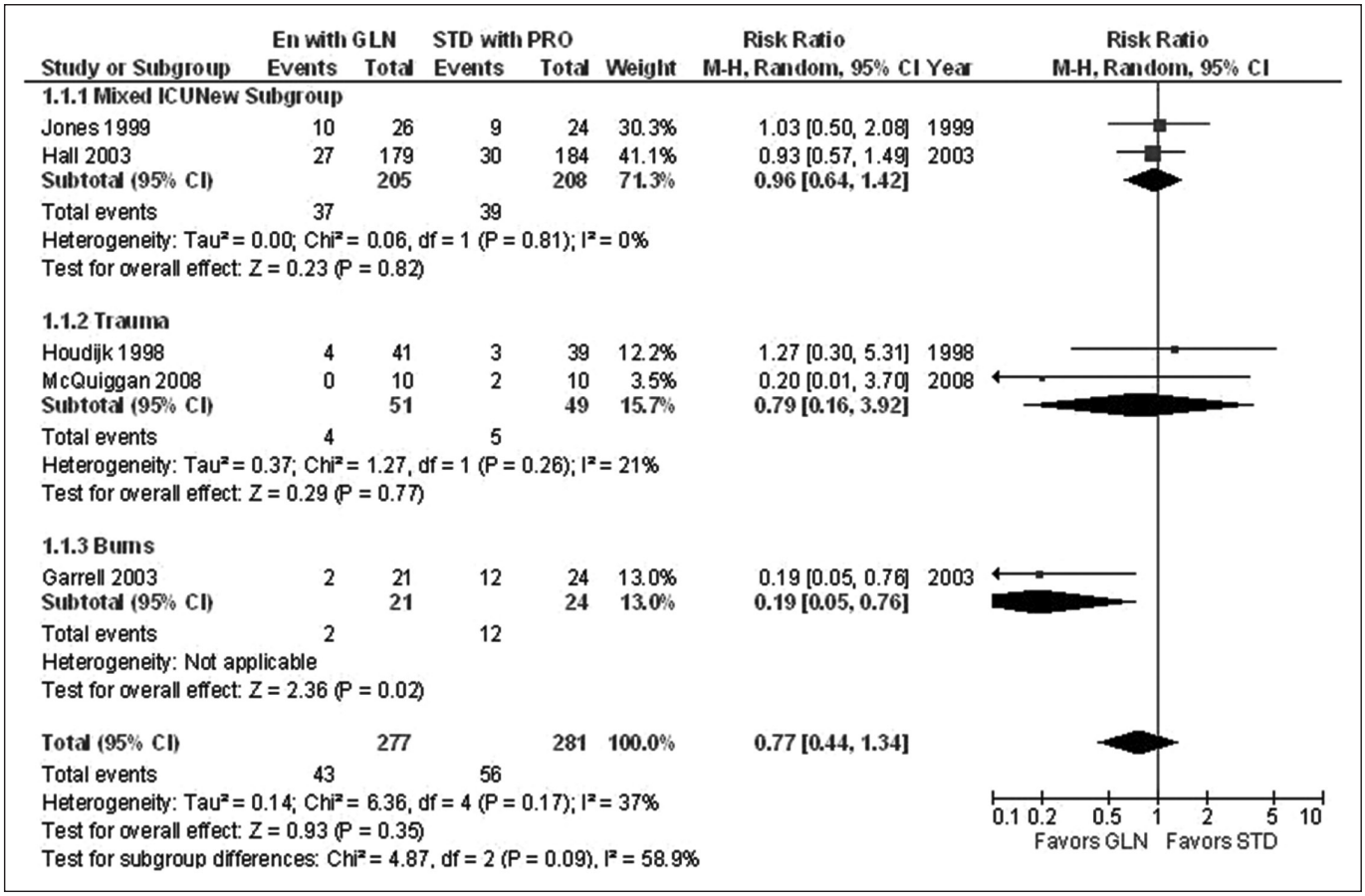


**Figure 9.** Enteral nutrition (EN) glutamine (GLN) vs control by subgroups, mortality. ICU, intensive care unit; PRO, protein supplement; STD, standard therapy.

risk in these populations, clinical judgment should be used to determine those less likely to benefit from PN.

An earlier meta-analysis by Braunschweig of patients ranging from pancreatitis, trauma, and inflammatory bowel to MOF, comparing use of PN with STD supports delay in PN in well-nourished patients (55). In hospitalized patients with the absence of preexisting malnutrition (when EN is not available), aggregating seven studies (243–249) showed that use of STD was associated with significantly reduced infectious morbidity (RR = 0.77; 95% CI, 0.65–0.91; $p < 0.05$) and a trend toward reduced overall complications (RR = 0.87; 95% CI, 0.74–1.03; $p$ value not provided) compared to use of PN. In similar circumstances (critically ill, no EN available, and no evidence of malnutrition), Heyland aggregated four studies (246, 247, 250, 251) that showed a significant increase in mortality with use of PN (RR = 0.1.78; 95% CI, 1.11–2.85; $p < 0.05$) and a trend toward greater rate of complications (RR = 2.40; 95% CI, 0.88–6.58; $p$ value not provided), when compared to STD (252).

With increased duration of severe illness, the risk for deterioration of nutrition status increases, and priorities between STD and PN become reversed. Little data exist to direct the timing of initiating PN in the ICU. Sandstrom first showed that, after the first 14 days of hospitalization had elapsed, continuing to provide no nutrition therapy was associated with significantly greater mortality (21% vs 2%, $p < 0.05$), and longer hospital LOS (36.3 days vs 23.4 days, $p < 0.05$), when compared respectively to use of PN (246). Although the literature cited recommends withholding PN for 10–14 days, the Guidelines Committee expressed concern that continuing to provide STD beyond 7 days would lead to deterioration of nutrition status and an adverse effect on clinical outcome.

**Question:** When should PN begin in the critically ill patient at high nutrition risk?

**G2. Based on expert consensus, in the patient determined to be at high nutrition risk (for example, NRS-2002 ≥ 5 or NUTRIC score ≥ 6) or severely malnourished, when EN is not feasible, we suggest initiating exclusive PN as soon as possible following ICU admission.**

**Rationale:** In the situation where EN is not available and evidence of high nutrition risk (see section A) is present, initial priorities are reversed and use of PN has a more favorable outcome than STD. In the Heyland meta-analysis, use of PN in malnourished ICU patients was associated with significantly fewer overall complications (RR = 0.52; 95% CI, 0.30–0.91; $p < 0.05$) than STD (252). In the Braunschweig meta-analysis, STD in malnourished ICU patients was associated with significantly higher risk for mortality (RR = 3.0; 95% CI, 1.09–8.56; $p < 0.05$) and a trend toward higher rate of infection (RR = 1.17; 95% CI, 0.88–1.56; $p$ value not provided) compared to use of PN (55). For these patients, when EN is not available, there should be little delay in initiating PN after admission to the ICU.

**Question:** What is the optimal timing for initiating supplemental PN when EN does not meet energy or protein goals in the patient at low or high nutrition risk?

**G3. We recommend that, in patients at either low or high nutrition risk, use of supplemental PN be considered after 7 to 10 days if unable to meet > 60% of energy and protein requirements by the enteral route alone. Initiating supplemental PN prior to this 7–10-day period in critically ill patients on some EN does not improve outcomes and may be detrimental to the patient.**

[**Quality of Evidence: Moderate**]

**Rationale:** Early EN is directed toward maintaining gut integrity, reducing oxidative stress, and modulating systemic immunity. In patients already receiving some volume of EN, use of supplemental PN over the first 7–10 days may increase energy and protein provided (253). However, supplemental PN is a costly therapy with minimal benefits when provided early in the ICU stay (254). A large multicenter observational study found no additional outcome benefit when patients were provided early (< 48 hours) supplemental PN (255). In an RCT from two centers, supplemental PN added on day 3 after admission for patients getting < 60% of goal energy and protein by EN provided little outcome benefit compared to controls continuing to receive hypocaloric EN (only a lower incidence of other infections occurring after day 9 reached significance in study patients compared to controls) (257). In another multicenter RCT by Casaer, patients on hypocaloric EN who had late supplemental PN initiated on day 8 of ICU admission had a higher likelihood of being discharged alive from the ICU (HR = 1.06; 95% CI, 1.00–1.13; $p = 0.04$) compared to those for whom PN was initiated earlier on day 3 (240). Those patients randomized to late supplemental PN had a shorter LOS in the ICU ($p = 0.02$), fewer infections (22.8% vs 26.2%, $p = 0.008$), and a greater mean reduction of healthcare costs of about U.S. $1,600 ($p = 0.04$) in comparison to patients randomized to early PN (240).

The optimal time to initiate supplemental PN in a patient who continues to receive hypocaloric EN is not clear. At some point after the first week of hospitalization, if the provision of EN is insufficient to meet requirements, then the addition of supplemental PN should be considered, with the decision made on a case-by-case basis.

## H. WHEN INDICATED, MAXIMIZE EFFICACY OF PN

**Question:** When PN is needed in the adult critically ill patient, what strategies can be adopted to improve efficacy?

**H1. Based on expert consensus, we suggest the use of protocols and nutrition support teams to help incorporate strategies to maximize efficacy and reduce associated risk of PN.**

**Rationale:** After an ICU patient has been deemed an appropriate candidate for PN, care should be taken to reduce inherent risk from hyperglycemia, electrolyte imbalances, immune

suppression, increased oxidative stress, and potential infectious morbidity (256–259). Management of PN should include attention to rate of advancement of feeding, glycemic control, electrolyte monitoring and repletion (evidence of refeeding), duration of PN and transition to EN as feasible. Attention to refeeding syndrome is especially important for the patient with risk factors (alcoholism, weight loss, low body mass index [BMI], prolonged periods NPO). Although refeeding syndrome can occur with EN, the risk is higher with initiation of PN. In those patients, advancement of feeding should be slower, taking 3 to 4 days to reach goal. Use of protocols and nutrition support teams have been shown to decrease PN-associated complications (260–262). Permissive underfeeding has also been shown to be a potential short-term approach to avoid some of these complications (see section H2) (263–266).

**Question:** In the appropriate candidate for PN (high risk or severely malnourished), should the dose be adjusted over the first week of hospitalization in the ICU?

**H2. We suggest that hypocaloric PN dosing (≤ 20 kcal/kg/day or 80% of estimated energy needs) with adequate protein (≥ 1.2 g protein/kg/day) be considered in appropriate patients (high risk or severely malnourished) requiring PN, initially over the first week of hospitalization in the ICU.**

[**Quality of Evidence: Low**]

**Rationale:** Patients requiring PN in the ICU may benefit from a feeding strategy that is hypocaloric (≤ 20 kcal/kg/day or no more than 80% of estimated energy needs) but provides adequate protein (≥ 1.2 g protein/kg/day). This strategy may optimize the efficacy of PN in the early phases of critical illness by reducing the potential for hyperglycemia and insulin resistance. In some subsets of patients, avoiding excessive energy intake may reduce infectious morbidity, duration of mechanical ventilation and hospital LOS (266). A previous meta-analysis of 5 studies involving patients with trauma, pancreatitis, or major abdominal/chest surgery showed significantly reduced infection and hospital LOS with this strategy (20 kcal/kg/day) compared to full energy goal (25 kcal/kg/day) (267). A meta-analysis of 4 studies meeting our inclusion criteria did not demonstrate significant reduced mortality (RR = 0.61; CI, 0.20–1.85; $p = 0.38$) or infectious complications (RR = 0.68; CI, 0.30–1.57; $p = 0.37$) with hypocaloric PN (266, 268–270). However, hypocaloric PN is associated with decreased hyperglycemia, 0% (0–0.5%) versus 33.1% (0–58.4%), $p = 0.001$ (270). Once the patient stabilizes, PN energy may be increased to meet 100% of estimated energy requirements.

**Question:** Should soy-based IV fat emulsions (IVFE) be provided in the first week of ICU stay? Is there an advantage to using alternative IVFE (i.e., medium-chain triglycerides [MCT], olive oil [OO], FO, mixture of oils) over traditional soybean oil (SO)-based lipid emulsions in critically ill adult patients?

**H3a. We suggest withholding or limiting SO-based IVFE during the first week following initiation of PN in the critically ill patient to a maximum of 100 g/week (often divided into 2 doses/week) if there is concern for essential fatty acid deficiency.**

[**Quality of Evidence: Very Low**]

**H3b Alternative IVFE may provide outcome benefit over soy-based IVFE; however, we cannot make a recommendation at this time due to lack of availability of these products in the U.S. When these alternative IVFEs (SMOF, MCT, OO and FO) become available in the United States, based on expert opinion, we suggest that their use be considered in the critically ill patient who is an appropriate candidate for PN.**

**Rationale:** In the United States at the present time, the choice of IVFE for PN is limited to a soy-based 18-carbon omega-6 fatty acid preparation. RCTs have investigated the question of whether PN should be administered with or without SO-based IVFE during the first week of hospitalization. The answer remains elusive. The task force reached only 64% agreement (nine for and five against) to "withhold or limit" SO-based IVFE to 100 g/week, as opposed to simply "withhold." Trauma patients provided IVFE-free PN over the first 10 days of hospitalization had a significant reduction in infectious morbidity (pneumonia, $p = 0.05$; and catheter-related sepsis, $p = 0.04$) (**Figure 10**) (266, 268), decreased hospital and ICU LOS ($p = 0.03$ and $p = 0.02$), and shorter duration of mechanical ventilation ($p = 0.01$) compared to those receiving SO-based IVFE-containing PN (268). However, the IVFE-free PN formulation was hypocaloric (21 kcal/kg/day vs 28 kcal/kg/day) as a result of leaving off the fat (268). A similar study comparing a hypocaloric, IVFE-free regimen (1000 total kcal/day and 70 g of protein/day) versus an SO-based IVFE standard admixture (25 kcal/kg/day and 1.5 g protein/day) found no significant differences in infectious complications, hospital LOS, or mortality (266). This finding was confirmed by a large observational study that reviewed outcomes in patients who received PN for ≥ 5 days in multi-international ICUs. No statistically significant difference in clinical outcomes between IVFE-free PN and PN with SO-based IVFE were found (271).

