CHEST Postgraduate Education Corner
CONTEMPORARY REVIEWS IN CRITICAL CARE MEDICINE

Nutrition in the ICU

An Evidence-Based Approach

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Providing artificial nutrition is an important part of caring for critically ill patients. However, because of a paucity of robust data, the practice has been highly variable and often based more on dogma than evidence. A number of studies have been published investigating many different aspects of critical care nutrition. Although the influx of data has better informed the practice, the results have often been conflicting or counter to prevailing thought, resulting in discordant opinions and different interpretations by experts in the field. In this article, we review and summarize the data from a number of the published studies, including studies investigating enteral vs parenteral nutrition, supplementing enteral with parenteral nutrition, and use of immunonutrition. In addition, published studies informing the practice of how best to provide enteral nutrition will be reviewed, including the use of trophic feedings, gastric residual volumes, and gastric vs postpyloric tube placement. ***CHEST 2014; 145(5):1148–1157***

Abbreviations: ALI = acute lung injury; EN = enteral nutrition; GLA = gamma-linolenic acid; GRV = gastric residual volume; PN = parenteral nutrition; RR = relative risk; SSC = Surviving Sepsis Campaign; VAP = ventilator-associated pneumonia

The majority of critically ill patients are unable to provide their own nourishment, particularly while receiving mechanical ventilation. Observational data suggest that malnutrition is associated with worse outcomes in critically ill patients,[1,2] and many have assumed this means that providing artificial nutrition to critically ill patients improves outcomes, regardless of baseline nutrition status. Although the practice of providing nutrition to these patients is almost universal, the specifics vary widely from one ICU to another and even among providers. This holds true for both routes of nutrition (parenteral, enteral, or enteral supplemented with parenteral) as well as the specific practices of providing enteral nutrition (EN) (location of feeding tube, gastric vs postpyloric feeding tube, gastric residual volumes [GRVs]). The reason for this variability is at least in part due to the paucity and quality of data. Over the last decade, clinical research in critical care nutrition has expanded and advanced, resulting in the recent publication of numerous large, well-conducted randomized studies surrounding the practice of providing artificial nutrition to critically ill patients. These studies have helped clinicians better understand many elements of critical care nutrition and help differentiate myths from established facts. However, although these studies have certainly advanced what is known about critical care nutrition, they have also resulted in varying interpretations of the results, generating extensive discussion and some confusion among clinicians.

This article focuses on numerous aspects of critical care nutrition, with emphasis on topics with recently published data. Data informing the best route of artificial nutrition will be reviewed as well as practice aspects of providing EN. Specifically, this article reviews data comparing parenteral nutrition (PN) vs EN, supplementing EN with PN, trophic enteral feeding,

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immunonutrition, measuring GRVs, and determining the appropriate level of infusion within the GI tract (gastric vs postpyloric) for feeding tubes.

Parenteral vs Enteral Nutrition

Experimental and clinical studies have shown that EN has benefits over PN in the critically ill patient. EN has been reported to promote the protective effects of commensal bacteria, maintain the mass of gut-associated lymphoid tissue, and preserve GI mucosal structure and function.[3-12] Clinical studies have shown these effects translate into better outcomes with respect to infection, organ failure, and hospital length of stay.[4-6,8,13,14] The majority of these studies were conducted a while ago, without any standard control of hyperglycemia, and before recent improvements in the composition of PN, better infection control, and better care of central lines. However, despite advances in these areas, there are no recent data that demonstrate PN results in improved outcomes over EN in critically ill patients. As such, consensus guidelines continue to recommend the preferential use of EN in critically ill patients whenever possible.[15-18]

