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# Advances in nutrition for the surgical patient

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## Introduction

Nutrition is an undeniably important component of the optimal care of the surgical patient. Therefore, it is incumbent that surgeons stay abreast with emerging developments in this field, critically interpret the literature, and correctly apply new evidence to their clinical practice. In this review, we provide a comprehensive summary and synthesis of the rapidly evolving nutritional literature, starting from the preoperative assessment and extending through the postoperative period. We introduce the concept of "prehabilitation," review the controversy surrounding gastric vs postpyloric enteral feeding, provide evidence-based recommendations for nutrition in pancreatitis, analyze the rationale of using immune-modulation pharmaconutrients, explore the emerging interest in protein, review the evidence supporting early postoperative nutrition, provide an update on modern-day parenteral nutrition (PN), discuss new developments in parenteral lipid formulations, and end by dissecting the recently published high-profile critical care nutrition studies.

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## Prehabilitation before elective surgery

"Prehabilitation" describes the strategy of increasing the functional capacity of an individual prior to a stressor to improve tolerance and recovery.[1,2] This is especially relevant in cases of major surgery where preoperative optimization through exercise, nutrition, and lifestyle changes have been shown to improve functional measures after surgery.[3]

Nutritional prehabilitation presents an opportunity to optimize an important modifiable preoperative risk factor. However, studies have yet to show a consistent relationship between nutritional prehabilitation and traditional postoperative outcomes, likely because of significant heterogeneity in nutritional route, dose, duration, and patient selection.[4] Although some studies show a reduction in postoperative complications in malnourished patients,[5–7] others show no benefit when applied to well-nourished patients.[8,9] Variable prehabilitation regimens may also explain the discrepant results. The minimum intensity and duration of treatment and the most sensitive and appropriate endpoints to measure are currently unknown.

There is a clear rationale for considering nutritional prehabilitation. The prevalence of malnutrition in surgical patients is nontrivial, with up to 60% of patients undergoing elective surgery identified to be at risk for malnutrition.[10–12] It is indisputable that malnourished patients have increased hospital complications, length of stay (LOS), hospital costs, and mortality when compared to well-nourished patients.[13,14] Targeted interventions for these high-risk surgical patients would thus have significant impact on patient outcomes and hospital costs.

In order to identify patients at risk, screening programs must be an established part of the preoperative evaluation. As an example, the Prognostic Nutritional Index has been shown to predict overall survival and cancer-specific survival in cancer patients,[15] and can be used as a tool to determine the optimal timing of surgery. Other assessments include Subjective Global Assessment (SGA), Nutritional Risk Screening (NRS), Reilly's NRS, and Nutritional Risk Index. All of these assessments stratify patients into 3 categories of nutritional risk. The SGA assesses the medical history including weight change, dietary intake change, gastrointestinal (GI) symptoms, and changes in functional capacity along with the physical examination findings (eg, loss of subcutaneous fat, muscle wasting, edema, and ascites) to determine if a patient is considered well-nourished, moderately malnourished, or severely malnourished.[16] The NRS evaluates undernutrition and severity of disease across 4 domains with a score that dictates whether patients should receive oral supplementation or artificial feeding.[17] Reilly's NRS score factors degree and duration of weight loss, body mass index (BMI) for adults or percentile charts for children, food appetite, intake and retention, and stress-inducing medical conditions.[18] The Nutritional Risk Index uses recent weight loss, usual weight, and serum albumin concentration to calculate a score to indicate if a patient is well-nourished, moderately malnourished, or severely malnourished. Preoperative parameters of $\geq$10% weight loss and low serum albumin in elderly patients have also been shown to predict postoperative outcome.[19]

Despite the widespread acknowledgment of the significance of nutritional status in the surgical patient population, comprehensive preoperative nutritional screening is rare.[20] Ideally, full nutritional assessments and the initiation of interventions should occur several weeks prior to elective surgery.[21] Unfortunately, the reality is that preoperative nutritional screening is underutilized, malnutrition is often misclassified, and the majority of at-risk patients do not receive nutritional therapy.[22,23] Although there is a strong impetus to operate in an expeditious fashion, especially for time-sensitive disease such as localized cancer, the rush to operate must be balanced against the risk of bringing a malnourished and deconditioned patient to major surgery. A recent study demonstrated that a multimodal prehabilitation intervention in nonmetastatic esophagogastric cancer is feasible without significantly delaying operation and results in clinically significant improvements in functional outcome.[24]

The earliest and simplest prehabilitation programs focused on providing PN to severely malnourished patients undergoing elective operations. In these highly selected patients, several randomized trials have consistently demonstrated that adequate perioperative PN (7-10 days preoperatively and 3-9 days postoperatively) resulted in significantly decreased incidence of postoperative complications.[25,26] The most famous trial, the Veterans Affairs (VA) Total PN (TPN)

Cooperative Study, published more than a quarter century ago, demonstrated that borderline or mildly malnourished patients suffered *increased* infectious complications when randomized to PN.[26] This dampened the initial enthusiasm for perioperative nutritional "prehabilitation," but it should be noted that the caloric prescriptions in this trial were very high, and there was no mention of glycemic control. Thus, it is likely that the morbidity observed was likely due to the manner in which PN was prescribed, rather than the PN itself. Since the landmark "VA TPN" trial, subsequent studies have explored using enteral nutrition (EN), immunonutrition, and multimodal bundles of varying preoperative duration in a diverse range of patient populations.

Preoperative carbohydrate treatment is frequently incorporated as part of multimodal Enhanced Recovery after Surgery (ERAS) pathways (see also "Early enteral feeding after surgery—what is the evidence?" Section) to mitigate the transient postoperative insulin resistance seen after elective surgery. This reduction in insulin sensitivity leads to hyperglycemia via increased glucose production, decreased tissue uptake of glucose, and decreased glycogen synthesis. Postoperative hyperglycemia is associated with increased surgical site infections and other complications.[27,28] The original nil per os (NPO) after midnight for solids and liquids alike was born from concerns of aspiration during intubation, but may partially account for the catabolic response after the stress of an operation. In addition to reducing thirst and increasing feelings of well-being by allowing patients scheduled for elective surgery to have liquids up until 2 hours prior to surgery, relative changes in insulin resistance following elective cholecystectomy,[29] colorectal surgery,[30] and arthroplasty[31,32] are reduced in patients receiving preoperative carbohydrate-rich beverage compared to placebo. Current fasting guidelines[33,34] and evidence of insulin resistance avoidance support consumption of carbohydrate-containing clear liquids up to 2 hours prior to surgery.[35,36] Development of clear liquid carbohydrate-rich beverages can help bring patients into the operating room in a fed state.[1] Preoperative nutrition supplement with carbohydrate-rich oral nutrition attenuated, but did not prevent, postoperative insulin resistance after surgery for rectal cancer.[37] Additionally, short courses of preoperative immune-modulating formulas using a combination of arginine, $\omega$-3 fatty acids, and other nutrients have been associated with improved surgical outcomes.[38]

It is unclear if multimodal prehabilitation bundles synergistically improve outcomes beyond unimodal bundles. In addition to nutritional counseling and prescription, multimodal prehabilitation bundles such as the Michigan Surgical and Health Optimization Program and the American College of Surgeons Strong for Surgery Program include aerobic and resistance exercise, smoking cessation, pulmonary rehabilitation, and stress reduction, and have been shown to be clinically beneficial and cost-effective when compared to postoperative rehabilitation treatments.[39–42] In two trials using 4-week preoperative whey protein supplementation within a bundle of care, trimodal prehabilitation improved functional recovery at 8 weeks postsurgery while protein supplementation in the unimodal models did not demonstrate a significant improvement in postoperative function.[39,41,43] A recent study by Howard and colleagues demonstrated fewer postoperative complications and decreased hospital cost after colectomy in patients who underwent formal multimodal prehabilitation when compared to patients who did not undergo prehabilitation. This prehabilitation program was comprised of physical activity, pulmonary rehabilitation, nutritional optimization, and stress reduction.[40] In a prospective, multicenter cohort study of 1085 patients, Jie and colleagues demonstrated in 102 high-risk patients (NRS >5) that a multimodal prehabilitation protocol (nutrition, exercise, glycemic control, and smoking cessation) decreased the incidence of major complications, at 50.6% vs 25.6% ($P$= 0.008), and the hospital LOS decreased from 17 days to 13 days ($P$= 0.018).[44] However, there was no identified benefit in patients considered low risk with NRS <5. This is one of the few trials to stratify patients by risk.

Special populations benefit from optimization of disease burden. Elevated markers of glycemic control such as hemoglobin A1c have been associated with increased rates of postoperative surgical site infections.[27,28] Likewise, preoperative weight loss in patients with obesity has been shown to reduce postoperative surgical site infections and pulmonary complications. Preoperative iron supplementation demonstrated a trend toward decreased transfusions in some studies[45–47] but no benefit in others.[48] Smoking cessation is well-known to be associated

with decreased postoperative complications such as wound infections and respiratory complications.[49–51] The overall theme is that preoperative nutritional interventions, whether enteral or parenteral, are most beneficial in malnourished surgical patients[52–54] and likely neutral in well-nourished patients[8,9]; the addition of immune-enhancing pharmaconutrients is of uncertain benefit (see also "Advances in immunonutrition in the surgical patient" section)[6,7,55–60]; and multimodal bundles are probably more effective than single modality interventions.

In summary, preoperative nutritional programs should aim to replenish nutritional stores, optimize metabolic reserve, prepare for stress-induced catabolism, and enhance immune response. We recommend formal universal preoperative nutritional risk assessment using validated tools to guide the intensity of nutritional support prior to elective operations, preferably in the context of a multimodal prehabilitation program that may include exercise, nutritional and immunonutritional supplementation, glycemic control, hemoglobin optimization, smoking cessation, and anxiety management. Compared to 6 or greater hours of preoperative fasting, a carbohydrate drink two hours prior to elective surgery may lead to better postoperative glucose control, reduction in insulin resistance, enhanced return of bowel function, and improvements in postoperative food intake. Although it is usually advantageous to resect a malignancy as soon as possible, determination of the optimal timing of surgery should nonetheless consider the benefits of prehabilitation on postoperative outcomes.

## Gastric vs postpyloric feeding

EN is frequently used to provide specialized nutritional therapy to surgical patients, particularly those who are critically ill. There is a general consensus that enteral is preferable to PN for this support, although controversies exist regarding the timing, amount, and type of EN. An additional area of contention to be discussed here relates to where nutrients should be delivered into the GI tract: can surgical patients safely receive administered enteral formulas into the stomach, or should they receive nutrients directly into the small bowel using a postpyloric feeding tube? It has been purported that postpyloric feeding allows patients to achieve full nutritional support more rapidly and decreases the risk of aspiration and consequent pneumonia.[61] However, proponents of gastric feeding cite data affirming the safety and efficacy of prepyloric EN and note that additional technical resources are often needed to successfully place postpyloric feeding tubes.[61]

A discussion of prepyloric vs postpyloric EN might best be approached by looking at the much broader issue of postoperative nutritional management. Disturbances of postoperative GI motility, frequently described as postoperative "ileus," are common following surgical procedures, particularly abdominal surgery. Recovery from this impaired motility is not uniform within different portions of the GI tract. Typically, small intestinal motility is characterized by rapid recovery within less than 24 hours, whereas recovery of gastric motility is delayed, requiring 48 hours or more. The colon is the last portion of the GI tract to recover.[62] Therapeutic agents, such as opioid analgesics, may further interfere with GI motility. The pathophysiology of impaired gastric motility in the postoperative patient is complex but includes early neurogenic influences following the operative procedure and subsequent inflammatory components brought about by activation of host defense mechanisms.[63,64]

Although early oral or EN into the stomach appears to be feasible, safe, and potentially beneficial for some surgical patients, it is unclear if data obtained from these studies can be extrapolated directly to all surgical patients receiving EN. Many patients requiring artificial nutrition therapy are critically ill, being treated for emergent conditions such as trauma or intraabdominal infection, have significant derangements of physiological functions due to shock, or may have significant pre-existing medical comorbidities. Thus, these patients do not resemble the types of patients undergoing elective surgical procedures enrolled in ERAS protocols. The assumption that any surgical patient can receive EN via the gastric route is not any more valid than the assumption that all gastric feedings need to be avoided in all surgical patients. To better ad-

dress the question of gastric vs intestinal feeding, it is appropriate to review studies performed in critically ill surgical patients.

Unfortunately, there are relatively few data specifically addressing this group of patients. Evidence examining the benefits and risks of prepyloric and postpyloric feeding comes from at least 24 English-language clinical trials.[65–88] The vast majority of these trials compared various outcomes in undifferentiated critically ill adult patients receiving gastric feedings vs those receiving duodenal or jejunal feedings. A single study was carried out in postoperative patients who had undergone resections for colorectal malignancies.[81] There were 5 studies in trauma patients[65,68,69,71,85]: 4 were restricted to patients with traumatic brain injury (TBI), and 3 studied patients with severe acute pancreatitis.[80,82,88]

Most of these studies were relatively small and underpowered; the largest reported results on 180 patients.[86] The quality rating of many of these studies was low to moderate, primarily because of inadequate blinding. To be fair, blinding is quite difficult in studies such as these in which different interventions are employed, in this case placement and utilization of gastric or intestinal access tubes for nutritional therapy. Additional problems with interpreting these data were that the time to initiation of nutritional support was not necessarily the same in the patients fed prepylorically vs those fed postpylorically and that different types of nutritional formulas may have been employed.

Given the limited power of most of these studies, a number of meta-analyses have been performed to better assess the efficacy and complications of gastric vs postpyloric feeding. Meta-analyses published since 2013 are summarized in Table 1.[61,89–95] Most of these meta-analyses included a heterogeneous population of critically ill and sometimes other patients, and did not focus specifically on surgical patients. One meta-analysis was limited to trauma patients, the majority of whom had TBIs.[94] Another was directed at patients with severe acute pancreatitis, who were not necessarily treated surgically.

Overall, the results of these meta-analyses have been relatively consistent: most found a significant decrease in the incidence of pneumonia in patients receiving postpyloric feedings compared to those receiving gastric feedings. In addition, a small but significant increase in nutrient delivery was noted in patients receiving postpyloric EN. However, this did not translate into a decrease in overall mortality or a decrease in the duration of intensive care unit (ICU) stay or of mechanical ventilation. Moreover, GI complications, including aspiration, did not seem to be decreased by postpyloric feeding. Thus, the overall impact of decreased pneumonia rates and improved nutrient delivery on patient outcome remains conjectural.

Based on this evidence, a number of professional societies have made recommendations on prepyloric vs postpyloric feeding.[96,97] These are summarized in Table 2. Of note, these recommendations are directed at distinct groups of patients. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines identify patients undergoing major upper GI and pancreatic surgery as those who might benefit from surgically placed access to the small intestine, but are otherwise silent on a preference between pre- and postpyloric feeding regimens.[98] The guidelines from the Society of Critical Care Medicine and the American Society for Parenteral and Enteral Nutrition (SCCM/ASPEN) are directed at adult critically ill patients receiving specialized nutritional support.[99] These guidelines provide a consensus recommendation that most critically ill patients can be safely started on EN delivered into the stomach. Nonetheless, these guidelines recommend that patients who cannot tolerate enteral feedings into the stomach and those that are at high risk for aspiration receive postpyloric nutritional support, although use of prokinetic agents has also been suggested as an alternative for those patients.[97,100] Among the reported risk factors for aspiration are a documented previous episode of aspiration; decreased level of consciousness including that due to sedation; endotracheal intubation; supine positioning; presence of a nasoenteric tube; abdominal/thoracic surgery or trauma; delayed gastric emptying due to diabetes; and increased age.[101] Unfortunately, most if not all critically ill surgical patients manifest 1 or more of these characteristics, and no further guidance has been provided as to how to further select critically ill patients who should be initiated on postpyloric EN. The American College of Gastroenterology targets nutritional therapy in adult hospitalized patients.[96] These guidelines emphasize use of gastric feeding as the initial approach for EN in hospitalized

**Table 1**
Meta-analyses on gastric vs postpyloric feeding.

| Reference | Number of studies | Patient population | Number of patients | Outcomes | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Mortality | Length of ICU stay | Duration of mechanical ventilation | Pneumonia | Gastrointestinal complications | Nutrient delivery |
| Chang and colleagues[89] | 3 | Patients with severe acute pancreatitis | 157 | No significant difference | Not reported | Not reported | Not reported | No significant difference in rates of aspiration, diarrhea, or exacerbation of pain. | No significant difference in achievement of energy balance. |
| Deane and colleagues[90] | 15 | Mixed adult critically ill patients | 1178 | No significant difference | No significant difference | No significant difference | RR 0.75, significantly in favor of postpyloric feeding | Not reported | Significantly greater nutrient delivery (11%) in patients fed postpylorically |
| Jiyong and colleagues[91] | 15 | Mixed adult and pediatric critically ill patients | 966 | Not reported | Not reported | Not reported | RR 0.63, significantly in favor of postpyloric feeding | No significant difference in rates of aspiration or vomiting | Not reported |
| Zhang and colleagues[92] | 17 | Mixed adult and pediatric critically ill patients and patients with severe acute pancreatitis | 1222 | No significant difference | Not reported | Not reported | RR 0.77, nonsignificantly in favor of postpyloric feeding | No significant difference in rates of aspiration. | Significantly greater nutrient delivery (12%) in patients fed postpylorically |
| Wang and colleagues[94] | 5 | Patients with traumatic brain injury | 325 | No significant difference | No significant difference | No significant difference | RR 0.67, significantly in favor of postpyloric feeding | No significant difference in rates of aspiration, diarrhea, or distention | Not reported |
| Li and colleagues[95] | 8 | Adult mechanically ventilated patients | 835 | No significant difference | No significant difference | No significant difference | RR 0.67, significantly in favor of postpyloric feeding | No significant difference in rates of diarrhea or vomiting | Not reported |

ICU, intensive care unit; RR, relative risk.