While the recommendation to leave off fat the first week is based primarily on the Batistella study, it is important to note serious criticisms of that trial. The study was completed 20 years ago, and the results have not been replicated (266, 271, 272). The caloric goals were based on nonprotein calories (not total calories), such that the total calories delivered were greater than what was stated in the paper. Faster infusion rates of the lipid emulsions over 12 hours might lead to clogging of the RES system, reducing clearance and leading to hypertriglyceridemia (however, these levels were not measured). As such, this overfeeding may have contributed to the observed poor outcomes.

Alternative IVFEs derived from sources other than SO provide a component that may improve the risk/benefit ratio for PN. Manzanares conducted a systematic review of 12 RCTS involving 806 patients evaluating the clinical outcomes of SO lipid-IVFE alone or combined with MCTs,

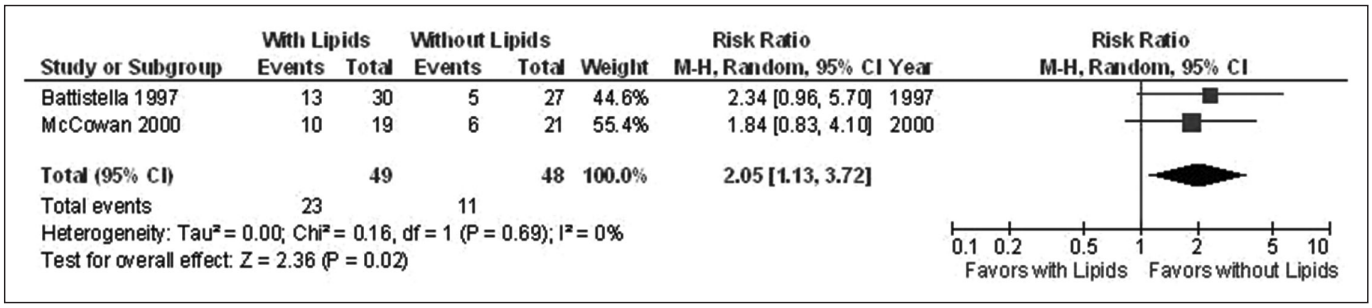


**Figure 10.** With or without soybean-based lipid emulsion, infectious complications.

OO, and FO (273). No significant difference in outcome benefits was demonstrated (273). The Palmer meta-analysis of 8 RCTs involving 391 patients compared the effects of omega-3 FO-based PN with either SO-based or SO+MCT-based IVFE (274). Results showed a significant reduction in hospital LOS by nearly 10 days (WMD = 9.49; 95% CI, –16.5 to 2.5; $p = 0.008$) from use of the FO-based regimen versus the other fat sources, but no differences were seen between groups with regard to ICU LOS, infectious complications, and mortality (274).

The strongest signal of benefit from use of FO-based IVFE is seen in observational studies. Data collected from an International Nutrition Survey showed a significantly shorter ICU LOS (HR = 1.84; 95% CI, 1.01–3.34; $p = 0.05$), a trend toward reduced duration of mechanical ventilation (HR = 1.67; 95% CI, 1.00–2.81; $p = 0.051$), and a significantly greater likelihood of being discharged alive from the ICU (HR = 2.40; 95% CI, 1.43–4.03, $p = 0.001$) with the FO-based product when compared to an SO-based IVFE (275).

Few studies have specifically compared OO-based IVFE (omega-9 fatty acids as oleic acid) with SO-based IVFE in critically ill patients. A subgroup analysis within the Manzanares meta-analysis found a significant reduction in the duration of mechanical ventilation (WMD = –6.47; 95% CI, –11.41 to –1.53; $p = 0.01$) in favor of the OO-based IVFE, although there were no differences for mortality or ICU LOS (273). Observational data from the International Nutrition Survey showed that use of an OO-based IVFE compared to an SO-based product was associated with a significant reduction in duration of mechanical ventilation (HR = 1.43; 95% CI, 1.06–1.93; $p = 0.02$), and patients were more likely to be discharged alive from the ICU (HR = 1.76; 95% CI, 1.30–2.39; $p < 0.001$) (275). Contrasting results were found by Umpierrez in a double-blind RCT that showed no outcome benefits from use of OO-based IVFE compared to an SO-based product in adult medical/surgical ICU patients requiring PN (276). Substitution of an alternative IVFE for PN, particularly an OO-based preparation, may improve outcomes when compared to the more standard SO-based product; however, the committee cannot make a recommendation at this time regarding substituting alternative IVFE sources for SO due to lack of availability on the market of these products in the United States, despite approval by the FDA in October 2013.

**Question:** Is there an advantage to using standardized commercially available PN (premixed PN) versus compounded PN admixtures?

### H4. Based on expert consensus, use of standardized commercially available PN versus compounded PN admixtures in the ICU patient has no advantage in terms of clinical outcomes.

**Rationale:** Standardized commercially available PN is a manufactured, sterile PN bag available in both central and peripheral line formulations, with and without electrolytes. The standardized commercially available PN products are regulated by the FDA, follow good manufacturing practices, and are compliant with U.S. Pharmacopeia General Chapter 797. Such a product may offer the advantage of improved safety over compounded PN admixtures; however, because of the limited standardized commercially available PN products, customization to the patient's specific macro- and micronutrient requirements and clinical parameters is difficult. This is especially true in critically ill patients who may have additional complications, including renal/hepatic dysfunction, fluid restrictions, and electrolyte imbalances. Additionally, the products have been criticized for the high dextrose content that may result in hyperglycemia and infection. Data on the use of standardized commercially available PN products in ICU patients are limited, and most of the research is retrospective or observational. Only one international multicenter RCT study has been completed (277). A standardized commercially available PN of MCT/long-chain triglyceride fat emulsions and OO fat emulsions were used, which is not currently available in the United States, making it difficult to extrapolate the findings. The authors reported a significant decrease in bloodstream infections but found no differences in 28-day mortality, ICU and hospital LOSs, organ failure, and hypo-/hyperglycemic events in ICU patients receiving the standardized commercially available PN products compared to those placed on compounded PN admixtures (277). No information on admixture compounding standards used by the multicenters was included. The A.S.P.E.N. Clinical Guidelines Recommendation for PN Ordering, Order Review, Compounding, Labeling, and Dispensing recommended standardized commercially available PN products be considered as an available option for patients alongside compounded (customized or standardized) PN formulations to best meet an organization's patient needs (278). The use of standardized commercially available PN may

be considered in ICU patients when the formulation meets the metabolic needs of the patient.

**Question:** What is the desired target blood glucose range in adult ICU patients?

**H5. We recommend a target blood glucose range of 140– or 150–180 mg/dL for the general ICU population; ranges for specific patient populations (post-cardiovascular surgery, head trauma) may differ and are beyond the scope of this guideline.**

[**Quality of Evidence: Moderate**]

**Rationale:** Hyperglycemia is a common response to acute illness and severe sepsis and may lead to poor outcomes. There continues to be controversy regarding the lower point of the range, with SCCM recommending 150–180 mg/dL (279), while A.S.P.E.N. recommends 140–180 mg/dL. In 2001, a landmark trial showed that tight glucose control (TGC) (80–110 mg/dL) with intensive insulin therapy (IIT) was associated with reduced sepsis, reduced ICU LOS, and lower hospital mortality compared to conventional insulin therapy (keeping blood glucose levels < 200 mg/dL) (280). The effect was more pronounced in SICU than MICU patients (280, 281). However, study results were controversial because it was a single-center unblinded trial with high mortality in both arms, and patients received 200–300 grams of IV dextrose in the early postoperative regimen (280). The Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) trial (282) of 535 patients conducted in 18 ICUs in Germany and the Corticosteroid Treatment and Intensive Insulin Therapy for Septic Shock (COIITSS) (283) trial of 509 patients conducted in 11 ICUs in France studied the effect of TGC in combination with another therapy compared to moderate glucose control (MGC) in a range of 140–180 mg/dL in a 2 × 2 factorial design. The VISEP trial was stopped early due to the potentially harmful increased incidence of severe hypoglycemia and the fact that no mortality benefit could be demonstrated. In the COIITSS study, the TGC group was shown to have a higher prevalence of hypoglycemia and a trend toward higher mortality compared to the MGC group. The largest trial, the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE SUGAR) study, randomly assigned 6104 patients in 42 hospitals who were primarily fed via the enteral route to a blood glucose target of approximately 80–100 mg/dL (TGC) or < 180 mg/dL (MGC). Patients in the TGC group had an increased risk of death at 90 days (27.5% vs 24.9%, $p = 0.02$) (284). There was concern that severe hypoglycemia in this study might exacerbate deficits in the injured brain. A review of three RCTs (285–287) representing 773 patients found that, although TGC led to a higher incidence of hypoglycemia compared to more conventional MGC, TGC lowered infection rates with no effect on mortality.

For specific patient populations (e.g., post-cardiovascular surgery, head trauma, etc.), we defer to SCCM published guidelines on glycemic control (279).

**Question:** Should parenteral glutamine be used in the adult ICU patient?

**H6. We recommend that parenteral glutamine supplementation NOT be used routinely in the critical care setting.**

[**Quality of Evidence: Moderate**]

**Rationale:** Several recent trials and meta-analyses have brought into question the safety and efficacy of parenteral glutamine administration in critically ill patients. In the REDOX trial, a large RCT with 2 × 2 factorial design involving 1223 critically ill adults in 40 ICUs around the world, patients were randomized to one of four groups: placebo, glutamine (enteral and parenteral), antioxidants (IV selenium with oral selenium, zinc, beta-carotene, vitamin E, and ascorbic acid), and a combination of glutamine with antioxidants (288). Mortality, in-hospital and at 6 months, was significantly higher in those patients who received glutamine compared with those who did not (37.2% vs 31%, $p = 0.02$ and 43.7% vs 37.2%, $p = 0.02$, respectively) (288). The greatest concern for a potential adverse effect from glutamine was seen in those patients who received a higher dose > 0.5/g/kg/day in the early stages of critical illness with MOF or ongoing shock requiring vasopressor support. Another large study of parenteral glutamine use in ICU patients, the SIGNET trial, failed to demonstrate an outcome benefit in terms of infectious complications and mortality (289).

Better short-term survival with glutamine supplementation is associated with single-center clinical trials and those trials published before 2003 (290). In contrast, mortality is no different or may be increased in multicenter trials or those published after 2003. A meta-analysis of five multicenter trials involving 2463 patients showed a significantly greater mortality in those patients receiving glutamine than in those randomized to placebo (35% versus 31%, respectively, $p = 0.015$). This contrasts sharply from a meta-analysis of single-center trials involving 1645 patients in which a significant decrease in mortality was observed in patients receiving glutamine compared with controls (20% versus 23%, respectively, $p = 0.019$) (291). Others have proposed that the amino acid imbalance created by supplemental glutamine (providing 60% of total exogenous protein intake) coupled with the severity of illness (e.g., MOF, shock) account for the increased mortality (292). Also, more recent trials that measured baseline glutamine levels failed to show a glutamine deficiency at the time of initiating supplemental therapy (293).

**Question:** In transition feeding, as an increasing volume of EN is tolerated by a patient already receiving PN, at what point should the PN be terminated?

**H7. Based on expert consensus, we suggest that, as tolerance to EN improves, the amount of PN energy should be reduced and finally discontinued when the patient is receiving > 60% of target energy requirements from EN.**

**Rationale:** Because of the marked benefits of EN, for the critically ill patient stabilized on PN, repeated efforts should

be made to transition the patient to enteral therapy. To avoid the complications associated with overfeeding, the amount of energy delivered by the parenteral route should be reduced appropriately to compensate for the increase in the energy being delivered enterally. Once the provision of EN exceeds 60% of target energy requirements and continues to be advanced toward goal, PN may be discontinued (253).

## I. PULMONARY FAILURE

**Question:** What is the optimal carbohydrate-to-fat ratio for the adult ICU patient with pulmonary failure?

**I1. We suggest that specialty high-fat/low-carbohydrate formulations designed to manipulate the respiratory quotient and reduce $CO_2$ production NOT be used in ICU patients with acute respiratory failure (not to be confused with recommendation E3).**

[**Quality of Evidence: Very Low**]

**Rationale:** An early, very small trial (20 patients) (294) showed that use of a high-fat/low-carbohydrate enteral formulation in patients with respiratory failure reduced duration of mechanical ventilation, compared to a standard formulation. However, these findings could not be reproduced in a subsequent larger RCT (50 patients) of similar type (295). Results from uncontrolled studies would suggest that increasing the composite macronutrient ratio of fat to carbohydrate becomes clinically significant in lowering $CO_2$ production only in the ICU patient who is being overfed. Macronutrient composition is much less likely to affect $CO_2$ production when the design of the nutrition support regimen approximates energy requirements (296). Effort should be made to avoid total energy provision that exceeds energy requirements, as $CO_2$ production increases significantly with lipogenesis and may be tolerated poorly in the patient prone to $CO_2$ retention (294, 296, 297). Rapid infusion of IVFE (especially SO-based), regardless of the total amount, should be avoided in patients with severe pulmonary failure.