Supplemental PN

Despite tolerating some EN, the average delivery in most patients fails to reach goal or target feeding rates, as calculated from estimated or measured protein and calorie requirements. Subsequently, some practitioners have adopted the practice of supplementing whatever the patient can tolerate enterally with PN to achieve delivery of full estimated caloric and protein requirements. A meta-analysis of five studies comparing EN alone with combined EN and PN found no difference in any clinical outcome, including mortality, infectious complications, time on the ventilator, or hospital or ICU lengths of stay. There was considerable heterogeneity among the studies, and none of the studies was done using tight glucose control. Differences in interpretation of these studies led to a divergence in consensus guidelines, with one recommending for and one against adding PN to patients who were unable to tolerate full nutrition enterally.[15,18] A phase 2, open-label, single-center randomized trial of 130 patients who were mechanically ventilated that were expected to stay in the ICU at least 3 days found that using serial metabolic cart measurements to guide the supplementation of EN with PN resulted in a trend toward lower hospital mortality (32.3% vs 47.7%, $P = .058$) compared with a strict target delivery of 25 kcal/kg/d of EN.[19] However, overall lengths of time on ventilation and ICU stay were longer in the intervention group. A subsequent very large, open-label, randomized, multicenter trial investigated the role of supplementing EN with PN in critically ill adults at moderate nutritional risk.[20] Of the 4,640 patients enrolled, 2,312 were randomized to receive only EN as tolerated for up to 7 days before initiating PN (late initiation group) compared with 2,328 patients randomized to receive supplemental parenteral calories in addition to whatever EN they could tolerate during the first 7 days (early initiation group). All patients in this study were managed with a tight glucose control (ie, 80-110 mg/dL) strategy. The study, Impact of Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients (EPaNIC), found that early supplementation of EN with PN resulted in lower rates of early, alive discharge from the ICU (hazard ratio, 1.06; $P = .04$) and hospital (hazard ratio, 1.06; $P = .04$) than EN alone. In addition, patients in the late-initiation group had lower rates of ICU infections (22.8% vs 26.2%, $P = .008$). Interpretation of the EPaNIC study results have varied. At the end of January of 2013, the Surviving Sepsis Campaign (SSC) issued updated guidelines regarding the care of patients with severe sepsis. In this third edition of the SSC, the committee recommends avoiding the use of PN alone or as a supplement to hypocaloric enteral feeding.[21] Others criticize the EPaNIC study for what was interpreted to be a detrimental effect from IV glucose given in the early supplemental PN. In addition, critics worry that the patients enrolled were only moderately critically ill overall and, therefore, not representative of most patients considered candidates for PN at other institutions. They cite a smaller study by Heidegger and colleagues,[22] which showed some improvement in nosocomial infection late in ICU admission with use of supplemental PN started after 72 h in patients receiving $< 60\%$ of goal enteral feedings. Subsequently, a post hoc reanalysis of the EPaNIC data showed that the detrimental effect in the early PN group was not due to glucose but instead to the early receipt of parenteral protein.[23] By examining quartiles of the APACHE (Acute Physiology and Chronic Health Evaluation) II score, it was evident that greater degrees of critical illness were associated with a worsening adverse effect from early PN regarding mortality and nosocomial infection. Furthermore, in a complicated post hoc analysis, Casaer and colleagues[23] showed that the more feeding a patient received through either day three or seven, the lower the likelihood of being discharged alive from the ICU. The effect, however, appeared to be driven by the early receipt of PN, as the receipt of enteral nutrients was similar between the groups throughout the first week. Although the nutrition community might have interpreted the findings that EN and PN are not equal and that early PN is bad in the ICU, Casaer and colleagues[23] and Schetz and colleagues[24] interpreted results to

suggest that all early nutrition was bad and should be withheld or minimized in the first week following ICU admission. They hypothesize that early nutrition, regardless of route of administration, exerts its detrimental effects by suppressing autophagy, or the natural recycling of intracellular nutrients to maintain energy homeostasis during starvation. Autophagy may be important for recovery of organ dysfunction through both the immune response and the removal of toxic intracellular proteins and damaged organelles.[24] However, given other contradictory data suggesting benefit to early EN[25] and similar outcomes with trophic and full enteral feeding,[26,27] this hypothesis needs further testing in a prospective study.