**Table 2**
Guideline recommendations regarding pre-pyloric versus post-pyloric enteral nutrition.

| Professional Organization | Type of Patients Addressed in Guideline | Recommendations |
|---|---|---|
| European Society for Clinical Nutrition and Metabolism (ESPEN)[98] | Surgical patients | In general, oral nutritional intake shall be continued after surgery without interruption.<br>Grade of recommendation A, strong consensus (90% agreement).<br>It is recommended to adapt oral intake according to individual tolerance and to the type of surgery carried out with special caution to elderly patients.<br>Grade of recommendation GPP*, strong consensus (100% agreement).<br>Oral intake, including clear liquids, shall be initiated within hours after surgery in most patients.<br>Grade of recommendation A, strong consensus (100% agreement).<br>Early tube feeding (within 24 h) shall be initiated in patients in whom early oral nutrition cannot be started, and in whom oral intake will be inadequate (<50%) for more than 7 days.<br>Special risk groups are:<br>Patients undergoing major head and neck or gastrointestinal surgery for cancer,<br>Patients with severe trauma including brain injury,<br>Patients with obvious malnutrition at the time of surgery.<br>Grade of recommendation A/GPP*, strong consensus (97% agreement).<br>With special regard to malnourished patients, placement of a nasojejunal tube (NJ) or needle catheter jejunostomy (NCJ) should be considered for all candidates for tube feeding undergoing major upper gastrointestinal and pancreatic surgery.<br>Grade of recommendation B, strong consensus (95% agreement).<br>If tube feeding is indicated, it shall be initiated within 24 h after surgery.<br>Grade of recommendation A, strong consensus (91% agreement). |
| Society of Critical Care Medicine (SCCM) and the American Society for Parenteral and Enteral Nutrition and Society (ASPEN)[99] | Adult, critically ill patients | We recommend that the level of infusion be diverted lower in the GI tract in those critically ill patients at high risk for aspiration or those who have shown intolerance to gastric EN. (Quality of evidence: Moderate to high).<br>Based on expert consensus we suggest that, in most critically ill patients, it is acceptable to initiate EN in the stomach.<br>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). |
| American College of Gastroenterology (ACG)[96] | Adult, hospitalized patients | A nasogastric or orogastric feeding tube should be used as the initial access device for starting EN in a hospitalized patient (conditional recommendation, very low level of evidence).<br>Conversion to a post-pyloric feeding tube should be carried out only when gastric feeding has been shown to be poorly tolerated or the patient is at high risk for aspiration (strong recommendation, moderate-to-high level of evidence). |

EN, enteral nutrition; GI, gastrointestinal.
* GPP: Good practice point.
Recommended best practice based on the clinical experience of the guideline development group.

patients, including critically ill patients. Although not a formal recommendation, the document indicates that certain patients with greater disease severity, for instance, those with an APACHE II (Acute Physiology and Chronic Health Evaluation) score >20, might be at higher risk for GI dysmotility and benefit from placement of a small bowel feeding tube. Otherwise, conversion to a postpyloric feeding tube is not recommended unless there is poor tolerance of gastric feeding or the patient is at high risk for aspiration. No guidance has been provided regarding how to identify patients who are at high risk for aspiration.

The decision between prepyloric and postpyloric feeding should also take into account the technical expertise at a given institution. For most patients, enteral access is obtained via blind or assisted bedside techniques. Although only short-term NG or orogastric tubes were formerly placed at the bedside, many facilities now have trained clinicians who can successfully insert both long-term gastric tubes and short- and long-term postpyloric tubes. Available assistive devices, such as an electromagnetic placement apparatus, have increased the success of feeding tube placement and improved safety compared to blind placement, although usually at increased cost.[102] Newer approaches such as use of feeding tubes with a distal camera allowing direct visualization of anatomic landmarks have also been developed to facilitate placement of enteral access tubes.[103] If bedside techniques are unsuccessful or unavailable, placement of an enteral access device using radiologic or endoscopic techniques is an option.

*Summary*

The available information does not justify a uniform approach to feeding access in all surgical patients receiving EN. The data from ERAS protocols and from many studies of critically ill patients suggest that gastric feeding is acceptable in most patients, which has been emphasized in the available guideline recommendations. There does not appear to be a major long-term benefit in patient-centered, clinically important outcomes with routine use of postpyloric feeding. The perceived risks of aspiration and pneumonia in patients receiving gastric feedings and the benefits of additional nutrient delivery with postpyloric feedings have probably been overemphasized.

Nonetheless, it would be premature to conclude that postpyloric feeding has no benefit at all. Patients with intolerance of gastric feeding and those at high risk of aspiration are appropriate candidates to receive postpyloric EN. Patients who are more severely ill may also benefit from EN delivered directly into the small intestine. However, scoring systems to better identify these at-risk patients could help to stratify patients to early gastric vs postpyloric feeding.

There is little indication that postpyloric EN is associated with any increase in complications, although it does necessitate somewhat greater technical expertise for insertion of appropriate feeding tubes and may be associated with delay in EN initiation. Ultimately, the technical capacities at a given institution will usually dictate the frequency with which small bowel feeding is practiced.

## Nutrition in severe acute pancreatitis

Acute pancreatitis is the most common GI illness resulting in hospital admission in the United States, accounting for approximately 300,000 hospital admissions per year, with an annual incidence of 13-45 cases per 100,000 individuals.[104,105] This disease has a variety of etiologies, but it is most commonly caused by gallstones or alcohol use. The severity of an episode of acute pancreatitis is determined by the clinical manifestations, including local and systemic complications, for which a number of severity scores have been proposed over the years.[106] Nutritional practice in both mild and severe disease was long governed by tradition with very little evidentiary support. Although evidence-based consensus guidelines have been published by the International Association of Pancreatology and the American Pancreatic Association, clinical practice nationally continues to vary significantly. Here we present a summary of the current

**Table 3**
Diagnosis of acute pancreatitis.

| |
|---|
| Upper abdominal pain |
| Serum amylase or lipase >3× upper limit of normal |
| Characteristic findings on computed tomography (CT), magnetic resonance imaging (MRI), or transabdominal ultrasound |

Diagnosis of pancreatitis requires at least 2 of the above listed features.

literature and general recommendations for nutritional support in patients with an episode of acute pancreatitis ranging from mild to severe disease.

*Severity assessment*

Current International Association of Pancreatology/American Pancreatic Association consensus guidelines for the diagnosis of acute pancreatitis incorporate a combination of clinical (epigastric abdominal pain, vomiting), laboratory (amylase or lipase >3 times the upper limit of normal), and imaging markers (computed tomography [CT], magnetic resonance imaging, ultrasound; Table 3).

In patients with a diagnosis of acute pancreatitis, a number of variables have been used to develop different scoring systems to quantify the severity of the disease and prognosticate outcome. Examples of these pancreatitis-specific scoring systems include Ranson's Criteria, Modified Glasgow Score, Bedside Index of Severity in Acute Pancreatitis, and the Balthazar CT Severity Index.[106] These are now of primarily historic interest, with current severity assessment being based on the presence or absence of the systemic inflammatory response syndrome (SIRS), local pancreatic complications such as necrosis, and organ failure rather than on acute pancreatitis-specific variables.[106] Mild pancreatitis is defined by the complete absence of SIRS or local complications such as pancreatic necrosis. Moderately severe acute pancreatitis is characterized by transient organ failure (resolves within 48 hours) or local complications, and severe acute pancreatitis is characterized by persistent organ failure (lasting >48 hours). With regards to nutrition, the severity assessment can provide an initial starting point for determining how and when to provide nutritional support in a patient with acute pancreatitis.

*Mild pancreatitis*

Defined broadly as acute pancreatitis without local complications or systemic signs of organ failure, mild pancreatitis accounts for approximately 80% of cases of acute pancreatitis. Typically, these patients present with mild symptoms including abdominal pain and nausea, with associated laboratory abnormalities including elevated inflammatory markers (amylase, lipase, and C-reactive protein). Consensus opinion in cases of mild pancreatitis supports the initiation of oral/enteral nutrition once the abdominal pain is decreasing and inflammatory markers are improving. Randomized controlled trials (RCTs) have shown that not only is it safe to start with a full solid diet (without first transitioning through a liquid diet), but doing so also results in shorter hospital LOS.[107,108] Furthermore, there is no need to wait for normalization of lipase levels to initiate an oral diet as tolerated.[109] Although most studies have primarily investigated early EN in cases of severe acute pancreatitis, a recent meta-analysis in cases of mild pancreatitis demonstrated that EN was also beneficial compared to NPO when considering composite endpoints (including mortality, organ failure, hospital stay, infection, and readmission).[110] Considering that mild pancreatitis constitutes the vast majority of cases of acute pancreatitis, relatively rapid institution of oral nutrition in patients with mild acute pancreatitis is a simple maneuver with potential for a relatively large impact.


**Fig. 1.** Moderate-to-severe pancreatitis enteral nutrition algorithm. TPN, total parenteral nutrition.

*Moderate-to-severe pancreatitis*

Although the organized literature on nutritional strategies in mild acute pancreatitis has blossomed in the last decade, controversy has surrounded the optimal nutritional strategy in patients with moderately severe and severe pancreatitis. In both of these subsets, enteral feeding, either per os or via nasogastric (NG) feeding tube, should be initiated within 48 hours, if possible. Early initiation of EN in patients with severe pancreatitis is safe, though early initiation of EN has not been clearly shown to reduce infectious complications in randomized trials.[111–113] Furthermore, these studies demonstrate the lower cost associated with enteral support over early initiation of PN. If needed, promotility agents, such as metoclopramide and erythromycin, can be added as adjuncts. This pathway is depicted in Figure 1.

*Timing*

In cases of mild acute pancreatitis, initiation of a solid diet as tolerated is appropriate once abdominal pain is decreasing and inflammatory markers are improving. In cases of moderate-to-severe pancreatitis, the randomized, controlled PYTHON trial demonstrated that there is no benefit in reducing infection rates or mortality with immediate initiation of tube feeding (via placement of nasojejunal [NJ] tube) vs initial NPO with oral intake starting at 72 hours.[113] Notably, in this study, if patients had not demonstrated adequate nutritional intake by 96 hours after admission, NJ feeding was initiated. With regards to this study design, some critics have noted that 96 hours does not truly represent late initiation of feeding. Thus, as a “negative” study, the PYTHON trial showed us that immediate placement of an NJ tube within 24 hours is not necessary, but it does not elaborate further on timing and initiation of enteral feeding. To

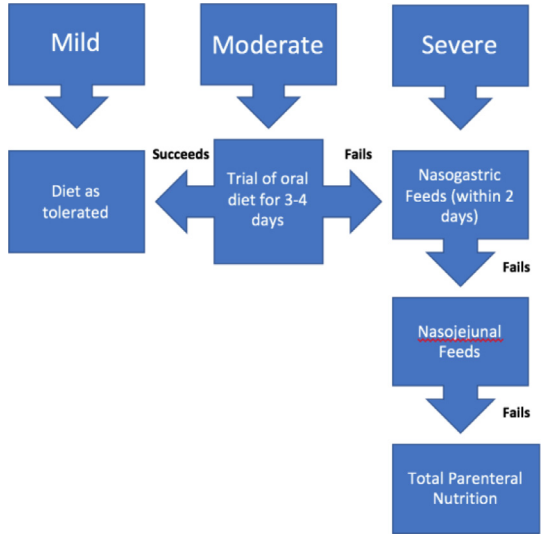


**Fig. 2.** Recommended nutritional algorithm.

this point, a second RCT demonstrated that early initiation of enteral feeding within 48 hours of hospital admission was safe, and associated with decreased incidences of multiple organ dysfunction syndrome, SIRS, and pancreatic dysfunction compared with initiation of EN after 7 days of NPO.[114] This same study also demonstrated decreased length of ICU stay favoring the early feeding group. The same findings, in addition to a decrease in mortality, were redemonstrated in a more recent study, which compared initiation of enteral feeding both before and after the 48-hour mark.[115]

In summary, while it is reasonable to delay NG tube placement and initiation of tube feeding in patients who have the potential to meet nutritional requirements ad lib, waiting longer than 5-7 days is too long. In cases of pancreatitis that are clearly severe at onset, with little chance of the patient being able to eat at an early interval, it is probably better to start EN early by placement of a NG feeding tube. A general flow diagram of these recommendations is shown in Figure 2.

*Method of feeding*

Some have proposed initiating EN via a NJ feeding tube rather than direct gastric feeding. This idea is based on theoretical reasons to avoid pancreatic stimulation and issues arising secondary to gastric dysmotility. Multiple studies on this topic have shown that not only is NG feeding safe and well tolerated, but when compared to NJ feeding, there are no differences in mortality rate, hospital LOS, infectious complications, or multisystem organ failure.[80,82,88,116,117] Thus, there is no need for immediate NJ feeding tube placement for initiation of EN in patients with severe acute pancreatitis, and NJ feeding can be reserved for patients unable to tolerate gastric feeding. If nutritional goals are not met within 5-7 days of the onset of disease, one should consider initiation of PN with continuation of EN as tolerated.

*Type of EN*

A systematic review and meta-analysis examined a total of 1070 patients from 20 RCTs, who were fed enterally with either elemental or standard polymeric tube feed formulations. The intent was to assess feeding intolerance, risk of infectious complications, and death in patients with acute pancreatitis. There was no difference between the 2 groups, and supplementation with probiotics or immunonutrition had no significant impact on clinical outcomes.[118] Currently, there is no strong evidence to support 1 EN formulation over another.

*Role of PN*

There is significant clinical benefit to early initiation of EN over PN in the setting of acute pancreatitis, including severe cases. In cases where patients are unable to tolerate enteral intake or are unable to meet their nutritional needs with enteral intake alone, PN is indicated as with any critically ill patient.[119] In these situations, it is our practice to continue EN via either NG or NJ feeding tube as tolerated, with the goal to increase EN and wean supplemental PN once calorie/protein needs are met.

*Role of early nutrition in infectious complications*

In addition to providing nutritional support in patients with severe acute pancreatitis, attention has been placed on the role of EN in aiding the immunologic response and decreasing infectious complications. In patients for whom EN was initiated within 48 hours of hospital admission, there was a significant reduction in rates of infectious complications, multisystem organ failure, and mortality.[120] Although mechanisms of bacterial superinfection of pancreatic necrosis have not been fully elucidated, it has been demonstrated that bacteremia can be detected as early as 7 days into an episode of acute pancreatitis.[121] Furthermore, the same study showed that infected pancreatic necrosis is detected on average 26 days after hospital admission. It has been theorized that early EN provides continued gut stimulation, resulting in decreased rates of bacterial overgrowth and intestinal atrophy, which may play a role in bacterial translocation through the intestinal barrier.

*Looking forward*

Recent attention has been placed on immunonutrition and its role in acute pancreatitis. The idea behind immunonutrition nutrition is to incorporate substrates into the enteral diet that have an impact on the host immune system and inflammatory response.[122] Immunonutrition formulations often include glutamine, arginine, nucleotides, $\omega$-3 fatty acids, and vitamins. Although some studies have shown beneficial effects of immunonutrition, there remain conflicting opinions regarding the clinical significance. Looking specifically at glutamine supplementation, 1 meta-analysis demonstrated a significantly reduced risk in mortality and total infectious complications in patients who received glutamine supplementation, specifically in patients who received PN compared to EN.[123] Conversely, the REDOX study, a large, international, RCT enrolling patients with multisystem organ failure, showed increased in-hospital and 6-month mortality associated with glutamine administration.[124] Similar to the use of glutamine, there is conflicting evidence around the routine use of probiotic supplementation as an adjunct to enteral feeding in patients with acute pancreatitis. Although 1 RCT showed decreased hospital LOS when probiotics and prebiotics (together synbiotics) were used in enterally fed patients with acute pancreatitis, the 2008 PROPATRIA trial showed comparable rates of infectious complications and an increased mortality rate in the synbiotic group, which was attributed to likely bowel ischemia.[125,126] Ultimately, more information is required to further define the potential role of immunonutrition in patients with acute pancreatitis.

*Summary*

In summary, acute pancreatitis is a disease resulting in large numbers of hospital admissions worldwide, ranging in severity from mild to severe cases. With the vast majority, upwards of 80% of cases, falling under the mild classification, it is important to embrace the recent literature supporting the initiation of early oral feeding once abdominal pain is decreasing and inflammatory markers are improving in these patients. In cases ranging from moderately severe to severe acute pancreatitis, it is reasonable to delay NG tube placement and initiation of tube feeding in

patients who have the potential to meet nutritional requirements ad lib within a few days. However, if there is failure to meet nutritional needs through oral intake alone, a stepwise approach should be used starting with NG feeding, the addition of promotility agents or NJ feeding, and finally escalating to PN with continued enteral feeding as tolerated, if necessary. The impact of such practices has been demonstrated not only to be safe, but also to positively impact patient outcomes as well as being cost-effective. Finally, more work is needed to elucidate the role of immunonutrition in patients with acute pancreatitis.

## Advances in immunonutrition in the surgical patient

Immunonutrition involves the supplementation of particular micronutrients to modulate the immune response to injury. In doing so, it is believed that one can lower the incidence and severity of infectious complications after injury or surgery and augment wound healing as well. Several micronutrients have been targeted for use in immunonutrition. The biochemical pathways involving these molecules are well understood; however, the myriad ways that the metabolic response to stress changes these processes has led to confusion about the role of perioperative or postinjury supplementation. In addition, the body of literature devoted to immunonutrition is plagued by heterogeneity in treatment formula composition, dose, population, and outcomes. The most promising and well-studied micronutrients include glutamine, arginine, and $\omega$-3 polyunsaturated fatty acids (PUFAs), commonly known as "fish oil."