**Question:** Does use of energy-dense EN formulas to restrict fluid administration benefit the adult ICU patient with acute respiratory failure?

**I2. Based on expert consensus, we suggest that fluid-restricted energy-dense EN formulations be considered for patients with acute respiratory failure (especially if in a state of volume overload).**

**Rationale:** Fluid accumulation, pulmonary edema, and renal failure are common in patients with acute respiratory failure, and have been associated with poor clinical outcomes. It is therefore suggested that a fluid-restricted energy-dense nutrient formulation (1.5–2 kcal/mL) be considered for patients with acute respiratory failure that necessitate volume restriction (297).

**Question:** Should serum phosphate concentrations be monitored when EN or PN is initiated in the ICU patient with respiratory failure?

**I3. Based on expert consensus, we suggest that serum phosphate concentrations should be monitored closely, and phosphate replaced appropriately when needed.**

**Rationale:** The incidence of moderate or severe hypophosphatemia (defined as serum phosphorus concentrations $\leq 2.2$ mg/dL and $< 1.5$ g/dL, respectively) is nearly 30% in the ICU (298–300). Phosphate is essential for the synthesis of adenosine triphosphate (ATP) and 2,3-diphosphoglycerate (2,3-DPG), both of which are critical for normal diaphragmatic contractility and optimal pulmonary function. Hypophosphatemia is a frequently encountered problem in critical illness, and may represent an occult cause of respiratory muscle weakness and failure to wean from the ventilator (301). In a cohort study of 66 MICU patients in whom 193 weaning trials were undertaken, weaning was improved in patients with a serum phosphorus of $1.18 \pm 0.27$ mmol/L vs $1.06 \pm 0.31$ mmol/L, $p = 0.008$. Those patients with a level $< 0.80$ mmol/L had a greater risk for weaning failure than those with values within the laboratory's normal limits (RR = 1.18; 95% CI, 1.06–1.32, $p = 0.01$) (302). As suggested by several uncontrolled studies, it is prudent to monitor serum phosphate concentrations closely (despite the fact that serum levels may not accurately reflect the total body phosphate pool) and replete moderate to severe hypophosphatemia, according to hospital-specific protocols when needed to optimize respiratory function in ventilated patients (303–305).

## J. RENAL FAILURE

**Question:** In adult critically ill patients with acute kidney injury (AKI), what are the indications for use of specialty enteral formulations? What are appropriate energy and protein recommendations to reduce morbidity in AKI?

**J1. Based on expert consensus, we suggest that ICU patients with acute renal failure (ARF) or AKI be placed on a standard enteral formulation, and standard ICU recommendations for protein (1.2–2 g/kg actual body weight per day) and energy (25–30 kcal/kg/day) provision should be followed. If significant electrolyte abnormalities develop, a specialty formulation designed for renal failure (with appropriate electrolyte profile) may be considered.**

**Rationale:** AKI seldom exists as an isolated organ failure in critically ill patients. When prescribing EN to the ICU patient, the underlying disease process, preexisting comorbidities, and current complications should be taken into account. In the absence of IC, no one predictive equation is better than another in AKI. Experts agree on using usual body weight for normal weight patients and IBW for obese and critically ill patients. Energy needs can be determined by IC, published predictive equations, or a simplistic weight-based equation (25–30 kcal/kg/day) (306–310). Specialty formulations lower in certain electrolytes (i.e., phosphate and potassium) than standard products may be beneficial in ICU patient with AKI (306, 308).

**Question:** In adult critically ill patients with AKI receiving hemodialysis or CRRT, what are appropriate targets for protein intake to support increased nitrogen losses?

**J2. We recommend that patients receiving hemodialysis or CRRT receive increased protein, up to a maximum of 2.5 g/kg/day. Protein should NOT be restricted in patients with renal insufficiency as a means to avoid or delay initiating dialysis therapy.**

[Quality of Evidence: Very Low]

**Rationale:** A significant amino acid loss (10–15g/day) is associated with CRRT (310). Lean body mass catabolism inferred from protein catabolic rate values is 1.4–1.8 g/kg per day in patients with AKI on CRRT (306, 310). Thus, patients on this therapy may require at least an additional 0.2 g/kg/day (311) totaling up to 2.5 g/kg/day (94, 312). No major advantages have been demonstrated with very high protein intakes (> 2.5 g/kg/day), as excessively high nitrogen intakes may simply increase the rate of urea production (94, 313) At least one RCT has suggested an intake of 2.5 g/kg/day is necessary to achieve positive nitrogen balance in this patient population (94).

## K. HEPATIC FAILURE

**Question:** Should energy and protein requirements be determined similarly in critically ill patients with hepatic failure as in those without hepatic failure?

**K1. Based on expert consensus, we suggest a dry weight or usual weight be used instead of actual weight in predictive equations to determine energy and protein in patients with cirrhosis and hepatic failure, due to complications of ascites, intravascular volume depletion, edema, portal hypertension, and hypoalbuminemia. We suggest nutrition regimens avoid restricting protein in patients with liver failure, using the same recommendations as for other critically ill patients (see section C4).**

**Rationale:** Heightened nutrition risk and deterioration of nutrition status is highly prevalent among patients with chronic liver disease and is nearly universal among patients awaiting liver transplantation. The degree of nutrition risk is directly correlated with the severity of liver dysfunction. The portal hypertension and impaired protein synthesis associated with liver failure contribute to ascites and edema, rendering weight-based tools of nutrition assessment inaccurate and unreliable. Usual or dry weights are often difficult to determine due to the chronicity of the disease. The primary etiology of malnutrition in hepatic disease is poor oral intake from multiple factors, including alterations in taste, early satiety, autonomic dysfunction with resultant gastroparesis, slow small bowel motility and slow orocecal transit. Malnutrition in patients with cirrhosis contributes to increased morbidity and mortality (314). Those patients who are severely malnourished before transplant surgery have a higher rate of complications and a decreased overall survival rate after liver transplantation (315–318). Energy needs in critically ill patients with liver disease are highly variable, difficult to predict by simple equations, and consequently best determined by IC (319). Historically, protein restriction was used to help reduce risk from hepatic encephalopathy, but such strategy may worsen nutrition status, decrease lean muscle mass, and ironically lead to less ammonia removal. Therefore, protein should not be restricted as a management strategy aimed at reducing hepatic encephalopathy, since the reverse may occur as a result (319, 320). Protein requirements for the patient with hepatic failure should be determined in the same manner as for the general ICU patient with the caveat that dry weight may need to be used for calculations (see recommendation C4).

**Question:** What is the appropriate route of nutrition delivery in patients with hepatic failure?

**K2. Based on expert consensus, we suggest that EN be used preferentially when providing nutrition therapy in ICU patients with acute and/or chronic liver disease.**

**Rationale:** Long-term PN can be associated with hepatic complications, including worsening of existing cirrhosis and liver failure with the concomitant risks of sepsis, coagulopathy and death (321). PN-associated liver disease usually occurs with prolonged use of PN; however, it can also be a significant problem in the acute ICU setting. EN improves nutrition status, reduces complications, and prolongs survival in liver disease patients, and is therefore suggested as the optimal route of nutrient delivery. In clinical trials, EN has been associated with decreased infection rates and fewer metabolic complications in liver disease and after liver transplant when compared to PN or STD (no specialized nutrition therapy) (322–324).

Encephalopathy occurs in patients with liver dysfunction due to complex multifactorial processes involving products of protein metabolism, and is worsened by inflammation, infection, and oxidative stress.

**Question:** Is a disease-specific enteral formulation needed for critically ill patients with liver disease?

**K3. Based on expert consensus, we suggest that standard enteral formulations be used in ICU patients with acute and chronic liver disease. There is no evidence of further benefit of branched-chain amino acid formulations (BCAA) on coma grade in the ICU patient with encephalopathy who is already receiving first-line therapy with luminal-acting antibiotics and lactulose.**

**Rationale:** There is no evidence to suggest that a formulation enriched in BCAA improves patient outcomes compared to standard whole-protein formulations in critically ill patients with liver disease. The rationale for use of BCAAs in the treatment of hepatic encephalopathy in liver failure is based on their reduced concentrations in liver failure, competing for binding sites in the central nervous system with aromatic amino acids, and their stimulatory effect on ammonia detoxification to glutamine. Findings from randomized outpatient trials suggest that long-term (12 and 24 months) nutrition supplementation with oral BCAA granules may be useful in slowing the

progression of hepatic disease and/or failure and prolonging event-free survival (325–327). In patients with hepatic encephalopathy already receiving first-line therapy (antibiotics and lactulose), there is no evidence to date that adding BCAA will further improve mental status or coma grade (325, 326).

## L. ACUTE PANCREATITIS

**Question:** Does disease severity in acute pancreatitis influence decisions to provide specialized nutrition therapy?

**L1a. Based on expert consensus, we suggest that the initial nutrition assessment in acute pancreatitis evaluate disease severity to direct nutrition therapy. Since disease severity may change quickly, we suggest frequent reassessment of feeding tolerance and need for specialized nutrition therapy.**

**Rationale:** *Mild pancreatitis* is defined by the absence of organ failure and local complications. *Moderately severe acute pancreatitis* is defined by transient organ failure lasting < 48 hours, and local complications. Organ failure is defined by shock (systolic blood pressure < 90 mm Hg), pulmonary insufficiency ($Pao_2/Fio_2 \leq 300$), or renal failure (serum creatinine ≥ 1.9 mg/dL) (328–331). Local complications on CT scan include pseudocyst, abscess, or necrosis. *Severe acute pancreatitis* is defined by persistent organ failure lasting > 48 hours from admission (332). Previous scoring systems also used the presence of unfavorable prognostic signs (Acute Physiology and Chronic Health Assessment [APACHE] II score ≥ 8, Ranson Criteria > 3, and CRP level > 150 mg/L) to identify patients with moderately severe to severe acute pancreatitis (328, 330).

Differentiating patients with moderately severe to severe acute pancreatitis from those with mild disease severity helps identify those patients who need admission to the ICU, receipt of adequate hydration, treatment for early organ failure, and provision of nutrition therapy (332). The positive predictive value of a patient with high scores, presence of SIRS, or necrosis on CT scan going on to have severe disease is less than 50% (332). Patients thought to have mild acute pancreatitis on admission can progress quickly to severe disease in some circumstances. The difficulty in determining where patients start and how they progress across this spectrum of disease activity helps explain why some patients with mild disease on admission may deteriorate and show significant intolerance to EN, while others with severe disease may advance to oral diet within a few days.

**Question:** Do patients with mild acute pancreatitis need specialized nutrition therapy?

**L1b. We suggest NOT providing specialized nutrition therapy to patients with mild acute pancreatitis, instead advancing to an oral diet as tolerated. If an unexpected complication develops or there is failure to advance to oral diet within 7 days, then specialized nutrition therapy should be considered.**

**[Quality of Evidence: Very Low]**

**Rationale:** Patients with mild acute pancreatitis have a much lower rate of complications (6%) than patients with more severe disease, have close to a 0% mortality rate, and have an 81% chance of advancing to oral diet within 7 days (247, 333, 334). Providing specialized nutrition therapy to these patients does not appear to change outcome. These patients may be advanced to a regular diet when the patient wishes, which has been shown to be more beneficial than a clear liquid diet alone in terms of hospital LOS (WMD = –2.62; 95% CI, –3.38 to –1.86, $p < 0.00001$) (**Figure 11**) (335, 336). A protocol of routine parameters (absence of pain, nausea, vomiting, and normalization of pancreatic enzymes) is not required, nor is advancing first to clear liquids (335–337).

**Question:** Which patients require specialized nutrition therapy early after admission for acute pancreatitis?

**L1c. We suggest that patients with moderate to severe acute pancreatitis should have a naso-/oroenteric tube placed and EN started at a trophic rate and advanced to goal as fluid volume resuscitation is completed (within 24–48 hours of admission)**

**[Quality of Evidence: Very Low]**

**Rationale:** The improved outcome in moderate to severe acute pancreatitis with early EN is based primarily on studies comparing EN with PN, and PN in such cases may be a negative control. Limited support comes from studies showing benefit (trend toward reduced mortality) from early EN compared to STD (338–340), and improved outcomes from early EN (reduced infection, organ failure, ICU LOS, and SIRS) versus delayed EN (341, 342). What is not known is what percentage of patients with moderate to severe acute pancreatitis would tolerate advancing to oral diet (similar to the data on patients with mild disease) within 3 to 4 days from the time of admission, and thus not need specialized nutrition therapy. Failure to initiate EN therapy for > 72–96 hours following admission in a patient with moderate to severe acute pancreatitis runs the risk of rapid deterioration of nutrition status and its inherent complications.

**Question:** Which is the most appropriate formula to use when initiating early EN in the patient with moderate to severe acute pancreatitis?