Timing of EN

Although consensus guidelines recommend the use of EN over PN when possible, the optimal time to initiate EN remains unknown. Because of its beneficial effects on intestinal epithelium and commensal bacteria, and the presumed benefit of providing caloric support during the early catabolic phase of critical illness, many advocate starting EN as soon as possible after the patient is resuscitated. Doig and colleagues[25] combined the data from six randomized controlled trials comparing "early" EN, defined as initiated within 24 h of admission, with later initiation. This meta-analysis found that initiation of EN within 24 h of injury or ICU admission resulted in a significant reduction in mortality, with an OR of 0.34 (95% CI, 0.14-0.85). The combined population was small, with only 234 total patients from the six studies, one-half of whom were trauma patients. In fact, only 28 were patients who were mechanically ventilated in the general ICU. The benefit of early EN is maintained if two studies with excessive loss to follow-up are included (324 patients total; OR, 0.40; 95% CI, 0.19-0.85). The authors also found a reduction in pneumonia when EN was initiated within 24 h, but this portion of the analysis was limited to 80 patients, since pneumonia was reported as an outcome in only two studies.

Some practitioners worry that initiating EN in patients who are in shock or not fully resuscitated may increase the risk of intestinal ischemia or necrosis.[28,29] However, these events are extremely rare, and the evidence supporting EN as the cause are suspect.[30,31] Conflicting data supporting the safety of enteral feeding in hemodynamically unstable patients come from retrospective analyses.[32,33] Although EN does increase intestinal oxygen demand, it also has been shown to increase intestinal blood flow and improve intestinal function, potentially protecting against bowel-related complications.[34-36] No studies have randomized hemodynamically unstable patients to receive EN while still in shock vs waiting until its resolution and compared clinical outcomes. However, the studies composing the meta-analysis of Doig et al[25] as well as randomized controlled studies evaluating EN or supplementation of EN included patients in shock.[26,27,37-41] Specifically, providing trophic feedings to patients in shock may balance the benefit of using the gut while lowering the risk of providing EN. Studies testing this hypothesis are currently lacking, however.

Trophic Feedings

Data on the optimal amount of EN to deliver are also contradictory. Several observational studies show improved clinical outcomes for patients receiving more of their caloric needs,[42-44] whereas other data suggest lower volumes of EN may result in less time on mechanical ventilation and improved mortality.[45-49] Full feeding, through the provision of more calories and reducing the caloric deficit early in the disease course, could preserve strength, support immune function, and improve outcomes. On the other hand, minimal amounts of EN (sometimes termed trophic nutrition for its effect on preserving intestinal epithelium, stimulating secretion of brush border enzymes, and preventing increased intestinal permeability) may still provide the benefit of full EN while limiting the potential detrimental effects of GI intolerance and minimizing the provision of those nutrients that might fuel an overzealous immune response.

The third edition of the SSC guidelines recommends against full caloric feeding in the first week of hospitalization in the ICU, instead recommending low-dose feeding at 500 cal/d.[21] This recommendation is largely based on two similarly designed studies. The first is a single-center, open-label study randomizing critically ill adults expected to need mechanical ventilation for at least 3 days to either trophic enteral feedings (delivering about 15% of goal calories) vs a full enteral feeding strategy early in the ICU course.[26] This study, which enrolled medical patients with acute respiratory failure, found no difference in ventilator-free days, lengths of stay, or hospital mortality between the two feeding strategies. A similar study design was tested in a large, multicenter, open-label ARDS Network study in patients with acute lung injury (ALI). Results showed that trophic feedings for up to 6 days (in which patients received 25% of goal calories) had similar clinical outcomes to patients randomized to full enteral feedings.[27] Analysis of these data showed that patients were young (average age, 52 years), with a relatively high mean BMI of 30 and an average ICU length of stay of about 1 week. The patients in the trophic feeding group received about 400 kcal/d for the first 6 days compared with about 1,400 kcal/d in the full feeding group. Patients randomized to the trophic feeding strategy experienced fewer interruptions