### *Glutamine*

Glutamine is the most abundant amino acid in the body and is involved in many physiological processes. It is a substrate for nitrogen transport and excretion of ammonia as well as gluconeogenesis, and is an essential fuel source for enterocytes, colonocytes, and lymphocytes. Sufficient stores of glutamine appear to be necessary to maintain gut mucosal integrity, and it has been implicated in the normal function of the immune system.[127]

During normal health, glutamine is plentiful and can be synthesized by the body. However, in disease states such as trauma/burns, critical illness, or major surgery, low levels of glutamine have been observed, and are associated with increased mortality.[128,129] Glutamine has thus been labeled as a "conditionally essential" amino acid. This led to the hypothesis that supplementation of glutamine during critical illness would lead to improved outcomes.[130] Earlier studies supported this hypothesis and demonstrated a benefit with supplementation of glutamine. In a meta-analysis by Heys and colleagues, supplementation with key nutrients (including glutamine) resulted in a decrease in infectious complications, as well as hospital LOS.[131] A systematic review by Heyland and colleagues concluded that supplementation with glutamine reduces infectious complications and showed a trend toward mortality reduction.[132] However, in each of these meta-analyses, the included studies (1) were heterogeneous in patients and interventions, (2) used varying doses of glutamine, and (3) included supplementation with multiple other immune-modulating pharmaconutrients besides glutamine. Additionally, levels of glutamine were not routinely measured prior to the supplementation, so it is difficult to determine if a deficiency actually existed.[127]

More recently, the idea that glutamine supplementation leads to improved outcomes has been challenged by two high-profile, randomized, placebo-controlled trials. In the REDOXS trial, 1223 critically ill patients were randomized to receive intravenous supplementation with glutamine, antioxidants, both, or placebo.[124] Not only did glutamine supplementation fail to show any improvement in rates of organ failure or infectious complications, but there was also a strong trend toward increased mortality at 28 days. In the Metaplus trial, 301 patients were randomized to receive high-protein EN with immune-modulating nutrients including glutamine, or standard high-protein EN.[133] Again, there was no difference in the rate of infectious complications, with a similar trend toward increased mortality at 6 months. Initial enthusiasm for

glutamine supplementation has been tempered by these high-quality studies, and some have even suggested that low glutamine levels seen in critical illness may possibly reflect an adaptive survival response.[134]

For these reasons, current 2016 SCCM/ASPEN guidelines state that routine supplementation with parenteral glutamine in ICU patients is not recommended and only recommend enteral glutamine as part of a tube feed formula with other supplements.[135] Still, glutamine supplementation shows promise in certain populations, and future studies on glutamine should attempt to identify subsets of patients who benefit from supplementation. For example, in burn patients, glutamine supplementation has been shown to reduce mortality in a single small study of 40 patients and is therefore recommended.[136] Currently, the REENERGIZE trial is underway and may shed light on the benefit of glutamine supplementation for burn patients.[137]

### *Arginine*

Arginine plays a critical role in the activation of T-cells and macrophages, and also serves as a precursor for collagen synthesis in wound healing. In addition to its role in the immune system, L-arginine is metabolized by nitric oxide synthase into nitric oxide, a potent vasodilator that also assists macrophages in eliminating bacterial pathogens.[138] Serum arginine levels have been shown to be depressed after major trauma and burns, mainly due to increased metabolism of arginine and unchanged rate of synthesis, leading arginine to also be considered a "conditionally essential" amino acid in states of stress.[139] This led to the hypothesis that supplementation of arginine in critically ill patients could enhance wound healing, immune function, and recovery.

Arginine use in the critically ill, however, is controversial. L-Arginine is metabolized to create nitric oxide, and supplementation in animal models has shown an increase in nitric oxide with the expected consequent hypotension that accompanies the loss of vascular tone. Although this effect has not been well-demonstrated in human trials,[140] arginine supplementation is not currently recommended in septic patients by the 2016 SCCM/ASPEN guidelines.[135] Similarly, the Canadian Critical Care guidelines recommend against the use of arginine in the critically ill.[141]

Interestingly, the recommendations differ for surgical patients, and the 2016 SCCM/ASPEN guidelines suggest considering arginine supplementation for trauma and specifically TBI patients.[135] The recommendation for trauma patients is based on theoretical benefit. A meta-analysis of 8 randomized trials involving the use of immune-modulating formulas in trauma patients failed to show an outcome benefit for LOS, infectious complications, or mortality.[142] In TBI patients, a small trial comprising 40 subjects compared an immune-modulating formula against standard tube feeds and found a decreased rate of infectious complications.[143] Therefore, the guidelines suggest the use of an arginine-containing immune-modulating formula.[135]

As with glutamine, the studies on arginine are heterogeneous in the dose and composition, and it is difficult to draw firm conclusions. More studies are needed to identify specific patient populations that may benefit from arginine supplementation.

### *The $\omega$-3 PUFAs*

The $\omega$-3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are less inflammatory than $\omega$-6 fatty acids and play an important role in gene expression, signaling pathways, and in the cell membrane structure.[144,145] Initial trials in critically ill patients with sepsis and acute respiratory distress syndrome (ARDS) arrived at conflicting conclusions. The largest of these, the OMEGA trial sponsored by the ARDS clinical trials network, was stopped early for futility, and patients receiving fish oil supplementation had higher rates of 60-day hospital mortality, fewer ICU-free days, fewer organ failure-free days, and higher rates of diarrhea.[146] Current guidelines do not make a recommendation regarding the use of fish oil in ARDS patients, citing

heterogeneity in the method of delivery and dose, along with variability in the ingredients in the treatment formulas.[135]

The 2016 SCCM/ASPEN guidelines, however, do recommend administration of $\omega$-3 PUFAs combined with arginine in postoperative patients in the surgical ICU.[135] In a meta-analysis of 35 trials, $\omega$-3 PUFAs combined with arginine demonstrated a benefit in incidence of postoperative infection, and in LOS compared to standard formula.[141] Another meta-analysis concluded that supplementation with $\omega$-3 PUFAs and arginine led to a reduction in postoperative infection and LOS compared with standard formula.[58]

*Summary*

The field of immunonutrition is promising based on the current understanding of the biochemical role of these nutrients, but questions remain regarding the timing, dose, delivery, and disease process to optimize care. Current guidelines recommend the use of immune-modulating formulas containing glutamine, arginine, and $\omega$-3 PUFAs only in trauma and critically ill postoperative patients who require EN support. Glutamine should not be given intravenously in patients receiving PN and arginine should be avoided in sepsis. Better studies on specific patient populations with harmonized formulations are required to determine the appropriate use of immunonutrition in surgical patients.

## Protein requirements in critical illness—more important than calories?

Historically, aggressive protein provision has been touted as the optimal strategy in critical illness. Multiple professional societies routinely provide guidelines relevant to nutrition support in the ICU to assist clinicians. The most recent (2016) SCCM/ASPEN guidelines recommend that protein provision in critically ill patients should be "sufficient and high dose (i.e., 1.2-2.0 g/kg actual body weight/day)".[135] The authors acknowledged the heterogeneity of the ICU population in the manuscript and have embraced the concept that specific subset populations (eg, burns, sepsis, multiple traumatic insults) should receive higher protein targets. ESPEN released guidelines in 2018 recommending that 1.3 g/kg can be delivered progressively, a recommendation receiving a low grade with regard to quality of evidence.[147] In addition, ESPEN did not refer to any subset of patients where protein recommendations might differ. Although SCCM/ASPEN suggested that there are patient populations who might benefit from higher protein targets than those recommended by ESPEN, it was readily apparent that high-quality, evidenced-based recommendations with regard to protein provision are lacking.

Regardless of recommendations, there is incredible variability in current practice with regard to protein provision in critical illness. For reference, recommendations in healthy nonhospitalized adults are usually cited at 0.8 g/kg/d. In a large international survey, observational data suggested that 0.3 g/kg/d was the typical protein provision in the first 12 days in the ICU.[148] Whether this is sufficient or appropriate remains in question. Two major issues arise when discussing protein provision in the ICU: timing and dosing. Opposing opinions on the appropriateness of protein provision early in critical illness have evolved as a result of the several recently performed trials. Current targets for protein provision are comprised of strategies ranging from aggressive protein provision (2 g/kg/d) to little or no protein provision in the setting of acute critical illness.

*Protein dynamics in the ICU*

During periods of critical illness, there are significant changes in the way that exogenous protein substrates are absorbed and utilized, skeletal muscle is catabolized, and new protein is

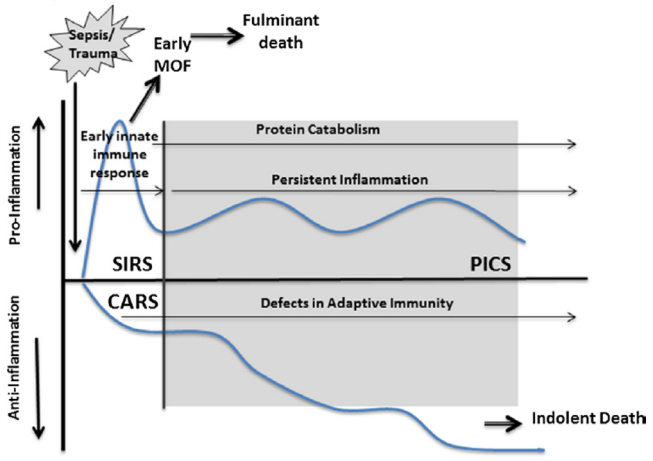


**Fig. 3.** Persistent inflammation-immunosuppression catabolism syndrome (PICS). CARS, compensatory anti-inflammatory response syndrome; MOF, multiple organ failure; SIRS, systemic inflammatory response syndrome.

synthesized. Substantial protein losses, up to 1 kg/d, have been demonstrated in the critically ill.[149] These alterations reflect a preserved physiological response to insult. Described as a "genomic storm, " the response to insult (trauma, burns, and sepsis) alters expression of protein metabolism and immune function as well as protein handling.[150] The SIRS and compensatory anti-inflammatory response syndrome were early descriptors relevant to alterations in both innate and adaptive immunity following insult. This concept was revised with the subsequent description of persistent inflammation catabolism syndrome (PICS) in certain subsets of critically ill patients (Fig 3).[151,152] PICS is characterized predominately by the inability to reverse catabolism, with ongoing protein losses and dysregulation. These clinical entities are generally recognizable by clinicians caring for patients, but represent a complex molecular milieu. Although the characteristics of these models have evolved over time, the recognition of the various phases of critical illness and associated patterns during these periods is extremely important. Protein dynamics are likely both contributory to and impacted by this progression through these phases. Clinically, these phases loosely correlate with active resuscitation, organ function stabilization, organ function recovery, and finally systemic functional recovery. Although most patients recover from critical illness, some do not. These latter patients exhibit poor wound healing, acquire decubitus ulcers, and sustain nosocomial infections, all of which are sequelae of the inability to utilize protein meaningfully. This is relevant since the phase of critical illness is believed to be a key determinant in how endogenous and exogenous protein is utilized.

In the acute setting following insult, endogenous energy stores are mobilized to provide the majority of requirements. Substrate mobilization involves glycogenolysis of hepatic glycogen stores, lipolysis from adipose sites, and gluconeogenesis from various catabolic byproducts including lactate, amino acids, and glycerol. Insulin resistance is protective during this period by shunting available glucose to essential areas (ie, brain and heart). The body has limited protein stores and losses accumulate early and predominately from the skeletal muscle pool. Historically, nonprotein (carbohydrate) provision was believed to have a protein-sparing effect during this period, serving to preserve lean body mass (LBM). But such beliefs have recently been challenged. During this period whereby endogenous substrate is mobilized and utilized, it is not well-understood how exogenously provided substrate, and particularly protein, is handled. Obligate glucose loads traditionally thought to be in the 150 g/d range are now believed to be substantially less (as low as 50 g/d).[153] Following the acute phase of critical illness, patients tend to become hypermetabolic, but aberrations in substrate handling may persist, as demonstrated by the patient population that progresses to PICS. Additionally, patients often lose a significant proportion of their LBM in all phases even when provided with optimal calories and

protein. Anabolic resistance refers to a global state where, regardless of the availability of adequate protein, the body is unable to utilize this protein for anabolic activities. This is somewhat analogous to insulin resistance in critical illness where insulin deficiency is not the underlying problem, but instead the ability for insulin to effectively result in downstream function is lacking.

Although protein synthesis appears to be maintained, there is a striking increase in protein catabolism occurring almost immediately following a severe physiological insult.[154] Muscle catabolism occurs relatively equally between contractile proteins and mitochondrial proteins. Immobility, which is extremely common in the ICU, exacerbates protein catabolism in part through protease activation with subsequent activation of ubiquitin-proteasome proteolysis. Mitochondrial protein depletion and dysregulation have been identified as potential contributors to mortality in critical illness.[155] When lean body losses are clinically evident at the bedside, the losses at the cellular level are likely substantial.

Protein recycling and the ability to clear cumulative nonfunctional protein aggregates are important mechanisms by which cells adapt to and survive periods of oxidative stress. Autophagy is a method whereby cells dispose of damaged organelles, bacteria, viruses, or protein aggregates too large for the proteasome ubiquitin system through envelopment and fusion with a lysosome for breakdown to amino acids.[156] Autophagy also serves to recycle amino acids for two purposes: (1) utilization in protein synthesis and (2) generation of adenosine triphosphate for energy production. Factors that stimulate autophagy include starvation and oxidative stress, whereas inhibitory factors include feeding, insulin, hyperglycemia, and the presence of excessive nutrients.[157,158] Exogenously provided protein may interrupt autophagy, the consequence of which may result in functional impairment and delayed recovery from the insult of critical illness. However, the importance of strategies to promote or sustain autophagy in these patients remains unclear.

Catabolism alone, however, does not account entirely for the overall differences in protein utilization observed in critical illness. Hyperglycemia and insulin resistance compound the issue. Altered insulin receptor activity results in the loss of a key pathway that triggers anabolic resistance. Protein absorption can be impacted such that exogenously provided protein via the enteral route may never reach the systemic circulation. Inflammation leading to mucosal compromise results in the downregulation of PepT1 in the small intestine, which is the transporter responsible for a majority of peptide absorption from the GI tract. In the absence of adequate transporters, decreased overall absorption occurs, potentially contributing to cumulative overall deficits. In addition, splanchnic sequestration of amino acids can further compromise bioavailability. Finally, various inflammatory signals can shift the amino acid profile, potentially further contributing to LBM losses in the critically ill patient. For example, leucine is an important signal for muscles to initiate anabolic pathways and downregulate catabolism, and has been considered (along with glutamine and arginine) as a targeted therapy to attenuate muscle loss. These amino acids converge on the mammalian target of rapamycin complex 1, currently thought to be the central regulator of protein synthesis and anabolism. Clearly, certain amino acids may play a more pivotal role than others in overall response. However, lack of clarity with the complexities of anabolic resistance has resulted in few strategies to reverse this pathophysiological process.

Clinically, manifestations of anabolic resistance and protein catabolism manifest in part by weakness, which is certainly common in the ICU. The net overall protein losses result in functional impairment of the patient, leading to a post-ICU weakness where they cannot ambulate or care for themselves, an impairment that persists even at 5-year follow-up.[159] Significant difficulties in the activities of daily living and instrumental activities of daily living are seen following critical illness. To further illustrate this point, a retrospective review of patients sustaining severe trauma suggested that the 1-year mortality following severe trauma has remained largely unchanged over the last 15 years, but more patients are dying in long-term acute care facilities rather than in the hospital.[160] Loss of muscle mass corresponds with increased LOS and worse clinical outcomes, and this loss coupled with anabolic resistance can set the stage for continued clinical decline.

Given the complexities described above, two opposing viewpoints have emerged in critical care nutrition. The "high protein" viewpoint proposes that through exogenous administration of protein, anabolic resistance can be overcome, thereby improving patient outcomes. The "no protein" viewpoint, in contrast, proposes that the presence of exogenous protein can result in overloading safety mechanisms such as autophagy or trigger refeeding physiology in high-risk patients and that withholding both protein and energy in critical illness prevents iatrogenic harm.

*High protein viewpoint*

If loss of LBM results in negative outcomes for patients, theoretically it follows that those outcomes might be improved by replacing what is lost. Several studies have demonstrated improved outcomes with early protein provision. In 2011, an observational trial by Weijs and colleagues demonstrated that achieving both protein and energy targets resulted in a 50% decrease in mortality, but meeting only the energy target was insufficient to achieve optimal outcomes.[161,162] Such findings suggested that protein provision might be more important than energy provision. Shortly thereafter, a second observational trial by Allingstrup had similar findings, showing that adequate protein and amino acid provision correlated with a decrease in mortality.[163] In 2015, a third observational trial by Nicolo and colleagues demonstrated a lower mortality rate associated with higher protein provision. It should be noted that these studies demonstrate an association between high protein provision and improved outcomes, and minimal association between outcome and energy provision.[164] Additionally, these were not RCTs and therefore fail to demonstrate causation. A valid argument can be made that less sick patients with better outcomes are more tolerant of nutrition support strategies and therefore receive more protein (selection bias). Such potentially biased findings from observational trials alone may result in an artificial signal of benefit from aggressive protein provision.

Two RCTs performed by the same group of investigators appear to support the strategy that high protein provision positively influences clinical outcomes. In the first trial, Rugeles and colleagues compared high protein hypocaloric feeding (12 kcal/kg/d and 1.4 g/kg/d protein) to eucaloric feeding (25 kcal/kg/d with 20% protein) strategies in ICU patients.[165] At the conclusion of the study, patients were found to have inadvertently received equivalent energy provision (12 vs 14 kcal/kg) but significant differences in protein provision (1.4 vs 0.7 g/kg/d). The higher protein group demonstrated better outcomes in terms of decline in Sequential Organ Failure Assessment score, lower blood glucose levels, and a tendency toward reduced duration of mechanical ventilation and ICU LOS. In the second trial, all patients were given 1.7 g/kg/d protein, with 1 group receiving 15 kcal/kg/d and the other receiving 25 kcal/kg/d.[166] There were no differences in outcomes between these groups with the exception of higher insulin requirements in the full feeding group. A 2016 trial randomized 119 ICU patients requiring PN to either 0.8 g/kg/d or 1.2 g/kg/d of intravenous amino acids.[167] Although there was no difference in mortality or LOS, the higher protein group had a trend toward improvement in several functional and muscle-mass measures. These studies taken together seem to support the contention that protein goals are of more importance than energy goals in the ICU, and that early and more aggressive protein provision results in better outcomes.