**L2. We suggest using a standard polymeric formula to initiate EN in the patient with severe acute pancreatitis. Although promising, the data are currently insufficient to recommend placing a patient with severe acute pancreatitis on an immune-enhancing formulation at this time.**

**[Quality of Evidence: Very Low]**

**Rationale:** A standard polymeric formula is appropriate for initiating early EN for patients with moderate to severe acute pancreatitis. While results from three small RCTs comparing an immune-modulating formula (two with arginine and FO, one with FO alone) to a standard enteral formula suggest that such an immunonutrition formula may be shown to provide additional outcome benefits in the future, numbers are insufficient to make a recommendation at this time (176, 343, 344).

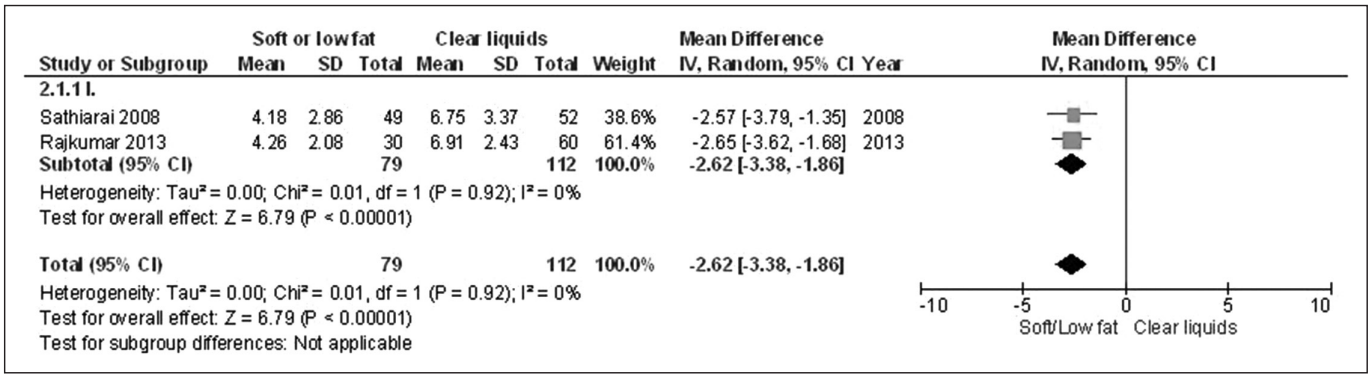


**Figure 11.** Soft/low fat diet vs clear liquid diet in mild acute pancreatitis, hospital length of stay.

**Question:** Should patients with severe acute pancreatitis receive EN or PN?

**L3a. We suggest the use of EN over PN in patients with severe acute pancreatitis who require nutrition therapy.**

[**Quality of Evidence: Low**]

**Rationale:** Use of PN in moderate to severe acute pancreatitis as initial nutrition therapy should be avoided. Use of EN is preferred to PN because of a better risk/benefit ratio with EN compared to PN. Three previous meta-analyses of ten randomized trials (47, 53, 61, 345–350) showed that use of EN compared to PN reduced infectious morbidity (RR = 0.46; 95% CI, 0.29–0.74; $p = 0.001$) (338), hospital LOS (WMD = –3.94; 95% CI, –5.86 to –2.02; $p < 0.0001$) (338), reduced need for surgical intervention (RR = 0.48; 95% CI, 0.23–0.99; $p = 0.05$) (351), MOF (OR = 0.306; 95% CI, 0.128–0.736; $p = 0.008$), and mortality (OR = 0.251; 95% CI, 0.095–0.666; $p = 0.005$) (352). In studies that met our inclusion criteria, 9 showed reduced mortality (RR = 2.17; CI, 1.13–4.17; $p = 0.02$) (47, 53, 61, 345, 347–350, 353), and 7 reduced infectious complications (RR = 2.45; 95% CI, 1.61–3.74; $p < 0.0001$) (47, 53, 345, 346, 348, 350, 353) in patients receiving EN as opposed to PN (**Figures 12 and 13**).

**Question:** Should patients with severe acute pancreatitis be fed into the stomach or small bowel?

**L3b. We suggest that EN be provided to the patient with severe acute pancreatitis by either the gastric or jejunal route, as there is no difference in tolerance or clinical outcomes between these two levels of infusion.**

[**Quality of Evidence: Low**]

**Rationale:** Three RCTs comparing gastric with jejunal feeding in severe acute pancreatitis showed no significant differences between the two levels of EN infusion within the GI tract with regard to tolerance or clinical outcome (354–356). A meta-analysis by Chang showed that there was no difference between the levels of infusion with regard to pain sensation, diarrhea, or energy balance (energy provision) (357).

**Question:** In the presence of intolerance, what strategies can be used to enhance tolerance to EN in patients with severe acute pancreatitis?

**L4. Based on expert consensus, we suggest that, in patients with moderate to severe acute pancreatitis who have intolerance to EN, measures should be taken to improve tolerance.**

**Rationale:** Measures to improve tolerance to EN in patients with moderate to severe acute pancreatitis include minimizing the period of ileus by starting EN as soon as possible within the first 48 hours of admission to the ICU (358), diverting the level of infusion of EN more distally in the GI tract (353, 359), changing from a standard polymeric formula to one that contains small peptides and MCTs or to one that is a nearly fat-free elemental formulation (360, 361), and switching from bolus to continuous infusion (362, 363).

**Question:** Should patients with severe acute pancreatitis receive probiotics?

**L5. We suggest that the use of probiotics be considered in patients with severe acute pancreatitis who are receiving early EN.**

[**Quality of Evidence: Low**]

**Rationale:** Early experience with two small RCTs from Europe by Olah showed a benefit of probiotic therapy using one to four strains of *Lactobacillus* for patients with severe acute pancreatitis (364, 365). However, a large multicenter Dutch trial by Besselink (206) involving 296 patients showed increased mortality (16 vs 6%, $p < 0.05$), MOF (22 vs 10%, $p < 0.05$), and need for surgical intervention (18 vs 10%, $p < 0.05$) in patients randomized to aggressive prebiotic and probiotic (six strains of *Lactobacillus* and *Bifidobacter* at $> 10^{10}$ cfu/L) therapy delivered directly into the jejunum, compared to controls given prebiotic therapy only. In both Europe and the United States, probiotics are designated as GRAS (Generally Recognized As Safe) under sections 201(s) and 409 of the Federal Food, Drug, and Cosmetic Act. No other RCT in pancreatitis or critical care has shown such a deleterious effect from the use of probiotics in an ICU setting as was seen in this trial.

A 2010 meta-analysis of 507 patients by Zhang, which included the Besselink multicenter trial as well as four other

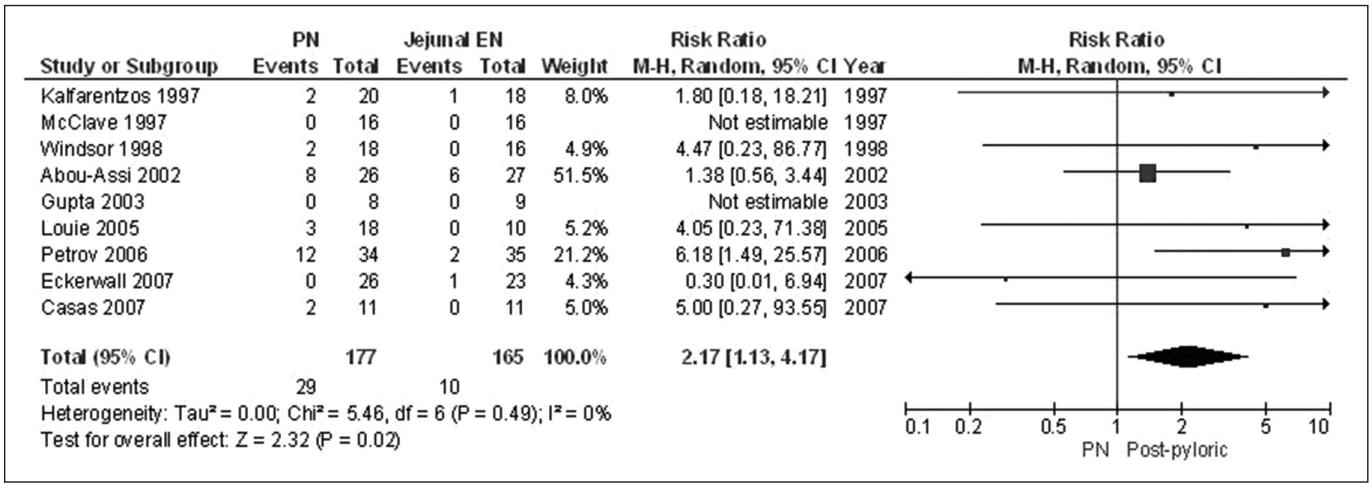


**Figure 12.** Parenteral nutrition (PN) vs enteral nutrition (EN) in severe acute pancreatitis, mortality.

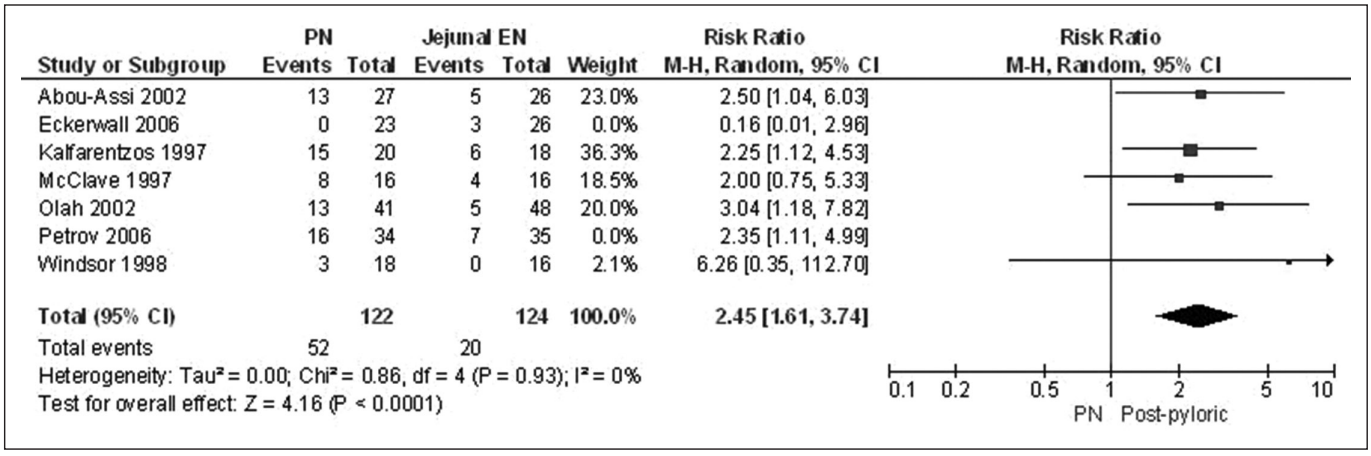


**Figure 13.** Parenteral nutrition (PN) vs enteral nutrition (EN) in severe acute pancreatitis, infections.

smaller RCTs, showed a reduction in infection (30.7% vs 43.0%, $p = 0.05$) and hospital LOS (–3.87 days; 95% CI, –6.20 to –1.54; $p < 0.001$) with use of probiotics compared to controls receiving only placebo (366). A larger RCT in 2013 by Wang involving 183 patients and two probiotic organisms (*Bacillus subtilus* and *Enterococcus faecium*) showed significant reductions in pancreatic sepsis (12.9% vs 21.3%, $p < 0.05$) and multiple organ dysfunction (11.3% vs 24.6%, $p < 0.05$), with no change in mortality in patients placed on EN with probiotic organisms compared to controls receiving EN alone, respectively (344).

A variety of probiotic organisms were used in these trials. In the absence of a commercial product, a recommendation for a specific dose and type of organism cannot be made at this time.

**Question:** When is it appropriate to use PN in patients with severe acute pancreatitis?

**L6. Based on expert consensus, we suggest that, for the patient with severe acute pancreatitis, when EN is not feasible, use of PN should be considered after one week from the onset of the pancreatitis episode.**

**Rationale:** For patients with severe acute pancreatitis, when EN is not feasible, timing of initiation of PN (and the choice between PN and STD) becomes an important issue. In an early randomized trial, Sax showed net harm from use of PN initiated within 24 hours of admission for patients with mild to moderate acute pancreatitis, with significantly longer hospital LOS than those patients randomized to STD (no nutrition therapy) (247). In contrast, a later study by Xian-Li in severe pancreatitis where PN was initiated 24–48 hours after "full liquid resuscitation," significant reductions in overall complications, hospital LOS, and mortality were seen when compared to STD (367). The design of this latter study may have led to a differential delay of several days in the initiation of PN, possibly after the peak of the inflammatory response (338).

## M. SURGICAL SUBSETS

### TRAUMA

**Question:** Does the nutrition therapy approach for the trauma patient differ from that for other critically ill patients?