due to GI intolerances, specifically elevated GRVs and diarrhea. Vomiting was relatively rare in both groups. The different feeding strategies did not result in significant differences in number of ventilator-free days, overall 60-day hospital mortality, or lengths of ICU or hospital stay. Long-term follow-up of these patients has been completed and recently published, demonstrating that both feeding strategies result in similar cognitive and physical activity outcomes at 3 months, 6 months, and 1 year.[50] Although the SSC committee interpreted the studies to recommend trophic enteral feedings in patients with severe sepsis, the nutrition community might interpret results that brief trophic feeding is acceptable in a patient population of medical patients with acute respiratory failure or ALI at moderate nutritional risk. However, both studies excluded malnourished patients and enrolled few surgical patients. As such, for patients at higher nutritional risk, determined by either disease severity or evidence of malnutrition, providing feedings closer to target goal calories and protein may be more appropriate. Furthermore, the effect of trophic enteral feedings in surgical subpopulations remains largely unknown. A practical strategy based on these studies would suggest that early enteral feedings be started in the ICU in all patients (unless contraindicated) to obtain the nonnutritional benefits on gut integrity, maintenance of GI-associated lymphoid tissue and commensal bacteria, and attenuation of the systemic inflammatory response syndrome, followed by assessment of risk and rapid advancement to goal calories and protein if the patient is determined to be at high nutrition risk (Fig 1). Although the optimal marker of nutritional risk remains unknown, factors such as age, recent weight loss and oral intake, time from hospital admission to ICU admission, decreasing or low BMI, and markers of disease severity should be considered in the assessment.[51] In patients not at high risk or those not tolerating full EN, continuing low-dose trophic feedings for up to 6 days does not appear harmful.

Commensal Bacteria

Separating the clinical effects of probiotic therapy and the role of commensal bacteria from the benefits of early enteral therapy and the provision of intraluminal nutrients is difficult. Although mechanisms may differ, the clinical responses are similar, with the effect of the EN being more operative in the small bowel and the commensal bacteria exerting their effect more in the colon. Commensal bacteria provide competitive inhibition of pathogens (such as *Pseudomonas*, *Staphylococcus aureus*, and enteroinvasive *Escherichia coli*), stimulate the physical barrier and mucous production of the gut, and reduce adherence and attachment of pathogenic bacteria to the intestinal epithelium.[52] Commensal bacteria produce bacteriocins, defensins, and trefoil proteins, which help bind pathogens.[52] Their presence interferes with quorum sensing by pathogens, which leads to reduced virulence expression. Commensal bacteria also increase expression of the zona occludens and decrease redistribution of tight junction proteins, all of which help maintain integrity of the gut and prevent increases in permeability.[53] Through induction of T-regulatory cells, commensal bacteria help stimulate production of T-helper cell-2 CD_4 helper lymphocytes, which lead to increased populations of B cells and plasma cells, as well as increased production of secretory IgA.[52] Finally, commensal bacteria act on carbohydrate fiber to produce short-chain fatty acids (which have a trophic effect on the colonic epithelial cell) and induce an antiinflammatory effect through increased expression of transforming growth factor-β and IL-10 via butyrate receptors in the colon.[54]

Immunonutrition

The new SSC guidelines recommend against the use of immunonutrition in patients with severe sepsis.[21]