In contrast, 2 other RCTs failed to support this strategy of high-protein provision. These trials primarily utilized supplemental parenteral amino acids, which somewhat limits generalizability to enteral protein administration. Doig and colleagues examined the addition of supplemental parenteral amino acids in early critical illness in patients on mechanical ventilation (excluding patients with acute kidney injury).[168] Patients in the experimental arm received short-term intravenous amino acids not to exceed 2 g/kg/d of total protein, while no additional protein was provided to controls. No difference was observed between the 2 groups in the primary endpoint (duration of renal dysfunction), nor in mortality, a tertiary endpoint. However, an exploratory post hoc analysis suggested clinical benefit (including mortality) of higher protein provision in patients with normal renal function at enrollment.[169] In the "TOP-UP" pilot trial, supplemental PN was feasible to optimize protein provision to one of two groups receiving EN without

any evidence of harm.[170] Although the TOP-UP pilot study was not specifically powered to compare clinical outcomes, trends of lower hospital mortality and improve functional outcomes and quality of life outcomes favoring the SPN arm were noted. Surgical ICU patients derived a greater benefit from the SPN compared to the medical ICU patients. Similar to the Doig study, the TOP-UP pilot study did not find any difference in mortality, although neither trial specifically defined mortality as a primary endpoint.

*No protein viewpoint*

The opposing argument proposes that early protein provision in the setting of critical illness not only lacks benefit, but may instead result in iatrogenic harm. Put simply, critical illness and substantial oxidative stress may create an environment where the provision of exogenous protein may exacerbate refeeding physiology and tax already exhausted compensatory mechanisms, such as autophagy, thereby resulting in poor outcomes. Although protein provision by itself has not been specifically examined, extrapolation from recent trials suggests that aggressive full feeding strategies during early critical illness are potentially harmful and that protein is a potential contributor to these poor outcomes.

Two large RCTs showed that early supplementation of PN to patients already on enteral tube feedings caused worse outcomes compared to delaying the supplementation until after the first week of hospitalization in the ICU. The first "EPaNIC" trial (see also "Dissecting the critical care nutrition literature" section) in adults showed that late initiation of supplemental PN was associated with a decreased ICU LOS, a reduced rate of acquiring new infections, and a greater likelihood of being discharged alive when compared to early initiation of supplemental PN.[171] The same results were demonstrated in pediatric ICU populations in the second "PEPaNIC" trial.[172] In response to criticism of the study, Casaer and colleagues published a post hoc analysis in 2013 that suggested the effects in the original study were not due to differences in the severity of illness (as their critics suggested), nor were the negative effects of early supplemental PN restricted to the patients receiving high carbohydrate and calorie doses.[173] They argued that protein, in fact, appeared to be a potent contributor to the adverse outcomes. A high protein-to-calorie ratio was associated with worse outcomes, suggesting that chasing high protein delivery is not the optimal strategy for nutrition therapy in the ICU. One mechanism suggested by the authors was that the high protein doses led to suppression of autophagy, thereby resulting in dysregulated muscle maintenance, synthesis, and increasing weakness. Additional studies by this same group used an animal model of critical illness to show that provision of high doses of parenteral protein did in fact inhibit autophagy, leading to abnormalities in muscle function and organ failure.[174]

Two issues are worth noting that could be of key importance when evaluating the available literature. First, the heterogeneity of the ICU cannot be overlooked, and is likely a key determinant in developing an appropriate strategy. Surgical, trauma, and burn patients have relatively high protein turnover when compared to their medical ICU counterparts. It may be naïve to believe that these divergent populations handle protein in a similar fashion, or that their protein requirements are comparable. Patients in the ICU are also incredibly variable with regard to underlying nutritional risk. High-quality observational data analyses demonstrate that optimizing macronutrient delivery seems to benefit only those patients at high nutritional risk with prolonged ICU stay.[175] However, defining nutritional risk has proven difficult. Through identification of patients at high risk by combining disease-specific severity of illness scoring systems with traditional nutritional assessment (including BMI, recent weight loss, and recent dietary changes), individualized nutrition support strategies could be created and likely are optimal. Incorporated within risk stratification tools should be imaging modalities that assist with quantification of LBM. In the surgical patient population, CT scans are often readily available and can be used by clinicians to rapidly identify sarcopenia in their patients.[176] Protein deficits have been correlated with deterioration of skeletal muscle size and quality.[177] Further refinement of these assessments will allow us to better identify at-risk patients and provide appropriate treatment.

Theoretically, patients at significant nutritional risk driven by disease severity might benefit from more aggressive protein provision strategies, whereas patients at high nutritional risk driven by pre-existing malnutrition may be more susceptible to refeeding physiology.

Second, patients in the ICU may respond differently to exogenous protein, depending upon their stage of critical illness. During the active resuscitative phase, it appears unlikely that protein provision would dramatically improve outcomes and may in fact be harmful, as endogenous supply appears to be sufficient in early illness. Support for this concept lies in the observation of a time-dependent association between protein intake and mortality: patients receiving low protein (<0.8 g/kg/d) before ICU day 3 and subsequently high protein intake (>0.8 g/kg/d) after day 3 had the best outcomes compared to patients with overall high protein intake and overall low protein intake.[178] An emerging strategy, hypocaloric, high-protein nutritional support in early critical illness is emerging,[166] whereby protein goals take precedence over meeting calorie goals in an attempt to avoid overfeeding. This strategy obviously has roots originating from the Allingstrup and Weijs observational trials emphasizing protein provision over caloric goals, but also considers the potential detrimental effects of early full feeding strategies. Overfeeding is clearly detrimental[179] and may result in suboptimal protein utilization, reduced insulin sensitivity, and the potential for refeeding physiology in patients at high risk. However, as critical illness is stretched over increasingly long intervals with partial organ recovery, protein provision may become more important. Unfortunately, there are few data with regard to protein provision improving long-term outcomes in this population, but one could surmise that at some point cumulative deficits must be accounted for in order to achieve optimal outcomes.[180]

*Summary*

In critical illness, factors of disease severity, level of oxidative stress, and muscle catabolism are compounded by futile systems of fuel utilization, anabolic resistance, and unloading of muscle. All of these factors contribute to post-ICU weakness and poor functional recovery. Biological processes such as autophagy, designed to maintain organ function and retain quality of skeletal muscle, compete directly with anabolic systems of mammalian target of rapamycin sensing and protein synthesis. Navigating these complex pathophysiological processes makes it difficult for clinicians to determine the appropriate prescription for protein and energy provision needed to achieve optimal outcomes.

There are incredibly divergent opinions with regard to optimal protein provision in the various phases of critical illness. There are limited convincing data to suggest that either strategy is definitively more effective than the other. Although both the “high protein” and “no protein” viewpoints present relatively compelling arguments as to why a particular approach is preferred, there are significant gaps in the support of both strategies. Unfortunately, as the controversy persists clinicians must continue to care for patients and develop strategies for nutritional support and protein provision in the critically ill patient.

An informed, evidence-based approach to macronutrient feeding in the ICU would synthesize the existing literature into a nuanced and individualized approach factoring the baseline nutrition status, the type of insult, and the phase of recovery. During the acute resuscitative phase of critical illness, an early, but moderate feeding strategy is appropriate, although burn patients appear to behave differently and EN support should be initiated very early, even during resuscitation, in this patient population. Following initial stabilization, high-protein, hypocaloric feeding strategies may be implemented. As organ function improves and clinical conditions progress, increased emphasis is placed on achieving protein and energy goals as attempts are made to facilitate “full” feeding strategies. Supplemental modular protein is utilized in patients with high protein losses, such as those with burns and polytrauma where goals of 2 g/kg/d of protein are prescribed. Finally, we would be remiss not to acknowledge that muscle loading (ie, physical therapy) is a key component in the optimal utilization of protein and the potential for such therapy to change outcomes.[181]

## Early enteral feeding after surgery—what is the evidence?

Surgical nutrition has advanced significantly since the era of mandatory prolonged fasting in the perioperative period. In recent years, the treatment paradigm in the postoperative period has shifted tremendously. Stimulated by the encouraging studies of ERAS, common practices of prolonged postoperative fasting are now being challenged for both critically ill and noncritically ill patients. Although the origins of ERAS began in colorectal surgery, it is now being applied after nearly every type of major surgery from transplant surgery to hip fracture repair.[182,183] Preliminary experience with ERAS appears promising, with very few associated risks and possibly long-term benefits.[184] Nevertheless, overnight preoperative fasting remains the standard for many surgical patients, and postoperative fasting, to some degree, is not uncommon. In this section, we discuss which surgical patient population may benefit from early postoperative EN. We limit the discussion to only the initiation of oral/enteral nutrition, as the optimal amount of calories/protein to prescribe and deliver remains highly controversial and is the topic of ongoing investigation.

Traditional dogma teaches that oral or enteral nutritional intake is frequently withheld from abdominal surgery patients until they manifest "return of bowel function," but with little or no supporting evidence. However, clinical assessment of return of GI activity is fraught with difficulties. Bowel sounds have little utility in determining the presence or absence of GI motility.[185–187] The amount of gastric drainage via a NG tube has been used as a measure of GI activity, but the potential utility of this approach has been called into question by analyses indicating no benefit and potential harm with routine NG tube decompression following abdominal surgery.[188–190] In healthy subjects, NG tube insertion results in increased scores on an airway penetration-aspiration score, increased pharyngeal residue, and increased pharyngeal transit, even with fine-bore small caliber tubes.[191] Furthermore, studies of patients fed enterally have not found measurements of gastric residual volume to decrease the risk for adverse outcomes such as pneumonia, regurgitation, or aspiration.[192–194]

There also persists a common belief that the presence of a bowel anastomosis is a contraindication to early feeding. However, multiple clinical trials and meta-analyses have not found any increase in anastomotic breakdown or other deleterious outcomes associated with early nutritional intake into the GI tract.[195–197] Indeed, the available evidence suggests that providing early intraluminal nutrition (compared to isocaloric PN) proximal to a "fresh" anastomosis results in a stronger anastomosis in the form of higher anastomotic bursting pressure and increased collagen content.[198–200] Additionally, using a high-fat enteral formula has been shown to reduce the intestinal mucosal barrier damage and inflammation caused by peritoneal air exposure.[201,202]

### *Early feeding and ERAS—nutrition in the elective patient without critical illness*

ERAS protocols began in Europe and require a multidisciplinary team including anesthesiologists, surgeons, nurses, dieticians, and other allied health professionals. ERAS involves all phases of care, with planning and coordination beginning during the preoperative clinic visit. The emphasis is on minimizing physiological stressors and maintaining homeostasis.[203] The approach has been very successful in the elective surgery setting and has expanded to emergency surgery as well. In order to facilitate ERAS goals, patients are screened for evidence of malnutrition and commence intensive nutritional therapy several days before surgery. Patients undergo preoperative carbohydrate loading; providers employ narcotic-sparing adjuncts especially through epidural or spinal analgesia; and initiate early feeding postoperatively to maintain energy intake. Perioperative fluid administration is also carefully managed to avoid excessive fluid gain.

ERAS has challenged traditional surgical management[204] and has demonstrated that the majority of patients can tolerate early oral intake and may derive benefit through decreased postoperative catabolism, reduced postoperative complications, and decreased hospital LOS. Re-establishing oral intake as soon as feasible postoperatively is a key aspect of enhanced

**Table 4**
Contraindications for enteral nutrition.

| |
|---|
| • Intestinal obstruction |
| • Severe ileus |
| • Severe shock |
| • Suspected or confirmed intestinal perforation |
| • Intestinal ischemia |
| • Intestinal discontinuity |
| • Intractable vomiting or diarrhea |
| • High output fistula |
| • Toxic megacolon |
| • Severe intestinal hemorrhage |
| • Need for surgical reintervention <24 h after admission |

recovery protocols[98] and most noncritically ill surgical patients are able to initiate oral intake within hours after surgery. Awaiting the return of bowel sounds or passage of flatus before resuming oral/enteral nutrition is strongly discouraged by multiple professional societies.[135,205] Additionally, a large number of randomized trials have demonstrated that routine NG tube decompression after abdominal operation does not lower the risk of anastomotic leak and is actually counterproductive by delaying return of bowel function and increasing pulmonary complications.[189] Early oral or EN within 24 hours has been demonstrated in multiple randomized trials to be safe and beneficial after both lower GI (ie, colorectal) operations,[206–210] as well as upper GI operations (ie, esophagectomy, gastrectomy, pancreaticoduodenectomy).[211–217] The majority of patients (75%-80%) tolerate such feeding strategies,[218–222] and the findings suggest that nosocomial infections, gut mucosal permeability,[223] postoperative ileus,[209] and even anastomotic leaks were reduced in those patients receiving early EN.[209,211] Additionally, multiple trials have demonstrated that progressing directly to solid food intake (without first transitioning through a liquid diet) after elective intestinal surgery is safe and advantageous.[213,224–226] In summary, the highest level of evidence on this topic supports the practice of initiating early oral/enteral nutrition (within 24 hours of operation) after elective intestinal operation of both the upper and lower GI tract.[195,196,227]

*Surgical ICU patients*

Due to the hypermetabolic response after emergency surgery or trauma, the ICU patient is susceptible to a myriad of complications including feeding intolerance, multiple organ failure, and septic complications. Meeting adequate protein and energy goals are believed to mitigate this response. Oral feeding is more physiological and is therefore preferred over EN, but many critically ill patients require mechanical ventilation or are severely debilitated and at risk for dysphagia and aspiration. Early EN may offer an excellent alternative for critically ill patients in the ICU for those unable to ingest adequate oral intake. Additionally, there seems to be a "window of opportunity" early after ICU admission during which initiation of EN can have important downstream effects on patient outcome.[228,229] Delaying EN initiation will miss this opportunity.

The vast majority of critically ill patients never reach daily nutritional requirements during their ICU stay due to a multitude of reasons.[230,231] Many causes include interruptions or failure to reach hourly EN requirements due to suspected intolerance or fasting for procedures or surgery. Compared to medical ICU patients, surgical ICU patients initiate EN later and receive less daily quantities.[230]

Many studies have advocated that EN be initiated within 24-48 hours in critically ill patients who are unable to maintain oral intake and without contraindications for EN (Table 4).[98,232–235] Contraindications to EN are not absolute, and depend upon disease severity and patient characteristics. As in non-ICU patients, clinical signs of intestinal function, such as bowel sounds

and flatus, are not required to initiate EN. Gastric feeding is considered preferable to postpyloric feeding in many patients because neurohumoral signaling is maintained and atrophic effects of fasting on the mucous membrane are prevented.[236] Gastric feeding is also usually logistically more feasible. Persistent feeding intolerance and ileus are considered barriers to reaching energy and protein goals in the ICU. Accepting higher gastric residual volumes should be weighed against the risks of theoretical aspiration in these cases.[237,238] This may need to be considered on a case-by-case basis.

*Vasopressors*

In the past, EN has not been recommended in critically ill patients requiring vasopressors due to concerns about precipitating or exacerbating nonocclusive mesenteric ischemia, a rare complication associated with an extremely high mortality rate.[239,240] However, experimental evidence shows that intraluminal nutrients improve mesenteric blood flow,[241,242] a phenomenon termed *postprandial intestinal hyperemia*, which has been shown to result from redistribution of cardiac output rather than an increase in overall cardiac output.[243–245] Since prolonged low-flow splanchnic ischemia results in altered mucosal permeability, endotoxemia, and multiple organ failure, any treatment that facilitates increasing intestinal blood flow has a theoretical basis for clinical benefit.[246] Although there is a lack of high-quality human clinical trials, the existing literature supports the safety of initiating EN in hemodynamically unstable patients.[247–250] Indeed, those with the most severe hemodynamic compromise may benefit the most,[251] although "full dose" EN may not be well-tolerated at high doses of norepinephrine.[252] EN should be withheld in a hemodynamically unstable patient with escalating vasopressor requirements.[135] However, if vasopressor support is decreasing or minimal, EN can be considered. Initiating early gastric EN at a "trophic rate" appears to pose little risk in the majority of critically ill patients and potentially improves outcomes,[240] although rapid advancement to goal rate may result in GI complications.[253] In the absence of strong evidence, expert opinion recommends starting with an iso-osmolar formula without added fiber (ie, low residue).[254]

*Trauma and burn injury*

Early EN within 24-48 hours after injury is generally recommended in stable trauma and burn patients.[98,233,255,256] Several studies have noted fewer infectious complications, shorter hospital LOS, and other clinical benefits in different trauma patient populations.[236,256–260] TBI patients receiving early EN have fewer infectious complications, improved survival, and reduced disability compared to other feeding strategies.[261–264] Starting EN within 6 hours in polytrauma and burn patients resulted in decreased intestinal permeability, decreased bacterial translocation,[265,266] and lower rates of multiple organ failure compared to starting EN 24 hours or later after injury.[266] A meta-analysis of all methodologically sound randomized trials conducted in trauma patients reported an overall significant reduction in mortality associated with early EN.[267] In summary, early EN should be considered the standard of care for trauma and burn patients unless contraindications exist.