**M1a. We suggest that, similar to other critically ill patients, early enteral feeding with a high protein polymeric diet be initiated in the immediate**

**post-trauma period (within 24 to 48 hours of injury) once the patient is hemodynamically stable.**

[**Quality of Evidence: Very Low**]

**Rationale:** Nutrition assessment with calculation of protein/energy requirements and determination of the route and timing of nutrition therapy for the trauma patient is similar to that for any critically ill patient in an ICU setting (see sections A and B). The metabolic response to trauma is associated with dramatic changes in metabolism, with utilization of lean body tissue to serve as gluconeogenic substrates and to support immune and repair functions (368). The hormonal milieu following trauma overrides the normal response to starvation where lean body mass is preserved, and instead promotes progressive loss of skeletal muscle (25). The physical unloading of muscle with inactivity, bed rest, and immobility is associated with decreasing muscle protein synthesis, mediated by multiple mechanisms, including calcium-dependent proteolysis, ATP-dependent proteolysis, lysosomal proteolysis, and free radical oxidative activation (369). These physiologic processes lead to deterioration of lean body mass in trauma and are compounded by the difficulty in providing nutrition therapy.

Timing of nutrient delivery in trauma may influence outcome. Although very few studies have been done in the past two decades, previous data support initiation of feeding into the GI tract once the trauma patient is adequately resuscitated (ideally within the first 24 hours). A recent meta-analysis by Doig et al, including three RCTs with 126 patients, reported a reduction in mortality when the patients were fed within this early time frame (370). The 2008 Trauma Nutrition Guidelines recommend starting nutrition within the first 24 to 48 hours via the gastric route, proceeding to post-pyloric access only with evidence of intolerance to gastric feeding (371). Often trauma patients require multiple trips to the operating room (OR) to address their injuries, leading to increased interruption of their nutrition therapy (372). This population may benefit from a volume-based feeding approach (see sections A and B).

Depending on the extent of the trauma, these patients may have prolonged stays in the ICU and should undergo timely nutrition reassessment. Energy requirements vary depending on numerous factors. Resting energy expenditure (REE) peaks over 4 to 5 days, but continues to remain high for 9 to 12 days (with some elevation in energy expenditure persisting for over 21 days) (373). Approximately 16% of total body protein is lost in the first 21 days, with 67% of that protein loss coming from skeletal muscle alone (373). Energy goals should be in the range of 20 to 35 kcal/kg/day, depending on the phase of trauma. Lower energy provision is suggested early in the resuscitative phase, with liberalization of energy delivery as the patient enters into the rehabilitation phase. Requirements for protein are similar for other ICU patients but may be at the higher end of the provision range, from 1.2 to 2g/kg/day (see section C4).

**Question:** Should immune-modulation formulas be used routinely to improve outcomes in a patient with severe trauma?

**M1b. We suggest that immune-modulating formulations containing arginine and FO be considered in patients with severe Trauma**

[**Quality of Evidence: Very Low**]

**Rationale:** The use of metabolic and immune-modulating formulations containing nutrients such as EPA, DHA, glutamine, arginine, and nucleic acids has been studied extensively in surgical populations. While several lines of evidence support use in trauma settings theoretically, documentation of outcome benefit is lacking. In a meta-analysis of 8 RCTS involving 372 trauma patients, use of immune-modulating formulas showed no difference in outcome with regard to infections, hospital LOS, or mortality compared to controls receiving standard enteral formulas (374). The optimal level and combination of these agents has yet to be determined.

## TRAUMATIC BRAIN INJURY

**Question:** Does the approach for nutrition therapy for the TBI patient differ from that of other critically ill patients or trauma patients without head injury?

**M2a. We recommend that, similar to other critically ill patients, early enteral feeding be initiated in the immediate post-trauma period (within 24 to 48 hours of injury) once the patient is hemodynamically stable.**

[**Quality of Evidence: Very Low**]

**Rationale:** Critically ill patients with TBI often have other injuries and organ damage, making them a heterogeneous population. In addition to the inconsistency of individual pathophysiologic immune and metabolic responses to trauma, the variability in management will also alter metabolic demands. The timing of initiating nutrition therapy has important outcome implications for the patient with TBI (368). An early Cochrane review demonstrated a trend toward better outcomes in patients who received early nutrition therapy (within 24–72 hours of injury) compared with those fed late (within 3–5 days of injury), regardless of route (early vs late EN, early vs late PN, early PN vs late EN, or both early EN vs PN) (375). A prospective study conducted by the Brain Trauma Foundation showed a significant relationship between the amount of early nutrition therapy provided and the risk of death (376). Optimal energy and protein intake following TBI predicted the mortality risk after 2 weeks, with a 30–40% decrease in mortality for every 10–kcal/kg/day increase in energy intake, achieving a plateau at approximately 25 kcal/kg/day.

Despite the fact that a Cochrane review and a meta-analysis by Wang showed no significant difference in outcome between routes of feeding (EN vs PN) in these patients, the committee suggests that EN is the preferred route of feeding in TBI, alluding to the beneficial effects of EN on immunologic responses and preservation of gut integrity seen in other patient populations in critical illness (see section M1a) (374, 376). Clinicians should be urged to start EN as soon as possible following resuscitation to maximize its benefits (but also have a low threshold for switching to PN with signs of EN intolerance).

Energy requirements are primarily influenced by the method of management of TBI. Actual measured energy expenditure can range from 100–200% of baseline-predicted REE, depending on variables such as use of paralytics and/or coma-inducing agents in early management (377). Protein requirements may be in the range of 1.5 to 2.5 g/kg/day (42, 378).

**Question:** Should immune-modulating formulas be used in a patient with TBI?

**M2b: Based on expert consensus, we suggest the use of either arginine-containing immune-modulating formulations or EPA/DHA supplement with standard enteral formula in patients with TBI.**

**Rationale:** Only one small trial in adults (40 patients) compared the use of immune-modulating formulations (containing arginine, glutamine, prebiotic fiber, and omega-3 fatty acids) with standard enteral formulations in TBI patients and demonstrated decreased infections (379). The use of EPA and DHA in the neurologically injured population has recently gained significant attention in accelerating recovery after TBI, and future studies may provide further support for this strategy (380).

## OPEN ABDOMEN

**Question:** Is it safe to provide EN to patients with an OA?

**M3a. Based on expert consensus, we suggest early EN (24–48 hours post-injury) in patients treated with an OA in the absence of a bowel injury.**

**Rationale:** The OA technique is often used in the management of abdominal contents following damage control laparotomy, when the abdominal cavity cannot be closed primarily without excessive intraabdominal pressure. This procedure is done primarily following abdominal trauma resuscitation and in cases of postoperative abdominal compartment syndrome. The OA technique is also useful in the management of gross peritonitis, tertiary peritonitis, or infected pancreatic necrosis when the abdomen is packed open. Risk factors that lead to consideration of use of the OA technique involve four distinct categories, including reduced abdominal wall compliance, increased intraluminal contents, increased contents within the abdominal cavity, and high-volume resuscitation with capillary leak. Patients may have an OA for days to weeks in some circumstances. The ideal outcome is timely definitive primary fascial closure (381, 382).

Many practitioners hesitate to enterally feed patients with an OA; however, retrospective data suggest that these patients can be fed safely, in the absence of bowel injury. A multicenter retrospective review of 597 patients with OA collected from 11 level 1 trauma centers reported providing EN to 39% of the patients prior to closure of the abdomen (383). Logistic regression analysis of the 307 patients with no bowel injury demonstrated that use of EN was associated with significant reductions in time to abdominal fascial closure, pneumonia, intraabdominal complications, and mortality compared to STD (all differences, $p \leq 0.02$) (383). In another retrospective review in which patients were grouped by timing of EN (early [≤ 4 days] vs late [> 4 days]), no differences in complications or mortality were found, but earlier fascial closure ($p < 0.02$) and less fistula formation ($p < 0.05$) was seen in the early-fed group (384). In a multicenter prospective cohort study of 100 patients with OA but no viscous injury, investigators compared patients who received early EN (within 36 hours of injury) to those who received late feeding (> 36 hours) and found early EN to be safe and independently associated with a reduction in pneumonia (OR = 0.32; 95% CI, 0.13–0.70; $p = 0.008$) (385).

**Question:** Do patients with OA have increased protein or energy needs?

**M3b. Based on expert consensus, we suggest providing an additional 15 to 30 grams protein per liter of exudate lost for patients with OA. Energy needs should be determined as for other ICU patients (see section A).**

**Rationale:** Patients with OA have essentially a large open wound equivalent to approximately 40% of total body surface. The peritoneum, which is exposed, produces a high-protein exudate that is essentially an ultra-filtrate of the serum. Consequently these patients lose a significant amount of protein. Protein losses are based on the volume of fluid lost in the drains and negative-pressure abdominal wound devices. A range of 15 to 30 grams of protein/L of exudate has been reported (386–388). Energy requirements are similar to those of other patients in a surgical or trauma ICU.

## BURNS

**Question:** What mode of nutrition support should be used to feed burn patients?

**M4a. Based on expert consensus, EN should be provided to burn patients whose GI tracts are functional and for whom volitional intake is inadequate to meet estimated energy needs. PN should be reserved for those burn patients for whom EN is not feasible or not tolerated.**

**Rationale:** When comparing EN to PN, patients randomized to EN tend to receive a smaller percentage of goal energy but have better outcomes. Although the data are mixed depending on burn model, body surface area of burn, and timing of delivery, EN has been shown to be associated with fewer infections and improved mortality compared to PN (389). In an early trial in burn patients evaluating the role of supplemental PN, Herndon showed that patients receiving both PN and EN had a higher incidence of infection and increased mortality compared to patients receiving EN alone (390). A clinical trial by Lam comparing early EN with PN in 82 burn patients found greater infectious morbidity (specifically pneumonia) and higher mortality in those patients randomized to PN, although energy needs were estimated by the Curreri formula, and PN patients received significantly more energy than those patients on EN (391). Providing early enteral feeding is associated with improved structure and function of the GI tract, as evidenced by significantly greater

contractility, less ischemia/reperfusion injury, and reduced intestinal permeability in burn patients receiving EN compared to those receiving PN (392).

**Question:** How should energy requirements be determined in burn patients?

**M4b. Based on expert consensus, we suggest that IC be used when available to assess energy needs in burn patients with weekly repeated measures.**

**Rationale:** As with other critically ill populations, IC is recommended as the most accurate means to assess energy needs. In situations where IC is not available, various published predictive equations have been used in the past, although their accuracy in burn patients is poor. In an evaluation of 46 predictive equations published between 1953 and 2000, Dickerson found none of them to be precise in estimating energy expenditure measured by IC in 24 patients with > 20% total body surface area burns (393). Changes in burn care, including early excision of nonviable tissue and grafting have reduced the hypermetabolic responses in energy expenditure that were reported over two decades ago (394).

**Question:** What is the optimal quantity of protein to deliver to patients with large burns requiring ICU care?

**M4c. Based on expert consensus, we suggest that patients with burn injury should receive protein in the range of 1.5–2g/kg/day.**

**Rationale:** In a crossover study conducted on six adults with a mean 70% total body surface area burn, Wolfe evaluated rates of whole-body protein synthesis and catabolism, and compared when protein was provided at 1.4 g/kg/day versus 2.2 g/kg/day (395). Study results showed that alterations in protein metabolism were unchanged between these two doses; however, the 2.2 g/kg/day dose led to an increased rate of protein catabolism (395). The 2001 American Burn Association guidelines and the 2013 ESPEN guidelines both recommended the provision of 1.5–2 g protein/kg/day for patients with burn injury (389, 396).

**Question:** When should nutrition support be initiated?

**M4d. Based on expert consensus, we suggest very early initiation of EN (if possible, within 4–6 hours of injury) in a patient with burn injury.**

**Rationale:** A nonrandomized trial of 20 burn patients, sequentially assigned to begin EN at < 5 hours versus > 48 hours after injury, showed that patients in the early EN group achieved positive nitrogen balance earlier, had lower urinary catecholamines and plasma glucagon levels over the first two weeks of hospitalization, and demonstrated significantly higher insulin levels compared to patients in the late group (397). Rates of bacteremia and hospital LOS were similar between groups (397). Peng compared early (within 24 hours of admission) to late (after 48 hours) provision of EN on infection rates, serum endotoxin, and TNF in 22 Chinese patients with total body surface area burns ranging from 50–80% (398). Significantly greater increases in serum TNF concentrations and serum endotoxin were shown in those patients who received delayed EN compared to patients who received early EN (398). Vicic compared very early EN via nasojejunal tube within 4 hours of injury to a normal oral diet in 102 patients with burns > 20% of total body surface area. Study patients in the early feeding group had a significantly lower incidence of complications ($p = 0.04$), pneumonia ($p = 0.03$), and sepsis ($p = 0.02$) than controls on the regular oral diet (399). Delivery of early EN may be facilitated by placement of a nasoenteric tube into the small bowel.

## N. SEPSIS

**Question:** Are patients with severe sepsis candidates for early EN therapy?

**N1. Based on expert consensus, we suggest that critically ill patients receive EN therapy within 24–48 hours of making the diagnosis of severe sepsis/septic shock as soon as resuscitation is complete and the patient is hemodynamically stable.**

**Rationale:** Studies specifically addressing nutrition therapy in the population of patients with severe sepsis/septic shock are lacking; this condition typically occurs in conjunction with numerous other critical illnesses, and studies to date reflect this heterogeneity. In the ICU setting it is widely believed that patients with severe sepsis and septic shock have GI dysfunction at a rate of up to 60% (70, 101, 400, 401). The combination of compromised GI function and hypermetabolism from an exaggerated acute phase response (402) likely leads to greater risk for malnutrition in this subpopulation of critically ill patients. Nutrition therapy, therefore, would be expected to offer a benefit for improved clinical outcomes (403).

