

volume of EN infused, reduce GRVs, and decrease the incidence of VAP (compared with placebo).<sup>132</sup> 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 1 study to reduce the incidence of pneumonia from 23% to 5%, comparing supine with semirecumbent position, respectively ( $P = .018$ ).<sup>140,141</sup> Optimizing oral health with chlorhexidine mouthwash twice daily was shown in 2 studies to reduce respiratory infection and nosocomial pneumonia in patients undergoing heart surgery.<sup>142,143</sup> While studies evaluating the use of chlorhexidine in general ICU populations have shown little outcome effect, 2 studies in which chlorhexidine oral care was included in bundled interventions showed significant reductions in nosocomial respiratory infections.<sup>144,145</sup> 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.<sup>104,146</sup>

**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 (eg, methylene blue, blue food coloring) interferes with other colorimetric tests, such as Hemocult, Gastrocult, and pH testing.<sup>147,148</sup> High-dose methylene blue may have effects similar to blue food coloring regarding mitochondrial toxicity and interference with oxidative phosphorylation.<sup>147</sup> Blue food coloring, an insensitive marker for aspiration, was shown to be associated with mitochondrial toxicity and patient death.<sup>147,149</sup> 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 receiving EN.<sup>150</sup> 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.<sup>151</sup>

**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.<sup>152</sup> 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.<sup>153,154</sup>

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*.<sup>152</sup> 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.<sup>155</sup> Most episodes of nosocomial diarrhea are mild and self-limiting.<sup>156</sup>

Assessment of diarrhea should include an abdominal examination, quantification of stool, stool culture for *Clostridium 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.<sup>157</sup>

## 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- 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), semielemental, 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.<sup>158</sup> Disease-specific and severe fluid-restricted formulas may be rarely used in a small percentage 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.<sup>159</sup>

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),<sup>160,161</sup> Heyland et al showed only a reduction in hospital LOS (WMD = -0.47; 95% CI, -0.93 to -0.01;  $P = .047$ ), specifically in a MICU.<sup>162</sup> 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),<sup>52,160,163-177</sup> infectious complications (9 studies, 1522 patients),\* or hospital LOS (11 studies, 147 patients).\*\*

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 anti-inflammatory lipid profile (eg, 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 anti-inflammatory 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 g of protein daily compared with study patients (20 vs 4 g of protein, respectively).<sup>179</sup> Furthermore, comparison with a commercial formula high in omega-6 fatty acids increased the risk for the effect of a negative control in 2 of the studies.<sup>180,181</sup> Aggregating all trials<sup>179-184</sup> 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 with 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 anti-inflammatory lipid profile in ARDS/ALI patients be used routinely until further data are available.

\*References 52, 165, 167, 168, 171-173, 175, 178

\*\*References 52, 65, 163, 167-171, 174, 177, 178

*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 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 semielemental 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.<sup>185,186</sup>

While mixed-fiber formulas have been shown to reduce diarrhea in critically ill patients receiving a broad spectrum of antibiotics,<sup>187</sup> 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.<sup>187</sup> 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.<sup>188</sup>

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.<sup>154</sup> 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 additive (eg, fructo-oligosaccharides [FOSs], inulin) be considered for routine use in all hemodynamically stable MICU/SICU patients placed on a standard enteral formulation. We suggest that 10–20 g 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.<sup>189–191</sup> Prebiotics (eg, 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 that those with feeding intolerance (14 patients) had significantly lower amounts of anaerobes, including *Bifidobacteria*, and higher amounts of *Staphylococcus* than those patients without feeding intolerance (49 patients;  $P \leq .05$ ). Patients with feeding intolerance were shown to have a higher rate of bacteremia (86% vs 18%;  $P < .05$ ) and greater mortality (64% vs 20%;  $P < .05$ ).<sup>192</sup> 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 g/d divided over 24 hours.<sup>193</sup>

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 (eg, 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.<sup>191</sup> 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.<sup>153,194–197</sup> Of the 4 trials that included diarrhea as a study end point, 3 showed significant reductions in diarrhea in critically ill patients.<sup>153,195,196</sup> No differences in duration of mechanical ventilation, ICU LOS, or MOF were reported.<sup>188,195</sup> An older prospective double-blind RCT in patients with severe sepsis and septic shock found that the mean frequency of