*Emergency surgery*

Compared with elective surgery, emergency surgery patients face higher morbidity especially wound complications, septic complications, and mortality. However, ERAS has been applied to many emergency surgery patients with evidence that it similarly benefits these patients.[268] In addition, early oral and EN seems to be acceptable and safe in most emergency surgery scenarios with little justification of prolonged postoperative fasting.[269,270]

*Perforated viscus and peritonitis*

Enteral feeding initiated within 48 hours has been shown to be safe after emergency surgical repair of perforated viscus. In fact, experimental models have shown that early EN within 48 hours after bowel surgery for peritonitis is associated with collagen accumulation and increased anastomotic strength.[271] Compared to late feeding, early feeding does not seem to incur additional risks and results in shorter hospital LOS; fewer infectious and pulmonary complications; faster return of bowel function; and reduced rates of in-hospital mortality.[272–276]

*Open abdomen*

The timing and route of nutritional feeding in patients with open abdomen (OA) is controversial. Patients are often kept NPO due to concerns about paralytic ileus, bowel edema, exacerbation of bowel distention, and the inability to close the abdomen. However, oral intake and EN can be tolerated well in patients with OA.[277,278] Early EN delivers considerable benefits in terms of clinical outcomes, including higher rates of fascial closure, reduced infectious complications, and reduced mortality.[279–284] Multiple professional guidelines now recommend early EN in patients with OA with GI continuity.[205] EN may be initiated at a low, "trophic" rate early in the course while the abdomen remains open, with slow advancement of tube feeds contingent upon close observation and patient tolerance. In addition, due to the significant exudative volume that is emitted from an OA, prescribing an additional 15-30 g of protein per liter of abdominal fluid drainage should be considered. It is critical that the plan for initiating enteral feeding in the OA patient be discussed with the responsible managing surgeon, and that the patient be monitored closely for signs of intolerance, worsening distension, or any other complication.

*Fistulae*

There is a lack of prospective trials comparing different nutritional therapies in this patient population. In practice, both PN and EN are used in intestinal fistulae patients.[285] A substantial intestinal length is required for EN to be sufficient for maintenance of nutritional requirements. However, if 20% of the proteins and energy can be delivered enterically, mucosal integrity, immune function, and hormonal signaling of the gut remain intact.[286] Unfortunately, EN may increase fistula output, and in patients with high fistula output, EN volumes greater than trophic feeds may result in fluid/electrolyte complications.[98] However, it seems that EN can still be successfully applied, if carefully monitored, and may result in improved outcomes compared to complete bowel rest.[285,287–289] Fistuloclysis, or feeding via an intestinal fistula, is a suitable way to administer EN, and can reduce PN requirements.[290,291]

*Extracorporeal membrane oxygenation and prone positioning*

Extracorporeal membrane oxygenation (ECMO) is increasingly used in ICU patients with severe respiratory and/or cardiac failure and guidelines are now tentatively recommending early EN for patients on ECMO.[205] Recent prospective and retrospective studies have shown that early EN can be used safely in critically ill ECMO patients, although delayed gastric emptying is a common complication and should be monitored closely.[292–296] Patients with venovenous ECMO appear to reach nutritional goals earlier than venoarterial ECMO[297] and a large nationwide registry study concluded that initiating early (<48 hours) EN in venoarterial ECMO patients was associated with improved survival.[298] In the absence of guidelines, we conditionally recommend early EN in ECMO patients, with careful attention paid to hemodynamic and GI tolerance.[299,300]

Despite a paucity of supportive data, at present it appears that early EN in the prone position is as safe, although vomiting and feeding intolerance may occur more often compared to the

supine position.[301–303] Thus, although prone positioning is not an absolute contraindication to EN, vigilance must be maintained to monitor for complications.[205]

*Summary*

The success of ERAS has revolutionized traditional perioperative practice, and is being applied to an expanding number of disciplines and scenarios. Early enteral feeding in the critically ill proposes substantial advantages in this already at-risk population and is endorsed by multiple professional societies.[135,205]

## Advances in PN—no longer "total poisonous nutrition"

Optimal nutritional therapy is fundamental to modern ICU care, as critically ill patients often exhibit a catabolic stress state that is associated with increased morbidity and mortality. Historically, one of the main problems with providing high quality ICU nutrition was the lack of a robust and high-quality evidence base, with very few large RCTS conducted. However, over the past 2 decades there has been an explosion of outstanding nutrition research including multiple large and multicenter RCTS. The current problem faced by the ICU physician is not the lack of an evidence base, but rather the difficulty in interpreting the continually evolving body of literature on this topic. Although there are multiple areas of controversy and debate in both the literature and clinical practice, arguably none of these engenders as much fierce debate as the indications and optimal use for PN. After an initial period of PN enthusiasm based on reports in the neonatal and pediatric population, PN in the critically ill adult was largely abandoned in favor of early and aggressive use of EN. This was primarily based on multiple uncontrolled series that associated excess adverse events and mortality with the use of PN, leading to the characterization of PN as a "poison," only to be utilized as a last resort.[304] This is further complicated by the fact that the delivery of PN, as well as general critical care practices, has markedly evolved over the past 2 decades. There is now ample high quality evidence that PN should no longer be considered a "poison," and in many instances may be equivalent to (or even more beneficial than) the enteral route.[305]

There are now several high-quality sources for ICU nutritional information, guidelines, and detailed synthesis and analysis of the existing literature (Tables 5 and 6). What is most notable is that all 3 sets of evidence-based guidelines have significantly liberalized their recommendations for when and how to use PN in the critically ill patient, based on modern evidence that largely refutes the dogma of PN as "poison." In addition, several additional major trials and meta-analyses have been published over the past several years that similarly support the safety and efficacy of PN, and we suspect the next update of these guidelines will even further liberalize indications for PN.

*Initiating nutrition: enteral vs parenteral*

The two most common and inter-related areas of contention and debate surrounding nutrition in the critically ill patient involve (1) the optimal timing for initiating supplemental nutrition and (2) the benefits or disadvantages of EN vs PN. The specific population of interest for providing either form of nutrition focuses on critically ill adult patients who have expected ICU stays of greater than 2-3 days. For the patient who is not critically ill, with no pre-existing malnutrition, and who is expected to resume oral intake within several days, there have been no demonstrated benefits of either aggressive EN or PN support. We can reasonably assume that this patient population would derive very few (if any) potential benefits of EN or PN, but would still be at risk for the potential adverse effects and complications associated with energy supplementation. For the remainder of the critically ill population, we can safely assume that any

**Table 5**
Summary of the 2015 Canadian Critical Care Nutritional Guidelines as compared to the previous (2013) guidelines.

| Topic | Recommendation | Change? | Reason for rec or change |
|---|---|---|---|
| **EN vs TPN** | **Recommend use of EN over TPN if GI tract intact and functional** | **Downgrade** | **Downgraded from "strongly recommend" due to better outcomes in more recent TPN trials** |
| Timing of EN | Start early EN within 24-48 h | No change | Strong evidence for benefit |
| Timing of TPN | Early TPN not indicated in nutritionally low-risk patients, insufficient data for others | No change | For high-risk patients or not tolerating EN, decision of when to start TPN made on case by case basis |
| Determining energy/calorie needs | Insufficient data to support indirect calorimetry vs predictive equations for est caloric need | No change | |
| **Hypocaloric EN** | **Hypocaloric feeding should be considered in patients at low nutrition risk** | **Upgrade** | **Several new PRCTs showing identical outcomes and improved tolerance with hypocaloric feeds** |
| Arginine supplemented EN | Do not recommend arginine supplementation in ICU population | No change | No proven benefit in PRCTs |
| Fish oils, borage oil, and antioxidant supplemented EN | Should be considered in patients with ALI or ARDS | No change | Improved pulmonary and overall outcomes in PRCTs in ALI/ARDS population |
| **Glutamine supplement: EN** | **Recommend that glutamine NOT be used in ICU patients** | **Downgrade** | **Evidence of harm among patients with shock, MSOF** |
| **Glutamine supplement: TPN** | **Recommend that glutamine NOT be used in ICU patients** | **Downgrade** | **Evidence of harm among patients with shock, MSOF** |
| High fat/low CHO or low fat/high CHO EN | Insufficient data to recommend in ICU patients | No change | |
| High protein vs low protein EN | Insufficient data to recommend in ICU patients | No change | |
| Use of motility agents for EN | Recommend the use of metoclopramide if EN intolerance | No change | Erythromycin not recommended due to safety concerns |
| Small bowel vs gastric feeding | Small bowel feeding may be assoc with decreased pneumonia; small bowel feeding indicated in high risk for gastric intolerance or demonstrated gastric intolerance | No change | Based on 11 level 2 studies, including 1 new PRCT. Rec small bowel feeding tube placement if local logistics facilitate, otherwise reserve for gastric intolerant patients |
| **Gastric residuals: threshold and timing of residual checks** | **Threshold of 250 to 500 cc checked every 4 or 8 h should be considered to optimize delivery of EN** | **Upgrade** | **Data demonstrating lower thresholds (<250 cc) have no benefit in preventing emesis/aspiration, and serve to decrease caloric delivery** |
| Combined TPN + EN | Recommend against combined EN + TPN. Consider on a case by case basis if not tolerating adequate EN and all strategies to improve EN delivery exhausted | No change | |
| **TPN vs standard care** | **TPN should not be used routinely, but should be considered for nutritionally high-risk pts with contraindication to early EN** | **Upgrade** | **Based on improved complication profile in recent TPN studies and evidence of benefit in malnourished subgroups** |
| Lipids with TPN | Withholding lipids high in soybean oil should be considered in pts who are not malnourished, are tolerating some EN, or require TPN<10 days; insufficient evidence for all others | No change | Large reductions seen when withholding soybean oil lipids in infectious complications; trends toward reduced mortality, LOS, and mech ventilation |

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CHO, carbohydrate; EN, enteral nutrition; GI, gastrointestinal; ICU, intensive care unit; LOS, length of stay; MSOF, multisystem organ failure; PRCT, prospective randomized controlled trail; pts, patients; TPN, total parenteral nutrition.
Changes from previous are highlighted in bold.[309]

**Table 6**
Summary of the new 2016 SCCM/ASPEN guidelines.[97]

| | |
|---|---|
| **Nutrition assessment** | Risk assessment should be performed (using NRS or NUTRIC) to identify "high risk" patients |
| **Determine energy requirements** | Indirect calorimetry if available; equation or simple weight-based calculations if not |
| **Initiation of feeding** | 1. Early EN within 24-48 h of ICU admission is preferred<br>2. Postpyloric feeding if aspiration risk or gastric intolerance<br>3. If unstable, EN withheld until hemodynamically stable |
| **Dosing of enteral nutrition** | 1. Either trophic or full feeding is appropriate in ARDS or expected vent >72 h<br>2. For high nutrition risk or severely malnourished, advance to goal (>80% of estimated calories) over 24-48 h<br>3. With either trophic or full, provide full protein (1.2-2 g/kg/d) |
| **Use of specialized EN formulations** | 1. Should NOT be used routinely in unselected ICU patients<br>2. Immune enhancing reserved for TBI and major gastrointestinal surgery patients perioperatively<br>**3. No rec regarding immune formula (ω-3 + borage oils) in ARDS/ALI patients*** |
| **Total parenteral nutrition (TPN)** | 1. No TPN until day 7 in low-risk patients not tolerating EN<br>2. Immediate TPN in high risk or malnourished who cannot tolerate EN<br>3. Supplemental TPN after 7 d if unable to deliver >60% energy and protein requirements by enteral route |
| **Dosing of TPN** | 1. Hypocaloric (<20 kcal/kg/d) with full protein be considered in high risk or malnourished for first week of nutrition |
| **Composition of TPN** | 1. Withhold or limit soybean oil lipids over first week<br>2. Alternative lipids be used when they become available in the United States |
| **Glutamine supplementation** | 1. Rec against enteral glutamine supplementation in the ICU<br>2. Rec against parenteral glutamine supplementation in the ICU |
| **Acute pancreatitis** | 1. Early enteral feeding at trophic rate in mod/severe pancreatitis<br>2. Use either gastric or jejunal route (no difference in outcomes)<br>3. TPN after 1 wk if EN not feasible or tolerated |
| **Trauma** | 1. Early EN with high protein within 24-48 h of injury<br>2. Immune formula with fish oils and arginine be considered in severe trauma and in TBI patients<br>3. Open abdomen give early EN if no bowel injury<br>4. Additional protein (15-30 g/L of exudate) for fluid output |
| **Sepsis** | 1. Early enteral nutrition once hemodynamically stabilized<br>2. Enteral preferred over parenteral route<br>3. No use of TPN in early phase of septic shock or severe sepsis<br>4. Trophic feeds for the initial phase of sepsis, advance to full feeds over the first week<br>5. Immune modulating formulas NOT be used |
| **Obesity** | 1. Hypocaloric, full protein feeding strategy be utilized initially<br>2. Goal should not exceed 65%-70% of estimated calories<br>3. If calorimetry not available, use 11-14 kcal/kg *actual* body weight for BMI 30-50, and 22-25 kcal/kg/d of *ideal* body weight for BMI >50<br>4. Protein should be given at 2-2.5 g/kg/d *ideal* body weight |

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; BMI, body-mass index; EN, enteral nutrition; ICU, intensive care unit; TBI, traumatic brain injury; TPN, total parenteral nutrition.

* Differs from Canadian Critical Care Nutrition Guideline rec for the use of these formulas in ARDS/ALI.

patient with an active illness requiring high levels of care is at a high risk for either having or developing both macro and micro-nutrient deficiencies and a so-called “energy deficit.” In addition, patients with pre-existing malnutrition (eg, BMI <19 kg/m$^2$, history of poor oral intake, weight loss >10%-15% of baseline, preillness albumin <3 mg/dL, or cancer with cachexia) should prompt initiation of nutritional supplementation at the earliest possible time.[305] Utilizing these factors to identify patients is critical, and are already considered in validated nutritional risk scoring systems such as the NRS and Nutritional Risk in the Critically Ill (NUTRIC) scores, and we would recommend automatically calculating either or both on every ICU admission.[18,306–308]

Although there is no universal agreement for when to initiate feeding in all ICU patients, there is a general consensus to start EN early for optimal care, defined as within 24-48 hours in the critically ill patient who is unable to maintain volitional intake unless there is an abso-

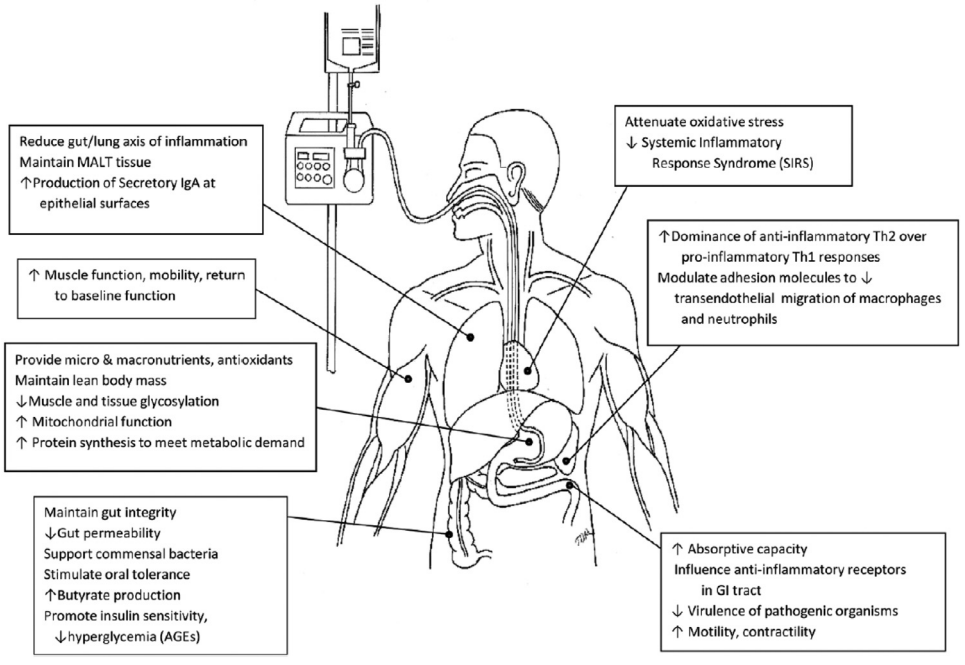


**Fig. 4.** Non-nutritional benefits of enteral nutrition.[407] GI, gastrointestinal; MALT, mucosa-associated lymphoid tissue.

lute contraindication.[135,309] Studies have consistently demonstrated that early EN confers clinical benefit through reduced infections, organ failure, decreased hospital LOS, and possible reduction in mortality rates, when compared to delayed initiation of enteral feeding (see also "Early enteral feeding after surgery—what is the evidence?").[175,267,310] Older studies also demonstrated a benefit of early EN over early PN, prompting the routine call to "use the gut" whenever possible for feeding the ICU patient. Interestingly, these benefits of early EN appear to be relatively independent of the actual nutritional dose (amount of calories delivered), and have been hypothesized to result from minimizing adverse changes in gut permeability or bacterial translocation, minimizing immunosuppression, or even positively impacting the gut microbiome (ie, non-nutritional benefits; Fig 4).[311] Although early EN became the de facto standard of care in most ICUs worldwide, and continues to be the default in most ICUs today, it is important to review and understand the most up-to-date evidence on this topic. The most recent series of studies, including multiple high-quality randomized trials, has shown a markedly improved outcome profile associated with PN, and several have concluded PN to be equivalent to EN in various ICU populations.[312,313]

For the subset of patients that require TPN due to contraindication to EN, there is unfortunately a paucity of evidence associated with the benefit of early administration. Clinicians should consider the pre-existing nutritional status of the critically ill patient. If no evidence of pre-existing malnutrition (by NRS or NUTRIC score) exists, then PN should be considered after 5-7 days of inability to initiate or tolerate EN. However, if there are signs that point toward protein/calorie malnutrition upon admission or those deemed high-risk for nutritional deficiency, PN should be started immediately.

### *Enteral vs parenteral—dogma vs data*

The debate over the indications, benefits, and risks of enteral vs total parenteral delivery of nutritional support has raged for decades, and continues to be a focus of scientific investigation.