Initiating EN within 24–48 hours of resuscitation or when hemodynamic stability is reached (defined as adequate perfusion pressure, stable doses of vasoactive drugs, stabilized or decreasing levels of lactate and metabolic acidosis, and mean arterial pressure of ≥ 60 mmHg) is associated with improved outcomes (404).

While no studies were found comparing early to delayed EN in patients with sepsis, on the basis of knowledge from general ICU patients of whom a proportion will have sepsis, we make our recommendation as in section B3.

In the review of studies involving a mix of critically ill patients, a meta-analysis by Simpson and Doig (59) found no benefit from early EN compared to PN, while a second meta-analysis by Peter et al (57) demonstrated that EN significantly reduced complication rates compared to PN (but had no effect on mortality). Both meta-analyses involved a mix of critically ill patients, with only a portion of patients with sepsis. A third meta-analysis by Gramlich et al (56) that again included a small subset of patients with sepsis reported a positive effect of EN on morbidity compared to PN.

**Question:** Should exclusive or supplemental PN added to EN providing < 60% of goal be used in the acute phase of severe sepsis or septic shock?

**N2. We suggest NOT using exclusive PN or supplemental PN in conjunction with EN early in the acute phase of severe sepsis or septic shock, regardless of their degree of nutrition risk.**

[**Quality of Evidence: Very Low**]

**Rationale:** There is a lack of studies addressing the use of exclusive or supplemental PN early in the acute phase of sepsis. The EPaNiC study by Casaer et al, in which one-fifth of patients had a sepsis diagnosis, reported that early supplemental PN added to hypocaloric EN resulted in longer hospital and ICU stays, longer durations of organ support, and a higher incidence of ICU-acquired infection than late supplementation (240). Because this patient population has an exaggerated stress response, and handles exogenous fuels poorly, the wide risk/benefit ratio with PN may be problematic (405).

Experience from two observational studies emphasizes the risk of early PN in this particular patient population. A prospective single-day point-prevalence trial by Elke focused specifically on nutrition support in 415 patients with severe sepsis and septic shock in German ICUs (406). Results showed that hospital mortality was significantly higher in patients receiving PN exclusively (62.3%) or mixed EN with PN (57.1%) compared to patients receiving EN exclusively (38.9%) ($p = 0.005$) (406). The finding of increased mortality with PN in this study population lends support to the use of EN for patients with severe sepsis and septic shock (406). In a secondary analysis, mortality at 90 days was lower with exclusive EN than EN plus PN (26.7% vs 41.3%, $p = 0.048$), as was the rate of secondary infections, renal replacement therapy, and duration of mechanical ventilation, despite energy intake and protein delivery being the least in the EN group during the first week of feeding (407). A second prospective observation of 537 patients with sepsis in the VISEP trial found that patients with EN alone had lower mortality than those with EN and PN (Elke 2013). The aggregated data from these two observational studies show a mortality benefit with EN (RR = 0.66; 95% CI, 0.5–0.88). However, as these patients were not randomized into EN versus PN, different levels of intestinal failure may bias the finding.

**Question:** What is the optimal micronutrient supplementation in sepsis?

**N3. We cannot make a recommendation regarding selenium, zinc and antioxidant supplementation in sepsis at this time due to conflicting studies.**

[**Quality of Evidence: Moderate**]

**Rationale:** The plasma concentration of several micronutrients with antioxidant capabilities is decreased in septic patients (408). Specifically, plasma selenium has been shown to be depressed in sepsis. Selenium is believed to be one of the most potent antioxidant agents in clinical settings (as well as zinc, ascorbic acid, vitamin E, and beta-carotene). The data from nine studies specifically addressing use of parenteral selenium that met our inclusion criteria (involving 1888 patients) were aggregated and demonstrated no difference in mortality (RR = 0.94; CI, 0.84–1.06, $p = 0.32$) (219, 220, 225, 226, 230, 231, 288, 409, 410). No difference was noted between study patients and controls with regard to ICU LOS, hospital LOS, or duration of mechanical ventilation. In contrast, a meta-analysis of 9 trials by Huang found a significant reduction in mortality (RR = 0.83; CI, 0.70–0.099; $p = 0.04$) with the use of higher doses of selenium in critical illness (411). The recommended optimal acute selenium dose for critically ill patients may range between 500 and 750 mcg/day, with ideal duration of supplementation being 1 to 3 weeks depending on severity of disease (412).

The magnitude of the inflammatory response following systemic infection is inversely correlated with plasma zinc levels, such that the lower the zinc level, the greater the likelihood for organ damage and mortality (413, 414). It is controversial whether lower concentrations reflect simply the acute phase response, relative deficiency, or reduced availability and sequestration by the body. While the optimal dose is not yet known, zinc supplementation in septic patients may help prevent innate immune suppression and risk of secondary infection (413).

**Question:** What are the protein and energy requirements for septic patients in the acute phase of management?

**N4. Based on expert consensus, we suggest the provision of trophic feeding (defined as 10–20kcal/hr or up to 500 kcal/day) for the initial phase of sepsis, advancing as tolerated after 24–48 hours to > 80% of target energy goal over the first week. We suggest delivery of 1.2–2 g protein/kg/day.**

**Rationale:** Wide variability in energy expenditure has been documented in advanced septic shock (415). For this reason, IC is recommended, if available, for baseline energy expenditure measurement, with follow-up measurement every 4 days. If IC is not available or patient conditions do not allow for it (e.g., $F_{IO2} > 0.60$), then simplistic weight-based equations (25 kcal/kg/day) or published equations may be used for predicting energy expenditure. In a cohort of patients with SIRS, sepsis, and septic shock, estimates from the Harris Benedict and Schofield published equations correlated well with energy expenditure measured by IC (all results within 8% of each other) (416).

Observational studies suggest that provision of a range of 25% to 66% of calculated energy requirements may be optimal (417). The strategy of providing trophic feeding, defined as up to 500 kcal/day, for the initial phase of sepsis, advancing after 24–48 hours to 60–70% of target over the first week may be most appropriate and optimal (403).

Protein requirements in sepsis are very difficult to determine. Current levels of 1.2–2 g/kg/day in sepsis are suggested, extrapolated from other ICU settings (91, 378).

**Question:** Is there any advantage to providing immune or metabolic-modulating enteral formulations (arginine with other agents, including EPA, DHA, glutamine, and nucleic acid) in sepsis?

**N5. We suggest that immune-modulating formulas not be used routinely in patients with severe sepsis.**

[**Quality of Evidence: Moderate**]

**Rationale:** Theoretically, use of arginine may pose a threat to the septic critically ill patient who is hemodynamically unstable by upregulating inducible nitric oxide synthase enzyme activity, increasing nitric oxide production, and causing greater hemodynamic instability and organ dysfunction (418). Several clinical trials in which arginine was supplied to septic patients reported no such adverse events (419). In fact, arginine may provide benefit in sepsis by promoting perfusion of tissues and increasing cardiac output.

In a multicenter RCT of 176 septic patients given a formula containing FO, arginine and nucleic acids, mortality (17 of 89 vs 28 of 87; $p < 0.5$), incidence of bacteremia (7 of 89 vs 19 of 87; $p = 0.01$) and incidence of nosocomial infection (5 of 89 vs 17 of 87; $p = 0.01$) were all reduced in the study group compared to the controls (171). The outcome benefits, though, were seen only in patients with moderate degree of critical illness (APACHE II scores 10–15), which limits the broader application of these results to all patients with sepsis. In a small RCT of 55 septic patients, Beale reported faster recovery in organ function as assessed by the Sequential Organ Failure Assessment, with use of an enteral formulation of glutamine, antioxidants, trace elements and butyrate (but no arginine) compared to use of a standard enteral formula (160). Similarly, an RCT of septic patients without organ dysfunction found that, when given early, prior to severe sepsis, an immune-enhancing enteral formula with omega-3 fatty acids, gamma-linolenic acid (GLA), and antioxidants reduced the development of organ dysfunctions, although it did not improve mortality or LOS (420). However, more recent RCTs comparing immune-modulating formulas with standard EN, of which a significant proportion of patients were septic, failed to show clear benefit in a MICU setting (see section E2).

## O. POSTOPERATIVE MAJOR SURGERY (SICU ADMISSION EXPECTED)

**Question:** Is the use of a nutrition risk indicator to identify patients who will most likely benefit from postoperative nutrition therapy more useful than traditional markers of nutrition assessment?

**O1. Based on expert consensus, we suggest that determination of nutrition risk (for example, NRS-2002 or NUTRIC score) be performed on all postoperative patients in the ICU and that traditional visceral protein levels (serum albumin, prealbumin, and transferrin concentrations) should not be used as markers of nutrition status.**

**Rationale:** While hypoalbuminemia has value as a valid preoperative prognosticator correlating to increased hospital LOS, infection, and mortality, it has limited usefulness in the postoperative setting. Traditional visceral proteins, including albumin, prealbumin, and transferrin are negative acute-phase proteins and, in the postoperative setting, reflect the dynamic and catabolic response to surgery, stress, injury, infection, or organ failure (renal, hepatic). They do not reflect the patient's nutrition status (20, 21). While hypoalbuminemia may have prompted the surgeon to initiate nutrition therapy in the first place, serum albumin concentrations would not be expected to change through the course of management until the stress metabolism abates. Thus, serum protein concentrations have no use postoperatively to measure adequacy of nutrition therapy (20, 21).

The NRS-2002 is an important predictor of postoperative complications, is validated for use in surgical patients, and is supported by evidence from RCTs (18). However, at the present time it is not clear whether aggressive nutrition therapy postoperatively benefits the high-risk patient any more than it does the low-risk patient as identified by the scoring system.

**Question:** What is the benefit of providing EN early in the postoperative setting compared to providing PN or STD?

**O2. We suggest that EN be provided when feasible in the postoperative period within 24 hours of surgery, as it results in better outcomes than use of PN or STD.**

[**Quality of Evidence: Very Low**]

**Rationale:** When feasible, EN is always the first choice over PN or STD. Two meta-analyses in the past by the same author showed that early aggressive use of the enteral route (either orally or by tube feeding) within 24 hours of surgery resulted in better outcome. In 2009, a meta-analysis by Lewis of 13 trials involving 1173 patients showed that absolute mortality was reduced from 6.8% to 2.4% with use of early EN postoperatively versus STD (RR = 0.42; 95% CI, 0.18–0.96; $p = 0.03$) (421). Based on very low-quality data, the 15 studies in the Osland meta-analysis, representing 1238 patients, demonstrated that complications (excluding nausea and vomiting) were reduced in the group receiving early EN (RR = 0.53; 95% CI, 0.33–0.86), but mortality and LOS were not significantly different (422).

EN is clearly not feasible postoperatively if there is evidence of continued obstruction of the GI tract, bowel discontinuity, increased risk for bowel ischemia, or ongoing peritonitis. EN may be feasible postoperatively in the presence of high output fistulas, severe malabsorption, shock, or severe sepsis if the patient remains stable for at least 24−36 hours. In these more complex situations, nutrition management must be individualized to allow for optimal care of the patient.

The need to achieve timely enteral access should be addressed when possible in the OR. Failure to plan for access through surgery or to develop and implement EN protocols postoperatively, often results in excessive use of PN. Additional measures that help promote tolerance and increase delivery of EN postoperatively include adequate resuscitation, correction of electrolytes and pH, appropriate (moderate) glucose control, and goal-directed conservative

fluid management (to decrease likelihood of over-hydration and bowel wall edema) (423).

**Question:** Should immune-modulating formulas be used routinely to improve outcomes in a postoperative patient?

**O3. We suggest the routine use of an immune-modulating formula (containing both arginine and fish oils) in the SICU for the postoperative patient who requires EN therapy.**

[**Quality of Evidence: Moderate to Low**]

**Rationale:** Specialized immune myeloid suppressor cells following insult, injury, or major surgery rapidly increase the levels of arginase 1, resulting in a relative arginine depletion (424, 425). An inadequate supply of arginine adversely affects T-cell function and causes subsequent immune suppression. The arginine deficiency may be severe enough to impact production of nitric oxide and negatively affect microcirculation. Formulas containing arginine and omega-3 fatty acids appear to overcome the regulatory effect of myeloid suppressor cells (425). In a dynamic fashion, the omega-3 fatty acids EPA and DHA displace omega-6 fatty acids from the cell membranes of immune cells, reducing systemic inflammation through the production of alternative biologically less-active prostaglandins and leukotrienes. EPA and DHA (FOs) have also been shown to downregulate expression of nuclear factor-kappa B, intracellular adhesion molecule 1, and E-selectin, which in effect decreases neutrophil attachment and transepithelial migration to modulate systemic and local inflammation. In addition, EPA and DHA help stabilize the myocardium and lower the incidence of cardiac arrhythmias, decrease incidence of ARDS, and reduce likelihood of sepsis (180, 181, 183, 426). Resolvins, produced endogenously from EPA substrates, have been shown to enhance phagocytic clearance of bacteria, reduce severity of inflammation, promote neutrophil apoptosis, and modulate neutrophil chemotaxis (427).