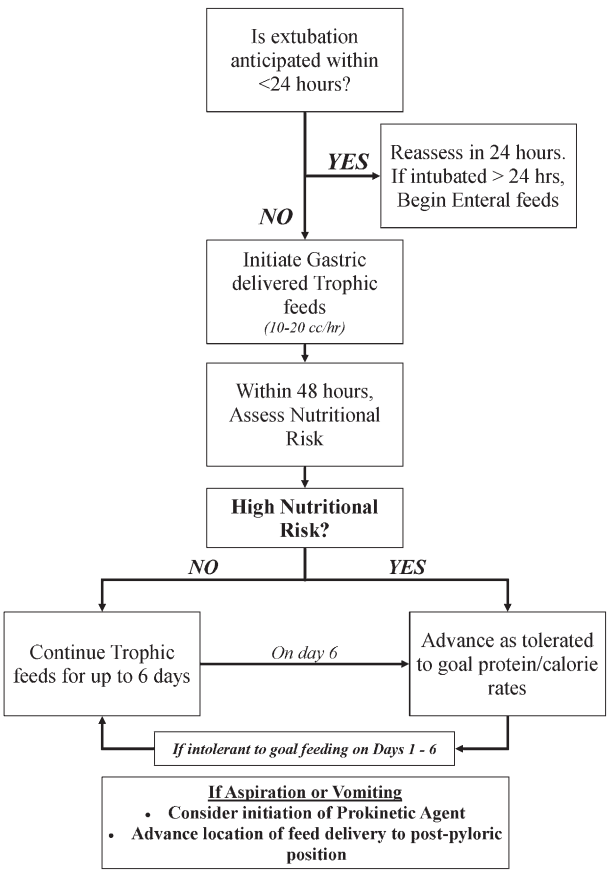

Figure 1. Algorithm for initiating enteral feeding in critically ill patients.

This recommendation against the use of immunomodulatory formulas most likely derives from the results of two large studies, the ARDS Network Omega trial[37] and the Canadian Reducing Deaths Due to Oxidative Stress (REDOX) REDOX trial.[38] Previous randomized studies found that EN formulas supplemented with omega-3 fatty acids, gamma-linolenic acid (GLA), and antioxidants resulted in improved oxygenation, shorter ventilator duration, development of less organ failure, and shorter ICU stays when compared with nonsupplemented enteral feeding formulas.[39-41] One study even found lower 28-day mortality.[41] However, concern over the use of enteral formulas enriched with omega-6 fatty acids in the control arm, as well as minimal feeding tolerances required for inclusion or analysis, resulted in some skepticism interpreting the results. Last year, the ARDS Network published the results of their randomized, controlled, double-blinded Omega trial, which was stopped early for futility after the first interim analysis of 272 of a planned 1,000 patients were enrolled.[37] This study separated the immunomodulatory components and administered the omega-3 fatty acids, GLA, and antioxidants as a twice daily enteral bolus separate from the continuous enteral feedings. The study found that patients who received bolus fish oil supplementation had fewer days alive and free from mechanical ventilation and higher 60-day hospital mortality than control subjects who received supplemental boluses of isocaloric, isovolumic commercially available enteral formula. The study has been criticized for the bolus delivery of the supplement (with uncertainty about its effect on incorporation of the omega-3 fatty acids into the plasma membranes), the effect of the factorial design with one-half the patients receiving trophic enteral feedings, and the relatively low mortality rate in the control arm. However, there was no interaction between the effects of the supplement and whether patients received trophic or full feedings, and a contemporaneously conducted study by the ARDS Network with similar inclusion and exclusion criteria had comparable mortality rates.[55] A similar, phase 2 study using intermittent bolus enteral administration of omega-3 fatty acids compared with normal saline control subjects also found no benefit in either serum or BAL inflammatory markers or clinical outcomes.[56] Another study, enrolling patients with early sepsis, found that a commercially available enteral formula containing omega-3 fatty acids, GLA, and antioxidants dramatically reduced the development of subsequent organ failures, specifically cardiovascular and pulmonary.[57] However, this study has been criticized for its design and definition of sepsis, inappropriate patient selection procedures, uncertainty about the enrolled population (patients without organ failure but receiving enteral tube feedings), and the fact that the reduced development of organ failures did not translate into a mortality benefit.[58,59]