Although the enteral route is the seemingly more "natural" and practical method of delivery, it does have significant limitations and unwanted side effects in many critically ill patients, particularly surgical patients. Accordingly, after landmark reports described using PN to successfully support infants with short bowel syndrome, adult intensivists widely embraced PN as an equally effective alternative to EN. However, multiple controlled trials consistently demonstrated worse outcomes in the PN cohorts, prompting the pendulum to swing back to EN as the clearly superior route. It is important to note that these adverse outcomes were primarily infectious complications, including central line-associated infections and pneumonia, and were used to justify recommendations to avoid using PN if at all possible. Currently, there is still general support for the superiority of EN over PN among patients who are able to receive and tolerate enteral feeding. However, the pendulum is again swinging back to a more balanced perspective and greater acceptance of PN as a viable option in the critically ill patient. This increasing acceptance is due to multiple factors, most notably the realization that the complications formerly associated with PN such as hyperglycemia, central line-associated infections, and ventilator-associated pneumonia have been drastically reduced with the evolution of modern ICU care.[314,315] This has been demonstrated in several recent prospective randomized trials that have shown no increased incidence of infections or other adverse outcomes among patients randomized to receive PN.[316,317] In addition, a recent meta-analysis of studies of EN vs PN demonstrated that there was no difference in mortality between the 2 routes, but there was a decrease in infectious complications and LOS associated with enteral feeding.[313] However, this difference appears to be attributable to studies where the PN groups were given significantly greater energy intake vs enteral feeding. This also concurs with the now well-validated concept that the majority of benefits of nutritional therapy in the ICU are not dose-dependent, and can be achieved with relatively low levels of energy delivery vs full feeding. Of interest in this meta-analysis, when only studies where energy delivery was equal between EN and PN were considered, there was no difference in either mortality or morbidities.[313] The concept of "hyperalimentation," or deliberate gross overfeeding of macronutrients compared to estimated requirements, is outdated and no longer routinely practiced by experienced PN providers.

The other proposed advantage of EN over PN is the maintenance of gut mucosal integrity and the prevention of "bacterial translocation" across the gut wall into the lymphatic and systemic circulation. These benefits of EN relative to PN have been validated in several animal models, but the data in humans are severely lacking. In terms of gut mucosal atrophy, the limited available data have been sporadic in showing any significant difference between PN vs EN vs no nutritional intake for short periods of time.[305,312,318] Several studies have shown no significant gut atrophy with PN for up to 3-5 weeks, whereas others demonstrate clinically significant gut atrophy only after 8 weeks or longer of PN.[319–321] The data on bacterial translocation as an actual cause of PN-associated morbidity are even less validated by any research or clinical experience. In one of the studies frequently cited as a basis for this claim, bacterial translocation was identified in only 2 of 132 trauma patients, was associated with small bowel obstruction, and had no relation to enteral vs PN as the route of nutrition.[322,323]

It should be noted that these data apply to short-term use of PN, typically for periods up to 4 weeks, but do not apply to long-term PN use. Although there is little to no direct evidence linking short- to medium-term PN use (less than 4-6 weeks) with gut mucosal atrophy/breakdown or bacterial translocation, there are multiple serious adverse effects when PN is used for prolonged periods of months to years. These adverse effects include vascular access complications (infection, thrombosis), cholestasis and hepatocellular injury, glucose and electrolyte disturbances, and gut mucosal disuse atrophy. In addition, there is a growing body of literature that implicates the gut as a primary driver of local and distant organ injury in critical illness, and that changes to the normal endogenous bacterial gut flora (aka "the microbiome") might be one of the primary factors in this process.[324,325] In these situations where a patient is receiving prolonged PN, aggressive attempts at initiating EN or improving tolerance to EN are warranted in order to avoid the severe potential complications with long-term exclusive PN use (ie, TPN).

The discussions and literature around EN and PN often refer to "TPN" as if that label has a high specificity and clear definition that can allow for comparisons between centers or between studies. Strictly speaking, TPN, refers to the practice of providing PN as the sole source of nutrition and hydration, without any oral or enteral intake. In modern practice, however, some form of oral or enteral intake is almost always present, even if only at non-nutritive doses, so most PN prescribed is in reality SPN (supplemental PN). Beyond the specific combination of nutritional route, "TPN" is a vague term with no specificity that is applied to a highly heterogeneous group of nutritional formulas and products that make generalization and direct comparison difficult and likely fraught with error. This includes marked variations in such critical factors as the total energy content of the PN, the key components of the formula (carbohydrates, proteins, and lipids) and their relative ratios, any carrier solutions or additives, and additional supplemental nutrients such as micronutrients, "immune-enhancing" elements, or specialized disease-specific formulas. In terms of making comparisons between routes of nutrition and in comparing older studies to more modern ones, it is critical to know exactly what all of these PN components were and how they were delivered since many of them have been found to have independent effects on outcomes. Among the most important of these considerations are (1) the total energy load delivered, (2) the amount of carbohydrate delivered, and (3) the amount and type of lipid component (see also "Intravenous lipid emulsions: olive oil, fish oil, and medium-chain triglycerides" section). The amount and type of carbohydrate is a critical factor due to the well-defined relationship between excess carbohydrate loads and the resultant hyperglycemia with adverse outcomes in the ICU population.[326,327] In older studies that delivered large carbohydrate loads and did not adequately address the frequently associated significant hyperglycemia, it is not surprising that complications would be higher in the PN groups. For example, the landmark "VA TPN" trial prescribed "a daily energy goal of 1000 kcal above the resting metabolic expenditure" and demonstrated significantly increased infectious complications.[26] Arguably the most important consideration in this aspect is the type and amount of the lipid component that is delivered. There are now ample data that soybean-based lipid formulas have significant proinflammatory properties and have been associated with higher rates of nosocomial infection, prolonged ICU LOS, and even excess mortality.[328] In contrast, $\omega$-3 containing (or "fish oil" formulas) have been shown to have a markedly different and improved immune enhancing effect, and have been found to be clearly superior to soybean or other lipid formulas in both retrospective analyses and prospective trials.[328,329]

### *When to use TPN: current guidelines*

Currently, there is no consensus regarding the utilization and timing of PN in the critically ill patient. This is mostly because the risk:benefit ratio does not appear to be as strong or as clearly demonstrated for PN compared to EN nutrition, but it also reflects the rapidly evolving data related to current PN use. In the modern era, using current best practices for delivery of nutrition and the formulation and use of PN, there is mounting evidence suggesting that PN can be considered as an equivalent delivery method to EN for short-term nutritional therapy in both medical and surgical ICU populations. This accumulating evidence is already reflected in the most recent updates of ICU nutrition guidelines from SCCM/ASPEN, the Canadian Critical Care Nutrition Guidelines, and ESPEN, where recommendations against TPN have been softened and indications and timing for TPN initiation have been strengthened (Tables 4 and 5).

The current versions of the SCCM/ASPEN and Canadian guidelines take a relatively similar approach to PN use in the ICU patient.[309,330] Both still recommend initiating early EN if possible, and then basing the decision on initiation of PN on the risk category of the patient. For low-to-moderate nutritional risk patients, they recommend deferring PN initiation until day 7, and then starting PN if the patient is still unable to tolerate EN to provide at least 60% of their caloric requirements. However, they both now recommend immediate initiation of PN for patients with pre-existing malnutrition or deemed to be at high nutritional risk. In contrast, the ESPEN guidelines recommend much earlier initiation of PN at 2 days for all ICU patients that

have a contraindication or intolerance to enteral feeding.[331,332] None of these guidelines specifies the exact criteria or definition to identify the high-risk patient, which is a much-needed area for further research. Current best practice is to use a validated nutritional scoring system such as the NRS or NUTRIC to make this determination. Future research in this area will likely lead to an enhanced ability to immediately identify these patients at high risk, and to individually tailor their nutritional therapy based on clinical features, physiology, and individual metabolic and inflammatory profiles.

An objective approach to decision-making with respect to PN utilization and timing begins with determining the nutritional status of the patient. As described earlier, the NUTRIC score is one method to help identify if a patient is at low or high risk for nutritional deficiency.[333] The literature supports delaying PN for the first week in patients who are at low risk for nutritional deficiency.[334] In fact, some studies have suggested that early PN in this subset of critically ill patients has been associated with increased morbidity.[171] However, for those found to be at high risk of nutritional deficiency, the recommendation is to begin PN immediately upon ICU admission if EN is not feasible. A meta-analysis specifically evaluating malnourished patients in the ICU found a significant decrease in complications when PN was initiated early.[335,336] Although the exact timing of PN is not always clear, expert consensus recommends beginning PN after 7-10 days regardless of nutritional status.[97,309]

During the initiation of PN, it is important to consider the dosing, especially in those patients who are found to be malnourished or at high risk for nutritional deficiency. Minimizing excess energy intake early in the ICU stay may reduce morbidity, and this may be most important among patients with a higher acuity of illness or more severe physiological disturbances.[337] The SCCM/ASPEN and Canadian guidelines both recommend hypocaloric dosing ($\leq$20 kcal/kg/d or 80% of estimated energy needs) with adequate protein ($\geq$1.2 g protein/kg/d) during the initial administration of PN.[97,309] In addition, the lipid component should utilize $\omega$-3 or fish-oil-based formulas wherever available (see also "Intravenous lipid emulsions: olive oil, fish oil, and medium-chain triglycerides" section), and soybean-based formulas should be avoided or utilized only in minimal amounts to prevent or correct essential fatty acid (EFA) deficiencies. This approach is particularly important among patients who are severely ill with major metabolic disturbances and are requiring active resuscitation, as adding a large glucose and energy load may result in increased metabolic demand and worsening of their already tenuous status.

### *Review of recent major studies of PN in the ICU*

Several recent prospective randomized trials (see also "Dissecting the critical care nutrition literature" section) and several systematic reviews/meta-analyses have examined multiple aspects of PN in the ICU population. In addition to their inherent value in terms of contributing to the evidence base on this topic, the findings and consistent trends in these studies provide a more global picture of how the associated risks and outcomes with modern PN are much improved compared to the older literature. Many of these studies also provide novel and interesting evidence that raises doubts or even directly contradicts several of the current guidelines on the use of PN in the ICU population.

A 2016 updated systematic review and meta-analysis examined 18 randomized trials of EN vs PN and found no difference in mortality between EN and PN strategies.[313] They also found a decrease in infectious complications associated with EN, which seems to agree with multiple previous studies. Interestingly, when they further divided the parenteral studies into studies where energy intake was higher in the PN arms vs those where energy intake was equivalent, they found that the decrease in infectious morbidity was only seen in trials where the PN group received significantly more energy vs EN. When the two groups were fed equivalent energy, there was no difference in either mortality or morbidity with PN vs EN (Fig 5). This analysis supports the assertion that older studies are flawed in that patients in the PN arms were overfed, and that there appears to be no identified adverse impact of PN using modern formulas and energy goals. In the more recently published TOP-UP pilot trial examining the impact of

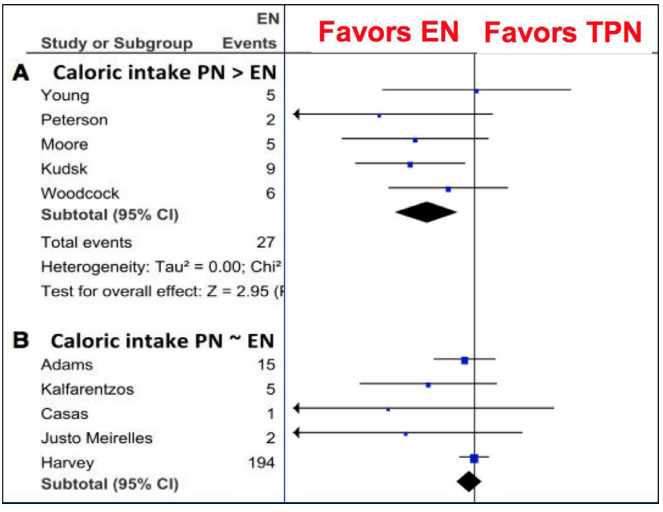


**Fig. 5.** Forest plot of morbidity from a meta-analysis of enteral nutrition (EN) vs total parenteral nutrition (TPN). Note that there is a clear finding favoring enteral nutrition among studies with higher caloric loads in the TPN group (large black diamond), and no difference when only studies using an isocaloric approach (small black diamond) are included. CI, confidence interval. (Modified with permission from Elke G et al.[313])

adding supplemental PN to either underweight or overweight patients with respiratory failure, the addition of parenteral supplementation achieved a significant increase in protein and energy delivery compared to enteral alone.[170] Importantly, there was no associated increase in infection or other adverse event in the parenteral arm of the study, confirming the safety of modern PN delivery. The study also demonstrated several trends suggesting improved outcomes in the parenteral supplementation arm, but will require a larger and more complete follow-on trial to confirm these pilot data. Similar findings that support the safety and possible benefits of SPN were reported in the 2013 Swiss SPN Trial, where patients randomized to receive EN plus PN at day 4 had lower rates of delayed infectious complications vs those receiving EN only (see also "Dissecting the critical care nutrition literature" section).[316]

*Special populations: trauma/burns*

Trauma patients comprise an important subset of the critically ill patient. These patients are often complex and can present with a variety of factors that might make early nutrition delivery difficult. In fact, the significant metabolic response associated with trauma results in the breakdown of LBM unlike what is seen during starvation. This change in metabolism is compounded by a variety of other factors such as the immobility of trauma patients and the subsequent difficulty in providing adequate nutritional therapy. Similar to other critically ill patients, starting nutrition early within the first 24-48 hours after completing resuscitation is associated with improved outcomes.[267,338] A meta-analysis demonstrated a reduction in mortality with early EN in trauma patients.[267] Clinicians should consider lower energy provision during the initial phases with a plan to ramp up to 20-35 kcal/kg/d. The amount of protein should be on the higher end of the range from 1.2 to 2 g protein/kg/d.[305]

TBI has been a widely discussed topic among this subset of patients. Like other trauma patients, those with TBI can have greatly improved outcomes with early EN.[262,339] Although some evidence suggests that the benefit of early nutrition does not depend on the route of admission (EN vs PN), expert consensus still recommends EN, if possible, as the first line of nutritional ther-

apy. These patients can have a measured energy expenditure that is 100%-200% of the predicted baseline resting energy expenditure.[340] As discussed earlier, there are also some data that suggest the utilization of arginine-containing immune-modulating formulations to supplement standard enteral formulas (see also "Advances in Immunonutrition in the Surgical Patient" section); however, at this point, it has not been studied sufficiently to make any strong evidence-based recommendations.[143]

Burn injury patients have also been found to require a significant amount of macronutrients.[341,342] Estimating the exact energy needs can be challenging. Expert consensus recommends measuring indirect calorimetry, as this is currently considered the gold standard for estimating caloric requirements.[135] Similar to trauma, patients with burn injuries require a higher level of protein, ranging from 1.5 to 2 g/kg/d, which is recommended by the numerous guidelines including the American Burn Association (see also "Protein requirements in critical illness—more important than calories?" section).[343] As with other critically ill patients, EN compared with PN has been historically associated with a reduction in morbidity and mortality,[342] and early initiation of EN (within 4-6 hours of injury) may be associated with a lower incidence of complications (see also "Early enteral feeding after surgery—what is the evidence?").[344,345] Table 6 shows a summary of the 2016 SCCM/ASPEN nutrition guidelines that includes recommendations for special subpopulations including trauma, sepsis, obesity, and acute pancreatitis.

*Summary*

Nutritional support in the critically ill patient may be a key factor in determining both the short- and long-term outcomes and the risk of major morbidity or mortality. The choice of the best route of feeding, dose, composition, supplementation, and adjustment strategy is highly variable and the complex decision-making requires understanding of multiple patient and disease factors and their interactions with each other. Simplistic policies that take a universal approach and attempt to provide full energy support regardless of the patient status and disease severity will often result in overfeeding and have no benefit (or even cause harm) to the patient. In particular, the decision of EN vs PN is a frequently encountered dilemma due to the common presence of factors or physiology that preclude full enteral feeding. There has been a marked shift in the PN data that clearly demonstrates that modern PN does not cause an increased infection risk, promote gut atrophy, or bacterial translocation with short-term utilization, or result in significantly worsened outcomes. In fact, the bulk of more recent randomized trials have found that PN appears largely equivalent to EN in many patient populations, and should be considered a key component of critical care management. Achieving these optimal outcomes requires an active and continuously adapting nutritional therapy plan that is tailored to individual patients, their disease severity and physiology, and their dynamic response to their illness or injury. Figure 6 outlines a tailored and personalized approach to ICU nutrition that considers baseline risk factors and then physiological readiness for full nutrient loads as the patient progresses through the typical phases of critical illness.

## Intravenous lipid emulsions: olive oil, fish oil, and medium-chain triglycerides

Our diets are divided into just 6 components: carbohydrates, proteins, lipids, minerals, vitamins, and water. Despite centuries of investigation, the complexity with which these nutrients interact within the living organism is still a matter of ongoing research and intense debate. The focus of this section is to discuss recent advances in the use of intravenous lipid emulsions (IVLE).

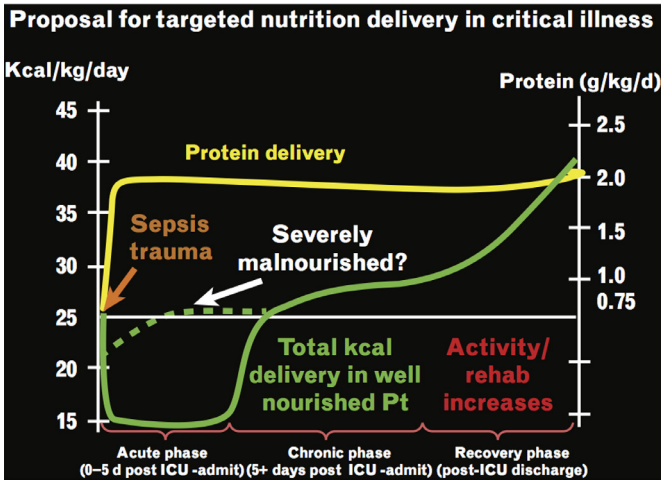


**Fig. 6.** Graph demonstrating targeted or "personalized" nutrition delivery in a standard ICU patient as the patient progresses through the standard phases of critical illness, and that also considers the disease severity and the presence of pre-existing severe malnutrition. ICU, intensive care unit. (Reproduced with permission from Wischmeyer PE.[318])

*Background*

Fats, or lipids, is a nonspecific term that refers to several types of molecules important for function in the human body, including sterols, phospholipids, and triglycerides. Triglycerides are composed of 2 major components: one glycerol molecule and 3 fatty acid chains. Each fatty acid chain has 3 important characteristics: length of the chain (number of carbon molecules), degree of saturation (number of double bonds), and the location of the first double bond. Varying these characteristics changes the physical properties of the fat.