The benefit of immune-modulating formulas compared to standard formulas in surgical postoperative patients appears to be derived in part from the synergistic effect of FO and arginine, as both must be present in the formula to see outcome benefits. Timing appears to be important, and is influenced by the nutritional status of the patient. In well-nourished patients undergoing elective surgery, preoperative or perioperative provision of immunonutrition is more important for metabolic conditioning than for the nutritional value of the formula (and provision postoperatively is less effective) (428). In patients with poor nutrition status, the provision of immune-modulating formulas perioperatively (both before and after surgery) and postoperatively result in positive outcome benefits. The effect in these latter patients may be lost when immunonutrition is provided only preoperatively (422). In a meta-analysis of 35 trials, Drover showed that use of an arginine/FO-containing formula given postoperatively reduced infection (RR = 0.78; 95% CI, 0.64–0.95; $p = 0.01$) and hospital LOS (WMD = –2.23; 95% CI, –3.80 to –0.65; $p = 0.006$), but not mortality, compared to use of a standard enteral formula (429). In the same studies from the Drover meta-analysis overall data through the surgical period from 2780 patients, infections were reduced with arginine supplementation (RR = 0.59; 95% CI, 0.5–0.7), and mean LOS was shorter by 2.38 days (95% CI, –3.39 to –1.36), but mortality was not different (429). Similar findings were seen when the immune-modulating formula was given perioperatively (both before and after surgery). In a meta-analysis of 21 trials involving 2005 patients, Osland showed similar reductions in infection (OR = 0.61; 95% CI, 0.47–0.79; $p < 0.01$) and hospital LOS (WMD = –2.30; 95% CI, –3.71 to –0.89; $p = 0.001$) when immune FO/arginine-containing formulas were given postoperatively compared to standard formula (430). A reduction in total complications was seen with use of immune-modulating formulas given postoperatively (OR = 0.70; 95% CI, 0.52–0.94; $p = 0.02$), but a reduction in anastomotic dehiscence was seen only when the immune-modulating formula was given perioperatively. In another moderate-quality meta-analysis by Marimuthu of 26 RCTs representing 2496 patients undergoing open GI surgery, provision of immunonutrition postoperatively resulted in a decrease in postoperative infection (RR = 0.64; 95% CI, 0.55–0.74), a reduction in noninfectious complications (RR = 0.82; 95% CI, 0.71–0.95), and a shortening of hospital LOS by 1.88 days (95% CI, –2.88 to –0.0.84) compared to standard formulas (431). No statistical benefit was seen with regard to mortality (431).

**Question:** Is it appropriate to provide EN to a SICU patient in the presence of difficult postoperative situations such as OA, bowel wall edema, fresh intestinal anastomosis, vasopressor therapy, or ileus?

**O4. We suggest enteral feeding for many patients in difficult postoperative situations such as prolonged ileus, intestinal anastomosis, OA, and need of vasopressors for hemodynamic support. Each case should be individualized based on perceived safety and clinical judgment.**

[**Quality of Evidence: Low to Very Low**]

**Rationale:** Increasing surgical experience and RCTs are showing safety and efficacy of enteral feeding in difficult surgical conditions. Evidence that early EN makes anastomoses stronger with greater collagen and fibrin deposition and fibroblast infiltration have been shown in meta-analysis of early EN versus STD with no worsening effect on anastomotic dehiscence (RR = 0.75; 95% CI, 0.39–1.4; $p = 0.39$) with the direction favoring early feeding (422). In a 2009 meta-analysis by Lewis et al, a decrease in mortality was demonstrated (RR = 0.41; 95% CI, 0.18–0.93, $p = 0.03$) (421). Although this difference was lost in the 2011 meta-analysis by Osland et al (RR = 0.71; 95% CI, 0.32–1.56; $p = 0.39$), the direction again favored early feeding (422). Concern that postoperative EN would increase aspiration pneumonia has been shown not to be warranted, as there was no difference in pneumonia between early EN and STD (RR = 0.76; 95% CI, 0.36–1.58; $p = 0.46$) (421). Feeding in the 24 hours following surgery helps reduce postoperative ileus, attenuate dysmotility, and prevent bowel wall edema. Studies of EN provision on gut perfusion in patients on mechanical ventilation receiving vasopressor

agents to maintain hemodynamic stability have yielded inconsistent results; however, only a few cases of non-occlusive bowel necrosis have been documented. Therefore, the majority of ICU patients on a low, stable vasopressor dose may be fed into the stomach with close monitoring for signs and symptoms of intolerance (432). A query of a large ICU database for patients fed while on vasopressor agents found that, among the 707 who received early EN compared with the 467 who received late EN, the early EN group had a lower mortality (22.5% vs 28.3%, $p = 0.03$) (86). In an RCT of 78 patients with postoperative enterocutaneous fistulas following a Whipple procedure, use of early EN increased the likelihood of fistula closure compared to use of PN (60% vs 37%, respectively, $p = 0.043$) (433).

**Question:** When should PN be used in the postoperative ICU patient?

**O5. Based on expert consensus, we suggest that, for the patient who has undergone major upper GI surgery and EN is not feasible, PN should be initiated (only if the duration of therapy is anticipated to be ≥ 7 days). Unless the patient is at high nutrition risk, PN should NOT be started in the immediate postoperative period, but should be delayed for 5–7 days.**

**Rationale:** Consistent benefit of PN over STD (when EN is not feasible) has been seen in those patients undergoing major upper GI surgery (esophagectomy, gastrectomy, pancreatectomy, or other major re-operative abdominal procedures), especially if there is evidence of preexisting protein-energy malnutrition or high nutrition risk and the PN is provided under specific conditions (55, 252). In an earlier meta-analysis by Heyland, SICU patients saw a significant reduction in total complications with use of PN compared to STD (RR = 2.40; 95% CI, 0.88–6.58, $p < 0.05$), an effect not seen in MICU patients (252).

Early reports suggested that the benefits from the use of PN are seen when the PN was provided preoperatively for a minimum of 7–10 days and then continued through the postoperative period (434). The pooled data from a separate meta-analysis by Klein showed a significant 10% decrease in infectious morbidity with PN compared to STD therapy when used in this manner (435).

The beneficial effect of PN appears to be lost if given only postoperatively and, if given in the immediate period following surgery, is associated with worse outcome (435). Aggregation of data from nine studies that evaluated routine postoperative PN (243, 244, 246, 249–251, 436–438) showed a significant 10% increase in complications compared to STD (435). Because of the adverse outcome effect from PN initiated in the immediate postoperative period, Klein recommended delaying PN for 5–10 days following surgery if EN continues not to be feasible. The recommendation that an anticipated duration of feeding of ≥ 7 days is necessary to ensure a beneficial outcome effect from use of PN postoperatively is extrapolated from the studies on pre-/perioperative PN (434, 435). The findings of Klein in 1997 may have been influenced by practice patterns at the time, including hypercaloric feeding and poor glycemic control, both which are no longer the norm in most ICU settings. In another meta-analysis, patients (> 60% surgical admissions) who had a relative contraindication to early EN randomized to early PN vs STD, showed no difference in 60-day mortality, ICU or hospital LOS, or new infections between the two groups (242). In a situation in which emergency surgery is performed in a patient at high nutrition risk patient and the option of preoperative PN or EN does not exist, shortening the period to initiation of postoperative PN may be a reasonable strategy.

**Question:** Is advancing to a clear liquid diet required as the first volitional intake in the postoperative ICU patient?

**O6. Based on expert consensus, we suggest that, upon advancing the diet postoperatively, patients be allowed solid food as tolerated, and that clear liquids are not required as the first meal.**

**Rationale:** There is no physiologic basis for the argument that patients should be advanced to clear liquids first following surgery prior to ingesting a solid meal. While clear liquids may be swallowed more easily and, if isotonic, may leave the stomach more rapidly, they are more readily aspirated (439). In an early RCT of 241 patients who had undergone an abdominal operation, there were no significant differences in dietary intolerance between those receiving a clear liquid diet ($n = 135$) or a regular diet ($n = 106$) (440). In an RCT involving over 400 patients undergoing major GI surgery, Lassen showed that giving "normal food" on the first day postoperatively did not increase morbidity or mortality (441). Postoperative nausea occurs with the same frequency (approximately 20%) whether patients are advanced first to clear liquids or to solid meals, symptoms are transient, and there is no difference in postoperative complications (439). Early advancement to oral diet attenuates postoperative dysmotility, and the time to resume bowel function (as evidenced by passage of gas and stool with normal intake of food at will) may be shorter with early diet advancement (441).

## P. CHRONICALLY CRITICALLY ILL

**Question:** How should the chronically critically ill patient be managed with nutrition therapy?

**P1. Based on expert consensus, we suggest that chronically critically ill patients (defined as those with persistent organ dysfunction requiring ICU LOS > 21 days) be managed with aggressive high-protein EN therapy and, when feasible, that a resistance exercise program be used.**

**Rationale:** Due to advancements in medical and surgical critical care, a greater number of patients are surviving acute critical illness. A syndrome of chronic critical illness has emerged, characterized by prolonged mechanical ventilation (> 6 hours) and persistent organ dysfunction requiring lengthy ICU stays (≥ 21 days) and extreme symptom burden to the survivors (442). Placement of an elective tracheostomy is also a common delineation to identify chronic critical illness in

the literature. The chronically critically ill are more prevalent and require a different set of defined outcome parameters and nutritional goals. Despite the increasing prevalence, there are very few RCTs to guide nutrition therapy in this population at this time. Therefore, the Guidelines Committee provides only a brief introduction to the topic.

Moore helped further define the process of chronic critical illness in severely injured trauma patients as the "persistent inflammation, immunosuppression, and catabolism syndrome (443)." In a series of studies, genomic and clinical data from trauma patients and SICU patients with a prolonged course of recovery (greater than 14 days) demonstrated chronic inflammation and a maladaptive immune response that contributed to secondary nosocomial infections and severe protein catabolism (443, 444). Clinical features reflect the consequences of chronic critical illness, and include prolonged ventilator dependence, brain dysfunction, neuromuscular weakness, neuroendocrine and metabolic changes, muscle wasting, malnutrition, skin breakdown, and symptom distress (such as pain, anxiety, and depression) (445).

Recommendations for the chronically critically ill patient have surfaced from experienced institutions and are extrapolated from the critical care literature presented throughout this guideline. Protocol-based enteral feeding and glycemic control are primary recommendations, with emerging investigations for mobility protocols and endocrine therapy (such as treatment for bone resorption and vitamin D deficiency) (446–448).

## Q. OBESITY IN CRITICAL ILLNESS

**Question:** Do obese ICU patients benefit less from early EN in the first week of hospitalization, due to their nutrition reserves, than their lean counterparts?

**Q1. Based on expert consensus, we suggest that early EN start within 24–48 hours of admission to the ICU for obese patients who cannot sustain volitional intake.**

**Rationale:** The importance of providing early EN is no different for the obese critically ill patient than for their lean counterparts. Non-nutritional benefits of early EN are seen in critically ill patients, including obese subjects. (see sections B1 and B3) (449).

The high nutrition risk associated with a low BMI (< 18.5) is readily apparent to the clinician on physical examination. But malnutrition has been shown to occur at both ends of the spectrum of BMI, and it is much less apparent when the ICU patient is obese. Fifty-seven percent of hospitalized patients with a BMI > 25 show evidence of malnutrition. Patients with a BMI > 30 have an odds ratio of 1.5 for having malnutrition ($p = 0.02$) (450). The reasons for the surprisingly high rate of malnutrition in obese patients may stem in part from unintentional weight loss early after admission to the ICU and a lack of attention from clinicians who misinterpret the high BMI to represent additional nutritional reserves that protect the patient from insult.

Obese ICU patients are more likely than lean subjects to have problems with fuel utilization, which predisposes them to greater loss of lean body mass. Obese patients are at greater risk for insulin resistance and futile fuel cycling of lipid metabolism (increases in both lipolysis and lipogenesis). In an early study of trauma patients, Jeevanandam showed that obese subjects in a SICU derived only 39% of their REE from fat metabolism, compared to 61% in their lean counterparts (451). These patients derived a higher percentage of energy needs from protein metabolism, indicating greater potential for erosion of lean body mass.

The obesity paradox may contribute to clinicians' illusion that obese patients do not need nutrition therapy early in their ICU stay. The mortality curve for BMI is U-shaped, with the mortality highest in class III severely obese patients with BMI > 40 and in people with BMI < 25. Mortality is lowest in subjects with BMI in the range of 30–40 (class I and II obesity) (452, 453). This protective effect of moderate obesity is the obesity paradox. This counterintuitive effect has raised the question of whether BMI in this range (30–40) may not be the best indicator of risk (see section Q3). Nonetheless, the argument of the obesity paradox should neither lull clinicians into complacency nor be used as a rationale to withhold feeding from the obese ICU patient.

**Question:** What additional parameters should be addressed with a nutrition assessment in critical illness when the patient is obese?

**Q2. Based on expert consensus, we suggest that nutrition assessment of the obese ICU patient focus on biomarkers of metabolic syndrome, an evaluation of comorbidities, and a determination of level of inflammation, in addition to those parameters described for all ICU patients.**

**Rationale:** Besides the routine elements of assessment in critical illness (see section A), the nutritional assessment in the obese ICU patient should focus on determining actual, usual, and ideal weight. BMI should be calculated, class of obesity identified, and, if possible, waist circumference measured. Use of adjusted body weight is not recommended due to lack of validation studies and variable definition in the literature (454).

Biomarkers of metabolic syndrome should be evaluated, which include serum glucose, triglyceride, and cholesterol concentrations. Attention to blood pressure together with these markers should be used to establish whether the patient has evidence of metabolic syndrome.