The multicenter, placebo-controlled, double-dummy, double-blinded REDOX trial was undertaken by the Canadian Critical Care Trials Group.[38] This study compared the effects of glutamine and/or selenium in 1,223 severely critically ill patients with multiorgan dysfunction using a factorial design. Daily glutamine supplementation was provided as both 30 g enterally and 0.35 g/kg of ideal body weight parenterally until the earliest of death, ICU discharge, or day 28. The antioxidant cocktail included 500 μg of IV selenium and enteral selenium, zinc, β carotene, and vitamins E and C daily for the same time period. The study demonstrated that glutamine supplementation resulted in a higher 28-day (32.4% vs 27.2%; OR, 1.28; $P = .05$), hospital (37.2% vs 31.0%, $P = .02$), and 6-month mortality (43.7% vs 37.2%, $P = .02$) than receiving placebo. Patients receiving glutamine also had significantly longer time to discharge from both the ICU and hospital. Interestingly, contrary to some preliminary data, glutamine levels were not low in the very limited number of patients in whom they were tested in this study, potentially explaining the lack of benefit and possible harm seen with glutamine administration. The antioxidant cocktail containing higher-dose selenium showed no effect on 28-day (30.8% vs 28.8%, OR = 1.09, $P = .48$), hospital (35.0% vs 33.1%, $P = .51$), or 6-month (40.4% vs 40.6%, $P = .87$) mortality. Given these data, administration of neither glutamine nor antioxidants can be recommended in the routine care of critically ill patients. Glutamine may continue to have a role in some subgroups of critically ill patients, such as burn patients.

Although most of the more recent studies involving immunonutrition have largely been disappointing, review of the literature shows that an arginine fish oil formula is likely still effective in reducing infection and hospital length of stay in patients undergoing elective major surgery.[60] Although it is clear that bolus administration of omega-3 fatty acids is not beneficial to critically ill patients with ALI, it remains uncertain whether continuous administration of enteral formulas containing omega-3 fatty acids or early initiation, when possible, might have benefit. However, all the available data are probably no longer sufficient to recommend immunonutrition use routinely in critically ill patients. Whether to provide an arginine fish oil formula in an elective surgery patient who becomes critically ill is somewhat controversial.

Gastric Residual Volume

The practice of checking GRVs has become a routine part of the enteral feeding protocol in the critical care setting. Its origins began in the 1980s in the

nursing literature. However, there have been no prospective randomized controlled trials to substantiate its use.[61-63] Despite this, many clinicians continue to use GRV to help prevent vomiting and aspiration. In fact, it has become the standard measurement to guide the delivery of EN, based on the assumption that an elevated GRV indicates poor enteral tolerance and identifies the patient at higher risk for aspiration and ventilator-associated pneumonia (VAP). However, using GRV as the sole determinant for altering enteral feeding rates lacks supportive evidence. Numerous studies have demonstrated that GRVs do not correlate with gastric emptying and are poor predictors of feeding complications. Mentec and colleagues[64] found that GRVs > 500 mL, but not those between 150 and 500 mL, correlated with vomiting. Data linking isolated elevated residual volumes with any other clinical outcome, including mortality, length of ICU stay, nosocomial pneumonia, or aspiration, are lacking.