The length of the chain affects the manner in which the body processes the fatty acids, with short-chain triglycerides (2-4 carbons) and medium-chain triglycerides (MCTs; 6-14 carbons) being easily metabolized by enterocytes with the help of the gut microbiome. Once metabolized, they are transported via the hematologic system to the liver and are ready for immediate use as fuel. Long-chain triglycerides (LCTs; $>$14 carbons) require extensive processing in the enterocyte followed by transportation in chylomicrons via the lymphatic system to the liver, where they are further processed. LCTs serve not only as a dense fuel source, but also serve multiple important biologic functions including cell membrane integrity, cell signaling, inflammation, platelet function, and coagulation.[346]

Saturation refers to the number of double bonds within the fatty acid chain and affects the physical characteristics of the fat with fully saturated fats being solid at room temperature and unsaturated fats typically being liquid. Unsaturated fats can be monounsaturated (MUFA) with 1 double bond or polyunsaturated (PUFA) with 2 or more double bonds. All unsaturated fats (MUFA and PUFA) are long chain. Polyunsaturated fats are further characterized by the location of their first double bond. There are 3 families of PUFAs: $\omega$-3, $\omega$-6, and $\omega$-9. The $\omega$ (omega) refers to the location of the double bond as either the third, sixth, or ninth carbon from the terminal end of the fatty acid chain.

It is now recognized that the body is able to synthesize the PUFA oleic acid ($\omega$-9) from acetyl-CoA (the byproduct of glucose and protein catabolism). However, mammals are incapable of forming a double bond at the third or sixth carbon from the terminal end of a long-chain fatty acid, thus rendering mammals incapable of synthesizing $\alpha-$linolenic acid ($\omega$-3) and linoleic acid ($\omega$-6). We must obtain these essential nutrients strictly from our diet. The lack of either of these

two EFAs in the mammalian diet can lead to dermatitis, developmental delay, fatigue, infertility, immunocompromise, and even pulmonary insufficiency.[346]

EFA deficiency (EFAD) was not recognized in humans until the advent of PN. TPN became accepted for mainstream use after Dudrick and colleagues demonstrated growth and anabolism in both animal and human subjects in two landmark publications in 1968.[347,348] Hypothetical fatty acid deficiency was anticipated in these studies, and small aliquots of intravenous plasma were administered to the subjects to prevent EFAD, as no IVLE was available in the United States at that time. No signs of EFAD developed in any of their subjects. In 1972, one of the first reports of EFAD in an infant supported on TPN was published, which was subsequently cured by administration of IVLE.[349]

These early studies emphasized the importance of lipids as a nutritional supplement for patients unable to maintain oral intake, and led to the creation of the myriad of supplements available today in Europe and Asia. The United States has been slower to adopt many of these formulations, leading to a restricted selection of emulsions.

### *The evolution of lipid emulsions in the United States*

Lipid emulsions have been under development since the 17th century when William Courten intravenously administered olive oil to dogs, which ended disastrously. It was soon recognized that fats could not be administered intravenously without modification.[350] Lipomul I.V. was the first lipid emulsion approved for use in the United States in 1957 and was composed of cottonseed oil, soy phospholipids, and ploxamer.[351] However, it was subsequently withdrawn from the market due to severe side effects, likely due to the emulsifier. This early failure led to a dampening of enthusiasm for IVLEs in the United States. PN development continued in the United States, but without the administration of lipids, as there was no FDA approved IVLE at the time. In Europe, approved emulsions continued to be developed and used. A dichotomy of treatment emerged: the “fat system” (European) and the “glucose system” (United States).[352] Many complications of fat-free PN were reported through the late 1960s such as hyperosmolar, hyperglycemic nonketotic diabetic coma; respiratory insufficiency; hepatic enzyme elevation; hepatic steatosis[353]; and EFAD.[354] Therefore, over a decade later, in 1972, a second IVLE was finally approved for use in the United States: Intralipid (Baxter International Incorporated, Deerfield, IL). This drug proved initially to be safe and successful in treating and preventing EFAD. It would be another 25 years before the FDA would approve a second lipid emulsion, Liposyn III (Hospira, Inc, Lake Forest, Illinois), and yet another 15 years would elapse before the third lipid emulsion was approved in 2013: Clinolipid (Baxter International Incorporated, Deerfield, IL). Nutrilipid (B. Braun Medical Inc, Bethlehem, PA) would be approved next in 2014, SMOFlipid (Fresenius Kabi/Baxter, Uppsala, Sweden) in 2016, and most recently, Omegaven (Fresenius Kabi/Baxter, Uppsala, Sweden) in 2018. Each of these parenteral formulations demonstrates increasing complexity due to our expanding knowledge in the field of nutritional science. Selection of the appropriate oil is the key component for creating an effective IVLE. ASPEN has defined “generations” of IVLE as technology and medical knowledge has increased (Fig 7).[355]

#### *First generation*

The composition of all IVLE in the United States prior to the approval of Clinolipid in 2013 was 100% soybean oil. Soybean oil is composed entirely of long-chain fatty acids, and is rich in linoleic acid ($\omega$-6) with much smaller amounts of linolenic acid ($\omega$-3). It was selected early in the development of lipid emulsions for its high EFA content. The metabolism of $\alpha$-linolenic acid ($\omega$-3) and linoleic acid ($\omega$-6) produce different downstream products. These fatty acids compete for the same enzymatic pathway with affinity greatest for $\omega$-3, then $\omega$-6, and lastly the $\omega$-9 series of fatty acids. The downstream products of linolenic acid ($\omega$-3) include EPA and DHA, vital for the production of series 3-prostanoids and 5-leukotrienes, known to have an anti-inflammatory effect. The downstream product of linoleic acid ($\omega$-6) is arachidonic acid (ARA), which is important for the production of series 2-prostanoids and 4-leukotrienes, known to

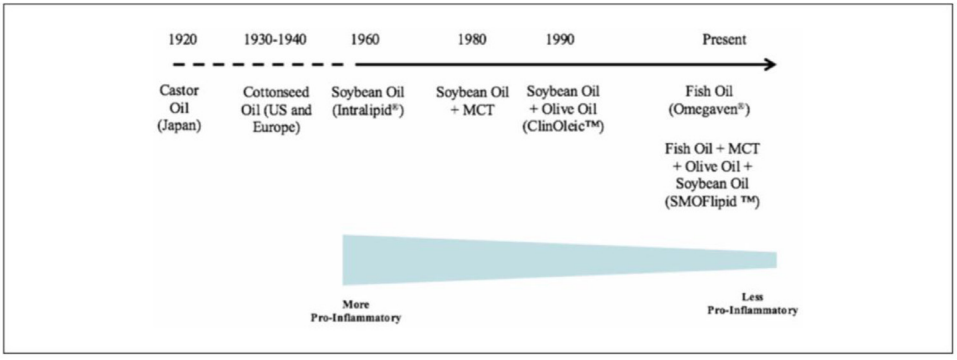


**Fig. 7.** Evolution of intravenous lipid emulsions in the United States.[351] MCT, medium chain triglycerides.

have a proinflammatory effect. After 25 years of being the only IVLE available in the United States, complications related to a 100% soy-based emulsion are well-documented in the literature, including an exaggerated inflammatory response and increased rate of infection.[356] It was hypothesized that not only was each of these FA essential, but that the ratio in which they were administered was also important. Soybean oil has an approximately 7:1 ratio of $\omega$-6 to $\omega$-3 fatty acids. This raised concerns about the proinflammatory profile of soy-based IVLE, as this might be instigating or exacerbating ongoing inflammatory cascade, thereby increasing infectious complications.

There are a few other shortcomings related to soybean oil as a nutritional supplement. It is low in $\alpha$-tocopherol, (vitamin E), which can scavenge the free radicals from lipid peroxidation.[357] It also has a high level of phytosterols (plant-based cholesterols, Fig 8) that cannot be metabolized by the human body.[346] Low levels of vitamin E and high levels of phytosterols have been associated with cholestasis and liver injury in animal models.[358,359] Therefore, although soybean oil can prevent EFAD, it comes at the cost of inflammation and cholestasis.

*Second generation*

Second generation IVLE were the first "mixed oil" emulsions. One of the first products introduced MCTs into the emulsion, typically in the form of coconut oil.[351] MCTs help to stabilize the emulsion because they are resistant to peroxidation, have fewer proinflammatory effects, and are easily metabolized.[360] None of the second generation IVLEs are currently available in the United States.

*Third generation*

The third generation of IVLE contains a mixture of 80% olive oil and 20% soybean oil. This formulation provides a small amount of short-chain triglycerides and a unique LCT ratio of 65% MUFA and 20% PUFA. Similar to MCTs, MUFAs are also less prone to peroxidation, thus enhancing the stability of the emulsion. Although the ratio of $\omega$-6 to $\omega$-3 is actually higher in this emulsion (9:1) than in 100% soybean oil emulsions (7:1), the third generation emulsions manage to maintain a neutral effect on inflammation, possibly due to the high levels of $\alpha$-tocopherol (vitamin E), which naturally occurs in the olive oil. In 2013, the FDA approved Clinolipid for manufacture and sale in the United States, but the manufacturer has not implemented production and therefore, no third generation IVLE is currently available for use in the United States.[352]

*Fourth generation*

Fourth generation IVLE are characterized by the addition of fish oil. Fish oil provides high levels of EPA and DHA, as well as providing a higher ratio of $\omega$-3 to $\omega$-6, giving this emulsion an overall anti-inflammatory profile.[356,361] Clinical trials in both children and adults sup-

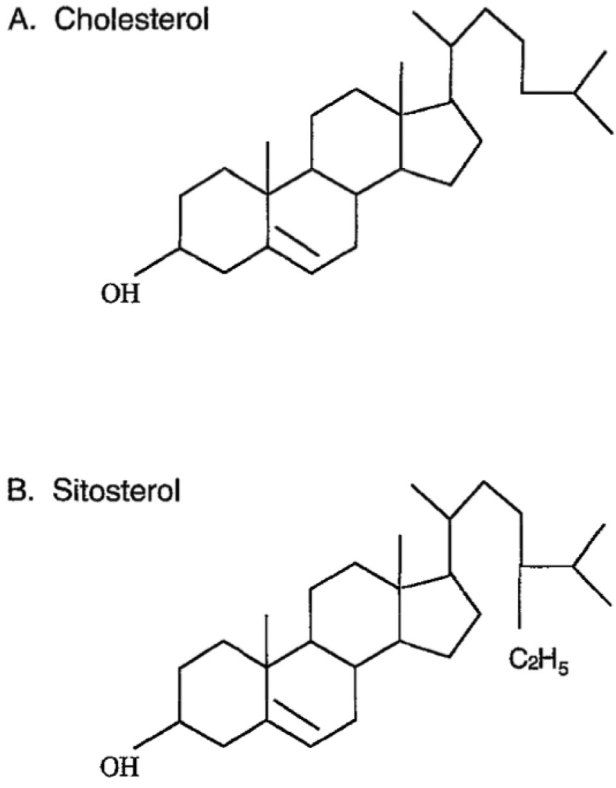


**Fig. 8.** Cholesterol and phytosterol.[408]

port the anti-inflammatory effects of fish oil infusion.[362–367] Additionally, animal studies have documented that fish oil can reverse severe steatosis and improve liver regeneration after injury.[368] There have been impressive reports demonstrating reversal of cholestasis and biopsy-proven PN-associated liver disease after conversion from soybean-based lipid emulsions to fish oil.[369,370] One randomized study from China reported significantly improved biopsy results and clinical outcomes in patients receiving fish oil-based PN (vs standard PN) after liver transplantation.[371] The current body of evidence, comprised mainly of trials conducted outside the United States, attests to the safety and potential beneficial efficacy of fish oil-based lipid emulsions in selected patients.[372–376] Omegaven is the only IVLE composed of 100% fish oil and was recently approved for use in the United States, but only in pediatric patients with PN-associated cholestasis. Omegaven is not recommended for monotherapy due to the relatively low amount of $\omega$-6; however, some have reported maintenance of EFA biochemical profiles on fish oil monotherapy and reversal of EFAD when switching from a lipid-free regimen to a pure fish oil-based regimen.[377,378] One case study reported on an infant who suffered severe hemorrhage while on fish oil monotherapy, which was thought to have occurred secondary to a relative deficiency of ARA, leading to decreased production of thromboxane A2, ultimately impairing platelet aggregation.[379,380] However, larger series have failed to show such an association.[381–383]

SMOFLipid is a unique mixture containing 4 different oils: 30% soybean oil, 30% MCT, 25% olive oil, and 15% fish oil. This emulsion takes advantage of the unique characteristics of each of these oils, and builds upon the scientific foundation that has thus far been accumulated. Although the $\omega$-6:$\omega$-3 ratio is still high (2.5:1), it is vastly improved over the 7:1 ratio present

**Table 7**
Summary of results of meta-analysis by Kreymann and colleagues.[356]

| | **Critically ill patients** (SIRS, sepsis, septic shock, ARDS, severe acute pancreatitis, polytrauma, complicated surgery, medical/surgical patients with APACHE ≥13) | **Surgical patients** (liver transplantation, aneurysm resection) | **Surgical patients with malignancy** (esophageal, gastric, colorectal) |
|---|---|---|---|
| Infection rates | Significant reduction: 21% vs 37.2% (3 studies; 380 pts) | Significant reduction: 9% vs 18% (1 study; 66 pts) | Significant reduction by 59% |
| Hospital LOS | | Significant reduction: 18.7 vs 20.6 d (1 stud; 66 pts) | Significant reduction in Hosp LOS by 1.84 d (13 studies; 1145 pts) |
| ICU LOS | No difference (3 studies; 350 pts) | | |

APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; LOS, length of stay; SIRS, systemic inflammatory response syndrome.

with soybean oil alone.[384] The $\alpha$-tocopherol content is very high, second only to emulsions made with 100% fish oil. It also has a low phytosterol content, making this combination an attractive option to minimize the risk of cholestasis. The majority of evidence demonstrating improvement of intestinal failure-associated liver disease is in neonatal and pediatric patients, but preliminary evidence describing conversion to long-term use of SMOFlipid (due to intolerance of soybean-based lipids) in adult chronic PN patients demonstrate encouraging trends in alkaline phosphatase, liver transaminases, and vitamin E.[385]

Multiple studies have been performed evaluating the efficacy of intravenous fish oil administration, but most are small and underpowered. Thus, several meta-analyses have been attempted to determine if an effect can be demonstrated by aggregating the studies. In 2010, Wei and colleagues evaluated 6 studies (611 surgical patients) comparing 2 groups given PN with or without fish oil.[376] The study found no significant difference in mortality; however, in the fish oil group, they did demonstrate a significant decrease in postoperative infections, and ICU LOS. Chen and colleagues evaluated 13 studies (892 subjects) comparing PN with or without fish oil after major abdominal surgery.[372] They also reported no difference in overall mortality, but did find significantly decreased hospital LOS, ICU LOS, and incidence of postoperative infections for subjects given fish oil. On postoperative day 6, the study evaluated multiple laboratory values and found that patients given fish oil had significantly lower serum aspartate transaminase (AST) and alanine transaminase (ALT); significantly higher plasma levels of $\alpha$-tocopherol, EPA, DHA, Leukotriene-$B_5$, Leukotriene-$B_5$:Leukotriene$B_4$ ratio; and no difference in serum bilirubin, triglyceride, ARA, or $LTB_4$ levels. The most recent meta-analysis by Kreymann and colleagues evaluated the use of Omegaven, Lipoplus, or SMOFlipid vs soybean or soybean/MCT emulsions.[356] The overall results of this meta-analysis are summarized in Table 7. The main purpose of the analysis was to determine if there were significant differences in the efficacy of these products. They were unable to discern a difference between the different IVLE; however, the authors were able to support the conclusion that fish oil provides benefit over soybean or soybean-MCT IVLEs in most patient populations.

### *Recommendations*

The 2016 SCCM/ASPEN consensus guidelines recommend withholding soy-based IVLE administration during the first week of PN, unless there is a concern for EFAD.[330] In this case, they recommend limiting IVLE to 100 g/wk. However, they state that, based on expert opinion, where available, newer generation IVLE formulations should be initiated at the same time as PN.

*Summary*

Fatty acids serve not only as an important fuel source for the human body, but they also sustain critical biologic functions such as cell membrane integrity, cell signaling, inflammation, platelet function, and coagulation. Our current understanding of fatty acid metabolism and function is still limited, but fourth generation IVLEs provide a promising therapy with less risk (and perhaps even benefit) for patients unable to receive adequate EN.

## Dissecting the critical care nutrition literature

The critical care community has recently invested significant resources toward an improved comprehension of nutrition support strategies in the critically ill patient. Over the last two decades, multiple large trials have been conducted, improving upon our pre-existing foundational knowledge. The care of the patient in the ICU is admittedly a subject bereft with complexity. In this morass, determining the overall contribution, whether positive or negative, of a single adjunctive intervention such as protein or energy provision can be exceedingly difficult. In this section, we will briefly discuss several high-profile nutrition trials and point out several caveats, which are important in putting them into context and applying them to clinical practice.

### *Dose of EN*

#### *EDEN*

The Early Vs Delayed Enteral Nutrition (EDEN) trial sought to determine if initial "trophic" enteral feeding would improve ventilator-free days at 28 days and decrease GI intolerance compared to "full feeding" in patients with acute lung injury (ALI).[386] Rice and colleagues performed an open-label multicenter trial, enrolling 1000 adults from 44 ICUs within 48 hours of ALI diagnosis. Patients were randomized to receive either trophic or full EN for the first 6 days after enrollment. After day 6, all patients were given full EN. "Full feeding" was defined as 25-30 kcal/kg (ideal body weight) per day of nonprotein calories and 1.2-1.6 g/kg (ideal body weight) per day of protein.