The focused assessment should identify preexisting as well as emerging comorbidities, including diabetes, hyperlipidemia, obstructive sleep apnea, restrictive lung disease, cardiomyopathy with congestive heart failure, hypertension, thrombogenesis, and abnormal liver enzymes to suggest fatty liver disease. An assessment of the level of inflammation should be done by looking at CRP, erythrocyte sedimentation rate, and evidence of SIRS.

These factors represent additional comorbidities that make management more difficult, placing the patient at higher likelihood of complications resulting from nutrition therapy (e.g., volume overload, hyperglycemia). Clinical awareness of these

comorbidities leads to more timely intervention and adjustments in the nutrition regimen when these complications arise.

**Question:** What factors on assessment identify obese patients in the ICU to be at high risk?

**Q3. Based on expert consensus, we suggest that nutrition assessment of the obese ICU patient focus on evidence of central adiposity, metabolic syndrome, sarcopenia, BMI > 40, SIRS, or other comorbidities that correlate with higher obesity-related risk for cardiovascular disease and mortality.**

**Rationale:** Obesity increases the complexity of management of the critically ill patient and impacts most aspects of healthcare delivery. Obesity changes the pattern of comorbidities, increases the technical difficulties of management (attaining vascular access, performing tracheostomy, interpreting radiologic images, etc.), and alters drug metabolism. Obese ICU patients require special teams and highly specialized equipment to provide the basics of daily routine nursing care. Physiologic consequences of obesity negatively impact organ function, predisposing to congestive heart failure (reduced left ventricular contractility, decreased ejection fraction, and increased left ventricular end-diastolic volume), respiratory abnormalities (obstructive sleep apnea, higher airway resistance, decreased vital capacity, total lung capacity, and chest wall compliance), and hepatopathy (nonalcoholic fatty liver, steatosis, and cirrhosis) (454).

Critically ill patients who are obese experience more complications than their lean counterparts with normal BMI (455). Compared to lean patients in the ICU, increased morbidity is seen with all three classes of obesity, including greater incidence of infection, prolonged hospital and ICU LOSs, increased risk of organ failure, and longer duration of mechanical ventilation (456–459). While a lower mortality may be seen in the cohort of ICU patients with a BMI between 30 and 40 (452, 459, 460), those with a BMI > 40 clearly have worse outcome and higher mortality than ICU patients with BMI ≤ 40 (459).

The factors that put the obese critically ill patient at the highest risk are the presence of metabolic syndrome, sarcopenia and abdominal adiposity. Central, truncal, or abdominal adiposity may better characterize obesity-related inflammation and visceral fat deposition; thus, measuring waist circumference, if possible, may be more relevant to clinical outcomes than BMI (461). Increased abdominal adiposity is associated with insulin resistance, hyperglycemia, and metabolic syndrome, and is a risk factor for ICU complications (462). In a study by Paolini, the presence of central adiposity and metabolic syndrome was associated with an increased ICU mortality of 44%, compared to lean counterparts in the ICU, with a mortality of 25% (463). In a trauma study involving 149 SICU patients, 47% of whom were overweight or obese, the presence of sarcopenia was shown to be associated with worsened outcome. Mortality increased from 14% to 32%, and there were fewer ICU-free days and ventilator-free days in the presence of sarcopenia compared to those cohort patients in the SICU without sarcopenia (464).

**Question:** In adult obese ICU patients, does use of high-protein, hypocaloric feeding improve clinical outcomes compared with use of high-protein, eucaloric feeding?

**Q4. Based on expert consensus, we suggest that high-protein hypocaloric feeding be implemented in the care of obese ICU patients to preserve lean body mass, mobilize adipose stores, and minimize the metabolic complications of overfeeding.**

**Rationale:** Use of high-protein hypocaloric feeding in hospitalized patients with obesity is associated with at least equivalent (and possible better) outcomes as use of high protein eucaloric feeding (455). In a retrospective study of 40 obese critically ill surgical and trauma patients, use of high-protein hypocaloric EN was associated with shorter ICU stay, decreased duration of antibiotics, and fewer days of mechanical ventilation compared to use of a high-protein eucaloric diet (465). In one of two RCTs, use of a parenteral high-protein hypocaloric diet resulted in similar outcomes (hospital LOS and mortality) as a high-protein eucaloric PN regimen (269). Multiple observational trials have shown equivalent nutrition outcomes and nitrogen balance studies between the two types of diets (whether by EN or PN) (455). Low intake of protein in combination with a hypocaloric diet may worsen mortality in obese patients, as was shown in a prospective observational cohort study of adult ICU patients with class II obesity (BMI 35–39.9) (466).

**Question:** In adult obese ICU patients, what are the appropriate targets for energy and protein intake to achieve nitrogen equilibrium and meet metabolic requirements?

**Q5. Based on expert consensus, we suggest that, for all classes of obesity, the goal of the EN regimen should not exceed 65–70% of target energy requirements as measured by IC. If IC is unavailable, we suggest using the weight-based equation 11–14 kcal/kg *actual body weight*/day for patients with BMI in the range 30–50 and 22–25 kcal/kg *ideal body weight*/day for patients with BMI > 50. We suggest that protein should be provided in a range from 2.0 g/kg ideal body weight/day for patients with BMI 30–40 up to 2.5 g/kg ideal body weight/day for patients with BMI ≥ 40.**

**Rationale:** Achieving some degree of weight loss may increase insulin sensitivity, facilitate nursing care, and reduce risk of comorbidities. Providing 60–70% of caloric requirements promotes steady weight loss. A retrospective study by Choban indicated that provision of protein at a dose of 2.0 g/kg ideal body weight/day was insufficient for achieving neutral nitrogen balance when BMI is greater than 40 (269). Infusing protein at a dose of 2–2.5 g/kg ideal body weight/day should approximate protein requirements, preserve nitrogen balance, and allow for adequate wound healing. Nitrogen balance was similar with these levels regardless of whether energy intake was hypocaloric or eucaloric (269, 465, 467). Use of BMI and ideal body weight is recommended for these calculations, while use of adjusted body weight should be avoided. Protein recommendations should be adjusted using nitrogen balance studies with a goal of achieving nitrogen equilibrium if possible.

Published weight-based predictive equations are less accurate in the overweight and obese ICU population (468). The reduced accuracy of predictive equations is related to many non-static variables affecting energy expenditure in the critically ill patient, such as weight, medications, treatments, and body temperature. In obese, heterogeneous adult ICU patients, none of the published predictive equations performed within 10% of measured REE using the Deltatrac or MedGem indirect calorimeters, leading investigators to recommend IC for this patient population (33, 468, 469). When IC is unavailable, simplistic weight-based equations provide a sufficient estimate, representing 65–70% of measured energy expenditure, using 11–14 kcal/kg actual body weight/day for BMI 30–50 and 22–25 kcal/kg ideal body weight/day for BMI > 50 (using the equation for actual body weight will over-predict this value when BMI > 50) (470).

**Question:** What indications, if any, exist for use of specialty enteral formulations for adult obese ICU patients?

**Q6. Based on expert consensus, we suggest that, if available, an enteral formula with low caloric density and a reduced NPC:N be used in the adult obese ICU patient. While an exaggerated immune response in obese patients implicates potential benefit from immune-modulating formulas, lack of outcome data precludes a recommendation at this time.**

**Rationale:** Most enteral formulas have a high NPC:N, which necessitates the routine addition of protein supplements in an ICU setting. For obese critically ill patients, these formulas are entirely inadequate in design to provide a high-protein hypocaloric diet. For example, provision of 22–25 calories/kg ideal body weight/day with 2.0–2.5 g/kg ideal body weight/day represents a 30–50:1 NPC:N, suggesting that a formula with a much lower NPC:N is needed for obese critically ill patients. Because fluid requirements may be higher in obesity, low-energy dense formulas (1 kcal/mL) may be more appropriate (454).

A baseline low-grade SIRS together with insulin resistance and metabolic syndrome may predispose obese patients to exaggerated immune responses when illness or injury necessitates admission to the ICU (471). Intuitively, obese ICU patients might then benefit from various pharmaconutrient immune-modulating agents provided in a formula or as a supplement (472). However, due to lack of outcome data, a recommendation for their use cannot be made at this time.

**Question:** What are appropriate monitors to follow for the obese critically ill patient receiving early EN?

**Q7. Based on expert consensus, we suggest additional monitoring to assess worsening of hyperglycemia, hyperlipidemia, hypercapnia, fluid overload, and hepatic fat accumulation in the obese critically ill patient receiving EN.**

**Rationale:** Because of the intentional permissive underfeeding of calories in the obese ICU patient, it is imperative to assess nutritional efficacy and follow intake and output, confirming receipt of the prescribed high-protein hypocaloric regimen. Repeating IC measurements and/or tracking the cumulative energy deficit to maintain energy provision at 65–70% of REE is important.

Obese ICU patients on nutrition therapy should be monitored to avoid worsening of hyperglycemia, hyperlipidemia, hypercapnia, fluid overload, and hepatic fat accumulation, all of which may be present upon admission. The higher incidence of diabetes mellitus seen in obesity is magnified by post-receptor insulin resistance and accelerated gluconeogenesis induced by critical illness. The challenges of glycemic control are further complicated by overly aggressive nutrition support and by medications administered in the ICU setting such as catecholamines, exogenous glucocorticoids, and adrenergic agents (473). Tolerance of nutrition therapy may be monitored by frequent serum glucose concentrations (particularly for the patient with diabetes or stress-induced hyperglycemia), serum triglyceride concentrations (especially if receiving IVFE), arterial blood gases for mechanically ventilated patients (in order to detect nutrition-related hypercapnia or to assess readiness for weaning), fluid status to detect volume overload, serial serum electrolytes, and blood urea nitrogen for patients receiving hypocaloric, high-protein nutrition support (especially in the setting of compromised renal function).

**Question:** Does the obese ICU patient with a history of bariatric surgery or other malabsorptive condition require any additional supplementation of micronutrients when starting nutrition therapy?

**Q8. Based on expert consensus, we suggest that the obese ICU patient with a history of bariatric surgery receive supplemental thiamine prior to initiating dextrose-containing IV fluids or nutrition therapy. In addition, evaluation for and treatment of micronutrient deficiencies such as calcium, thiamin, vitamin $B_{12}$, fat-soluble vitamins (A, D, E, K), and folate, along with the trace minerals iron, selenium, zinc, and copper should be considered.**

**Rationale:** Patients who have undergone procedures such as sleeve gastrectomy, gastric bypass, or biliopancreatic diversion (with or without duodenal switch) have an increased risk of micronutrient deficiency. Evaluation and repletion of these deficiency states is warranted in the critically ill patient. Nutrition and metabolic derangements are more commonly seen with malabsorptive procedures, such as biliopancreatic diversion and very long limb Roux-en-Y gastric bypass. It is critical to identify a possible thiamine deficiency prior to administration of dextrose-containing IV fluids. In addition, a daily multivitamin with iron and vitamin $B_{12}$, along with calcium and vitamin D supplementation, is encouraged. Currently, there is no consensus on the optimal regimen for micronutrient supplementation (474). Once normalized, serum micronutrient levels should be monitored annually.

## R. NUTRITION THERAPY END-OF-LIFE SITUATIONS

**Question:** What is the role of artificial nutrition and hydration (ANH) in end-of-life situations?

**R1. Based on expert consensus, we suggest that ANH is NOT obligatory in cases of futile care or end-of-life situations. The decision to provide ANH should be based on evidence, best practices, clinical experience and judgment, effective communication with the patient, family and/or authorized surrogate decision-maker, and respect for patient autonomy and dignity.**

**Rationale:** Neither EN nor PN has been defined to include basic IV hydration, but in the ethics literature, it is often considered part of the same treatment type, referred to as ANH (475).

Dehydration and poor oral intake are well tolerated and generate little symptomatology in the vast majority of terminally ill patients, although a reduction in patient volitional intake is often a source of anxiety for care providers and families (476, 477). This anxiety should be anticipated and accurately addressed by the caregiver to help dispel misperceptions and decrease emotional distress. Cultural, ethnic, religious, or individual patient issues may supersede scientific evidence, in some circumstances necessitating the delivery of ANH. In this unfortunate situation, there has been little data to clearly define the benefits and harm of ANH in terminally ill patients (478). ANH does not improve outcomes in terminally ill patients and may at times increase patient distress (see HPNA Position Statement 2011 at http://www.hpna.org/DisplayPage.aspx?Title = Position%20Statements, accessed on November 9, 2014) (476). Though high-quality studies in terminally ill patients are difficult to perform, Bruera published a well-designed multicenter double-blind RCT concluding that IV hydration, 1 liter per day, did not improve quality of life, symptoms, or survival, compared to placebo (479).

Scientific, ethical, and legal perspectives indicate that there is no differentiation between withholding or withdrawing ANH (475). Numerous professional organizations have published guidelines or position statements to help guide healthcare providers on the ethical considerations involved in deciding whether to initiate, continue, or forgo ANH (475, 480). Several themes remain constant: clear communication between providers, patients, family, or surrogate decision-makers; respect for dignity and patient autonomy; setting realistic goals of therapy; involvement of an interdisciplinary ethics committee or panel consultation when issues cannot be resolved; continuing care until any conflict around ANH is resolved; transferring care to equally qualified, willing practitioners if conflict cannot be resolved; and at no time should patients or families feel abandoned.

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