Two nonrandomized studies used the presence of pepsin in tracheal secretions as a marker for aspiration. Neither showed a significant correlation between GRVs and aspiration[65,66] in individual patients. However, when grouped together, patients with a high frequency of aspiration were more likely to have GRVs > 200 mL than patients with a low frequency of aspiration (75% incidence of GRVs > 200 mL vs 25%, respectively; $P = .08$).[66] However, the data from four prospective controlled trials randomizing patients to two different GRVs have not shown a correlation between elevated GRV and aspiration, vomiting, or pneumonia[63,67-69] (Table 1). Although a 150-mL threshold resulted in more than twice as many enteral feeding interruptions (53% vs 23% of patients), Pinilla and colleagues[67] found similar rates of vomiting in a group of patients randomized to 250 mL compared with 150-mL GRV threshold. McClave and colleagues[63] randomized patients to 200 mL vs 400 mL GRV cutoffs and looked for the incidence of regurgitation and aspiration using yellow colorimetric microspheres, a sensitive and specific aspiration marker in tracheal secretions. There was no difference in the incidence of aspiration between these groups.[63] In a study by Montejo and colleagues,[68] patients were randomized to 500-mL cutoff value for GRV compared with a control 200-mL cutoff value. In their study of 329 patients, the number of patients with ICU-acquired pneumonia was no different in the control vs high-residual groups (45 [27.3%] vs 44 [28.0%]; $P = .88$).[68] Other clinical outcomes, including duration of mechanical ventilation and ventilator-free days, ICU lengths of stay, and ICU and hospital mortality, were also similar. Reignier and colleagues[69] randomized 449 adults and 222 control subjects in whom GRV was used to adjust feeding rates per protocol and 227 patients whose GRVs were not checked (and whose enteral feeding was adjusted only when patients experienced vomiting or regurgitation). Patients in the intervention group experienced similar incidences of VAP, ICU-acquired infections, duration of mechanical ventilation, lengths of stay, and short- and long-term mortality.[69]

EN therapy in the critically ill patient in the ICU is difficult. Excessive emphasis on GRV, without correlation to the physical examination, consumes health-care resources and impedes EN delivery. Having protocols in place improves the interpretation and response to GI intolerances, reduces inappropriate cessation, and promotes a greater percentage of goal calories delivered. However, use of the GRV in isolation does not increase the safety of delivering EN or improve clinical outcomes. Other complications of enteral feeding, such as vomiting, abdominal distention, pain, or cramping, either alone or in conjunction with elevated GRVs, may represent better markers of intolerance to EN than isolated elevated GRVs alone. As such, it may be appropriate to cease performing GRVs to better allocate nursing time and health-care resources.

Gastric Vs Postpyloric

The preference of EN over PN has been well established as an integral component in the management of critically ill patients, having a significant effect on morbidity and outcome. Although the gastric route of enteral feeding is easier, cheaper, and quicker to achieve,[70-72] many clinicians remain concerned that gastric feedings increase the risk of aspiration and pneumonia compared with those delivered distal to the pylorus. This may be especially true for the subset of patients with gastroparesis.

A small (n = 33) prospective randomized controlled trial, by Heyland and colleagues,[70] comparing gastric vs postpyloric feedings, showed an aspiration rate of 5.8% with gastric feeding, 4.1% in duodenal bulb feeding, 1.8% when feeding into the second portion, and 0% if feeding was administered in the third portion of the duodenum. These data have been supported in a retrospective study by Metheny and colleagues[73] in a larger patient cohort. In their analysis, the risk of aspiration was 11.6% lower when feeding tubes were in the first portion of the duodenum, 13.2% lower when in the second/third portions of the duodenum, and 18.0% lower when in the fourth portion of the duodenum and beyond, as compared with gastric feeding (all significant at $P < .001$).

Although data support an increased risk of aspiration with gastric feeding, correlating this risk to pneumonia has not been as clear. Although the first meta-analysis conducted by Heyland et al[74] showed a decrease in pneumonia by 24% with postpyloric tube compared with gastric feedings (relative risk, 0.76;