In this trial, there was no significant difference in the primary endpoint (28 day ventilator-free days), or in 60-day mortality. Additionally, there were no significant differences in infectious complications. The full-feeding group, however, did have higher rates of vomiting, elevated gastric residual volumes, constipation, mean glucose values, and average hourly insulin requirements. The authors thus concluded that in patients with ALI, initial trophic enteral feeding for up to 6 days did not improve ventilator-free days, 60-day mortality, nor infectious complications, but was associated with lower incidence of GI intolerance.

There are several caveats to remember when applying this study to clinical practice. The study population was relatively young (mean age 52) and was comprised predominantly of medical patients. Additionally, the patient population was neither obese, nor overly malnourished, with an average weight of 86 kg and BMI of 30 kg/m$^2$. Prior large-scale international observational studies have suggested that the dose of EN has minimal impact on mortality for patients with BMI in the range of 25-35 kg/m$^2$.[148] Furthermore, although the full-feeding group did receive more enteral calories than did the trophic-feeding group (1300 kcal/d vs 400 kcal/d), when normalized by weight, the "full" feeding group received less than the target of 25-30 kcal/kg, even after accounting for the additional energy received as protein. Therefore, one could rightly consider this a trial comparison between trophic feeding and underfeeding (rather than "full" feeding) and neither group achieved adequate protein intake as recommended by SCCM/ASPEN (see also "Protein requirements in critical illness—more important than calories?" section). One final factor to consider is that for nearly every study day, the full feeding group had significantly higher fluid balance. Although this did not result in any detectable unto-

ward effects on ventilator days or mortality, it could have influenced the incidence of GI intolerances.

Thus, to summarize the EDEN study, in relatively young, normal weight patients (neither malnourished nor obese) with early and moderate ARDS, initial trophic enteral feeding was not superior to less than "full" enteral feeding, but it may be better tolerated and may result in less fluid gain.

*PermiT*

The PermiT trial evaluated the effect of "permissive underfeeding" compared to standard feeding on 90-day mortality.[387] A previous single-center randomized trial from the same group reported significantly lower hospital mortality in the permissive underfeeding group and a trend toward improved 28-day all-cause mortality.[388] In this follow-up confirmatory trial, Arabi and colleagues enrolled 894 patients from 7 ICUs and randomized them to either permissive underfeeding (target 50% of calculated energy requirements) or standard feeding (target 100% of calculated requirements) for up to 14 days while maintaining the same protein delivery (1.2-1.5 g/kg/d) in both groups.[387]

There was no significant difference in the primary outcome (90-day mortality) between the permissive underfeeding group (27%) and the standard feeding group (29%), nor were there any significant between-group differences in feeding intolerance, diarrhea, or ICU-acquired infections, ICU LOS, or hospital LOS.

Like the EDEN trial, the PermiT trial hypothesized that lower enteral nutrient delivery would be advantageous, and like the EDEN trial, the PermiT trial was a "negative" trial. This has led many to conclude that trophic/underfeeding and "full" or standard feeding are equivalent and some have extrapolated these findings to all patients. Once again, it is important to scrutinize the enrolled subjects and study results to determine applicability. In PermiT, the estimated calorie requirements were calculated according to the Penn State equation for those with a BMI $<30$ kg/m$^2$ and the 1992 Ireton-Jones equation for those with BMI $\geq 30$ kg/m$^2$. Similar to the EDEN cohort, the PermiT subjects were mostly medical patients (75%), relatively young (mean age 50), and were relatively well-nourished at baseline (mean weight 80 kg and mean BMI 30 kg/m$^2$). As in the EDEN trial and their previous pilot trial, the standard feeding group did not achieve their goal, receiving on average only 71% of their calculated energy requirement. Although this suboptimal delivery of energy is consistent with real world conditions,[389] this trial cannot be considered a true comparison between permissive and full enteral feeding. The investigators targeted 1.2-1.5 g protein/kg/d according to then-current guidelines,[390] but both groups received only about 58 g protein/d, which is less than 1.0 g/kg/d according to the average weight of enrolled subjects. This protein inadequacy is puzzling, as the PermiT trial protocol allowed for additional modular protein supplementation. Large-scale observational studies have suggested that outcomes are improved when patients receive $>80\%$ of prescribed protein targets and that protein delivery is likely more important and impactful than energy delivery.[164] Thus, this trial is truly a comparison between underfeeding and less underfeeding with protein underdelivery in both arms. The PermiT trial also reported increased glucose levels and insulin requirements in the standard feeding group, but did not report any improvements in protein catabolism, as measured by nitrogen balance and urinary nitrogen excretion. Finally, to overcome some of the criticisms of EDEN, the PermiT investigators administered enteral saline or water to equalize the fluid balance. Unlike EDEN, there was no significant difference between groups in GI complications.

Thus, to summarize the PermiT trial, in relatively young, well-nourished adults, a strategy of targeting 50% of calculated energy needs (according to Penn state equation or 1992 Ireton-Jones equation) did not improve 90-day survival compared to a strategy of targeting 100% of calculated caloric needs when both groups had suboptimal protein delivery and equal fluid balance.

*INTACT*

The Intensive Nutrition in Acute Lung Injury (INTACT) trial was a single-center trial that randomized subjects diagnosed with ALI to either intensive medical nutrition therapy (IMNT), defined as provision of >75% of estimated energy and protein requirements, or standard nutrition support care (SNSC). The investigators used 30 kcal/kg of admission weight (or obesity-adjusted ideal body weight) and 1.5 g protein/kg ideal body weight (or adjusted ideal body weight for obese patients). Unlike EDEN and PermiT, which both hypothesized superiority of underfeeding, INTACT was designed to test the hypothesis that aggressive "full" feeding was superior to standard care.

The IMNT group received significantly more kcal/kg/d (25.4 kcal/kg/d, or 85% of their estimated requirements vs 16.6 kcal/kg/d or 55% of estimated requirements, $P< 0.0001$) and received significantly more protein (82 g vs 60 g, $P< 0.0001$) than the SNSC group, though still less than 1.5 g/kg/d. This study was stopped early by the data safety monitoring board because of significantly higher hospital mortality in the IMNT vs SNSC group (40% vs 16%, $P= 0.02$). The sample size was initially calculated based on their primary endpoint of infectious complications and this mortality difference was an unexpected secondary finding. Ultimately, they enrolled less than 50% of their projected sample of 200 subjects. The enrolled subjects were similar to EDEN and PermiT, in that the average age was 50 years and the average BMI was around 30 kg/m$^2$. According to the SGA, the majority of enrolled subjects were either normal or moderately malnourished, with only 3 out of 78 (4%) of all subjects classified as severely malnourished. Although the baseline severity of illness was also comparable in terms of APACHE II score and $PaO_2$:$FiO_2$ ratio, and the energy/protein received by the "full"/"standard" arms of all 3 trials are nearly identical, the reported mortality rate in the control arm was much lower than the 22% and 29% reported in the EDEN and PermiT trials, respectively, and far below the 40% mortality reported in a large scale international epidemiologic study of ARDS.[391] This unexpectedly large difference in mortality rate should alert the reader that this control arm may not be representative of the usual patient population. Additionally, the cause of death for 18 of the 22 mortalities was "terminally extubated," and there was no difference in mean energy, protein, or lipids received between the group that died and those that survived, raising the question of whether or not aggressive nutrition therapy contributed significantly to the patient's demise.[392] The authors acknowledge that their target of 30 kcal/kg/d was not specifically targeted toward LBM. Recent evidence shows that LBM is relatively low in critically ill patients and thus, using admission weight may have led to overfeeding in the intervention group. The study intervention was carried forth beyond ICU stay through hospital discharge, and this also may have resulted in overfeeding relative to metabolic requirements.

Thus, to summarize the INTACT trial, in adults with ALI, aggressive provision of EN calculated based on admission weight and carried forth through hospital discharge did not improve clinical outcomes and may be associated with excess mortality. While the significantly increased mortality is concerning, it must be placed in the context of a single-center trial that was stopped early and had a significantly lower control group mortality rate than other trials from the same era enrolling similar patients.

Taken as a whole, the EDEN, PermiT, and INTACT trials allow us to draw some broad conclusions. In mostly medical ICU patients with moderate ARDS (the Berlin criteria equivalent of ALI), trophic or permissive underfeeding with low protein delivery in the first 6-14 days of illness is not superior to standard feeding (ie, delivery of ~70% estimated caloric needs) with low protein delivery. GI intolerance does not seem to be significantly affected once fluid balances are taken into account, but glucose levels and insulin requirements are higher with standard feeding. Aggressive enteral/oral nutrition carried forth through hospital discharge, however, is also not superior to standard nutrition practice and may be associated with excess mortality through an unknown mechanism.

*Route of nutrition*

*CALORIES*

The CALORIES trial hypothesized that early nutritional support with PN was superior to EN for 30-day survival.[393] Harvey and colleagues enrolled 2400 patients from 33 ICUs in a large, pragmatic trial. Subjects were eligible for either PN or EN and randomized to either route of delivery within 36 hours of ICU admission and continued for up to 5 days.

There were no significant differences between groups in the primary outcome (30-day mortality): 33% and 34% in the PN and EN groups, respectively. The PN group had lower rates of hypoglycemia and vomiting and there were no significant differences in other secondary outcomes such as infectious complications or 90-day mortality. Interestingly, the energy intake was identical in both groups, with the majority of patients unable to achieve target intake (25 kcal/kg actual body weight). Close inspection of the study cohort reveals that the subjects were well-nourished, with more than 90% of both groups classified as "None" for degree of malnutrition assessment.

Although the CALORIES trial failed to confirm the hypothesis that PN was superior to EN for the primary endpoint, it did prove that modern-day PN is not as harmful as once vilified.[304] Prescribed in the context of catheter-care bundles, moderate caloric prescription, and glycemic control, PN does not lead to increased infectious complications and is superior to EN regarding hypoglycemia and vomiting complications.

*EPaNIC*

The 2011 EPaNIC trial hypothesized that early SPN would reduce the rate of complications compared to delayed SPN.[171] In this large trial, 4640 subjects from 7 ICUs were randomized to either early SPN (within 48 hours) or delayed SPN (ICU day 8). In essence, this trial compared the ESPEN recommendation for early SPN to the ASPEN recommendation for delayed SPN. Importantly, all included subjects had an NRS score $\geq$3, indicating "nutritionally at risk."

Although rates of ICU, hospital, and 90-day mortality were similar, patients in the delayed SPN group had lower rates of ICU infections and cholestasis and had a higher likelihood of being discharged alive earlier from the ICU and the hospital. Other secondary outcomes favoring delayed SPN included proportion of patients requiring more than 2 days of mechanical ventilation, duration of renal-replacement therapy, and healthcare costs. The investigators concluded that late initiation of PN was associated with faster recovery and fewer complications. Subgroup analysis of this trial demonstrated that early PN reduced the quality of muscle tissue, causing increased lipid conversion in the femoral and abdominal muscles, and early PN were more likely to develop ICU-acquired weakness.[394,395]

Although these findings make a strong case to avoid early PN in ICU patients, several caveats are worth mentioning. As in other trials, close examination of the enrolled subjects reveals that the vast majority ($\sim$80%) of enrolled subjects had a BMI in the 20-30 kg/m$^2$ range and approximately 80% had NRS scores of 3 or 4 and were not considered at high nutritional risk. Scrutiny of the results shows that the subjects were not that ill, with a median duration of mechanical ventilation of only 2 days and a median ICU stay of only 3-4 days. Ninety-day mortality was approximately 11% and the majority of subjects were postcardiac surgery. It is important to note that the early SPN group immediately received intravenous 20% glucose solution infusion: 400 kcal on ICU day 1 and 800 kcal on ICU day 2. Infusion of such a large glucose load in the first two days of critical illness is not common practice in most ICUs. Others have pointed out that the early separation of outcomes (mechanical ventilation $>$2 days and ICU stay $>$3 days) is almost certainly attributable to this large, possibly harmful, early glucose load, as PN was not started in the early PN group until the third ICU day.[396]

Thus, to summarize the EPaNIC trial, in moderately nutritionally at risk postcardiac surgery patients with low severity of illness and expected short ICU stay, early SPN (including aggressive glucose infusion on ICU days 1 and 2) was not superior to delayed SPN and was associated with multiple worse outcomes.

*NUTIREA-2*

The NUTRIREA-2 investigators hypothesized that early aggressive EN would lead to lower 28-day all-cause mortality compared to early aggressive PN in mechanically ventilated patients requiring vasopressor support for shock.[253] Subjects randomized to EN could receive supplemental PN if energy targets were not met by day 8. The investigators targeted 20-25 kcal/kg of actual body weight during the first 7 days and then 25-30 kcal/kg thereafter. In both groups, nutrition therapy was started within 24 hours of ICU admission and rapidly advanced to goal by day 1.

The trial was stopped early for futility after 2410 patients had been enrolled. There was no difference in the primary outcome (28-day mortality) between groups: 37% in the EN group and 35% in the PN group. Similar to the CALORIES trial, there was no significant difference between groups in ICU-acquired infections. However, the EN group had higher rates of GI complications, including vomiting, diarrhea, and most concerning, bowel ischemia, and acute colonic pseudo-obstruction.

Thus, to summarize the NUTRIREA-2 trial, early aggressive EN in ventilated and hemodynamically unstable patients was not superior to early aggressive PN and led to increased incidence of GI complications, some life-threatening. This high-quality trial adds to our understanding of the role of EN nutrition in ICU patients. Regrettably, there was no control arm consisting of either no nutrition or trophic EN.

*Swiss SPN trial*

The multicenter Swiss supplemental PN trial by Heidegger and colleagues enrolled patients on their third ICU day if they had not yet achieved 60% of their energy goal through EN alone, were expected to require at least 5 days of critical care, and were expected to survive at least 7 days.[397] Patients were randomized to continued EN or EN with SPN adjusted daily using individualized daily indirect calorimetry measurements. The intervention was continued for the subsequent 5 days and subjects were assessed for the incidence of nosocomial infections between days 8 and 28, a meaningful and plausible outcome. There was adequate separation of groups (28 kcal/kg vs 20 kcal/kg in the SPN and EN groups, respectively) and a significantly decreased rate of new nosocomial infections (27% vs 38%, $P = 0.0338$) in the SPN group. This trial enrolled high-risk patients, used the gold standard indirect calorimetry to precisely target nutrient delivery, and chose a reasonable and relevant endpoint.

*Summation and synthesis of recent trials*

As in any medical intervention, nutrition therapy must be delivered to the right patient, at the right time, by the right route, in the right dosage. It has been repeatedly demonstrated that the ICU population is heterogeneous and that nutritional interventions seem to benefit only those at greatest risk. Those progressing to chronic critical illness seem to be most affected by differences in energy/protein delivery, particularly within the first week of ICU admission.[398,399] Unfortunately, in the early period of critical illness, it is extremely difficult to predict which patients will require a long ICU stay. Several critical care nutrition trials enrolled primarily nourished and/or low-acuity patients unlikely to benefit from nutritional optimization. Thus, it is unsurprising that these trials were unable to detect a clinically important difference. Another potential reason for the “negative” results may be delta inflation, or the overly optimistic exaggeration of the expected treatment effect size (delta). A recent review of 38 trials in 5 high impact journals reported that investigators routinely overestimated delta, resulting in inadequate sample size (type 2 statistical error) in the vast majority of studies.[400] The INTACT trial was stopped early because of an unexpectedly high mortality rate discovered on interim analysis, which did not seem to have a biologically plausible explanation given that many deaths were due to “terminal extubation.” It is possible that a type 1 statistical error was the cause. One final question to consider is whether mortality is the most appropriate endpoint to focus upon when considering critical care nutrition practice.[401] Although mortality is an objective and undeniably important clinical outcome, there are many potential confounding factors. Given the

complexity of critical care illness and the multitude of factors affecting such a blunt outcome, it is not surprising that trials enrolling a heterogeneous population with a range of nutritional risk and evaluating a single nutritional intervention have "negative" results. Other patient-centric endpoints, such as functional status, discharge disposition, and quality of life may be more relevant and meaningful. This focus on mortality as an endpoint is not limited to nutrition studies, as a review of 72 multicenter randomized trials in critical care demonstrated that only a minority reported positive survival benefits, with the great majority showing no effect.[402] Although more challenging to assess, other patient-centered and clinically important endpoints besides mortality should be considered.[403] The pilot trial preceding EDEN reported that survivors receiving "full" feeding were more likely to be discharged home (as opposed a to rehabilitation facility) compared to the trophic feeding patients.[404] A 12-month follow-up study of the EDEN trial reported a significantly lower cumulative incidence of admission to a physical rehabilitation facility in the "full" feeding group (14% vs 23%, $P = 0.01$).[405] Other studies have reported that higher energy and protein deficits accumulated in the first 14 days of critical illness are associated with lower rates of home discharge for survivors.[406] Thus, there remain many unanswered questions, but the recently published critical care nutrition literature may be summarized in the following points. First, well-nourished patients with low acuity of illness are unlikely to benefit from aggressive nutritional interventions. Second, modern-day PN is not more harmful than EN.

## Conclusions

Nutrition in the surgical patient is a rapidly evolving field. Previously ironclad traditions and dogmas have recently been challenged. It is now recognized that "bowel rest" for pancreatitis is no longer appropriate. Enhanced recovery pathways have unequivocally demonstrated that it is unnecessary to await clinical signs of intestinal function before initiating postoperative oral nutrition. The role of immunonutrition continues to confuse and bewilder, while the importance of preoperative rehabilitation ("prehabilitation") is becoming clear. Modern PN is not as harmful as once believed and newer generations of parenteral lipid formulations hold exciting promise for further improving the safety profile of PN. The boundaries of our scientific knowledge continue to expand and surgeons must continue to update their practice in order to provide high-quality care for their patients.

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