Table 1—*Randomized Trials Comparing Different Gastric Residual Volumes*

Study	Population	GRV Comparison	Notes	GI Outcomes	Clinical Outcomes
Pinilla et al[67]	Expected ICU stay ≥ 3 d without contraindications to EN (N = 96)	150 mL vs 250 mL	Prokinetics: Optional in 150 mL Mandated in 250 mL	↑ freq of elevated GRV with 150 mL More TF interruptions with 150 mL GRV No difference in: Emesis Diarrhea Total episodes of GI intolerance	…
McClave et al[63]	MV adults in medical, surgical, or coronary ICU NG tubes (n = 21) PEG tubes (n = 19)	200 mL vs 400 mL	Aspiration/regurgitation detected through use of microscopic beads and food coloring	No difference in freq of aspiration	No difference in VAP
Montejo et al[68]	MV adults (N = 329) 83% medical ICU 13% trauma	200 mL vs 500 mL	GRV measured: q6h on d 1 q8h on d 2 Daily thereafter	↑ Freq of total GI intolerances with 200 mL ↑ Freq of elevated GRV with 200 mL Higher % TF received with 500 mL	No difference in: ICU-acquired pneumonia Days on MV Ventilator-free days ICU length of stay ICU mortality Hospital mortality
Reignier et al[69]	MV > 2 d and provided EN within 36 h of intubation (N = 449)	250 mL vs none	Noninferiority design GRV measured q6h in 250 mL group	More vomiting in group without measured GRVs No difference in diarrhea More patients in no-GRV group reached calorie target TF held for GI intolerance more in GRV group	No difference in: VAP ICU-acquired infections Days on MV ICU length of stay Hospital length of stay 28-d mortality 90-d mortality

EN = enteral nutrition; freq = frequency; GRV = gastric residual volume; MV = mechanically ventilated; NG = nasogastric; PEG = percutaneous gastrostomy; TF = tube feeding; VAP = ventilator-associated pneumonia.

95% CI, 0.59-0.99), some critics questioned the inclusion of trials in which both different feeding strategies and different levels of infusion for the feeding tube were studied, or trials in which, although intended to be postpyloric, many feeding tubes were actually gastric in location. More recent meta-analyses have not found a significant difference in rates of pneumonia between gastric and postpyloric feeding tubes.[71,75]

Three randomized trials have added to the evidence comparing gastric and postpyloric feedings. White and colleagues[76] enrolled 104 patients in an open-label randomized trial comparing the two. Although the overall number of episodes of VAP was increased in the gastric group (11 vs five episodes), the difference was not statistically significant.[76] Similarly, Hsu and colleagues[77] randomized 121 medical patients in the ICU receiving enteral feedings to either nasoduodenal or nasogastric delivery using the same enteral feeding protocol.[77] Patients receiving nasoduodenal feedings achieved goal rates sooner and received higher average daily calories and protein. Although the duodenal position had lower rates of vomiting and VAP, other clinical outcomes, including ventilator days, ICU days, hospital days, GI intolerances, and mortality, were similar between groups. This was a single-center, open-labeled study that enrolled a heterogeneous population of patients with acute respiratory failure, without regard for feeding tolerance. In contrast, Davies and colleagues[78] enrolled 181 patients that were being mechanically ventilated and receiving narcotics and demonstrating intolerance to gastric feedings from 17 mixed medical-surgical ICUs, randomizing them to continued nasogastric feeding (n = 89) or to postpyloric infusion of feedings at the level of the jejunum (n = 92).[78] Almost one-fourth of the enrolled patients had traumatic brain injury, a condition previously demonstrated to potentially benefit from postpyloric feedings.[79] Despite this, they found no difference between the groups with respect to the primary outcome of proportion of estimated energy requirements delivered. The

incidence of VAP, GI intolerances, and hospital mortality were also similar. Further confounding the picture, three recent meta-analyses have found a reduced risk of pneumonia with postpyloric feedings,[80-82] albeit with a low quality of evidence, but no difference in aspiration or vomiting[80,82] or the clinical outcomes of mortality, duration of mechanical ventilation, or ICU length of stay.[81,82]

Although there may be a decreased risk of aspiration and vomiting with postpyloric feedings, the effect on rates of pneumonia, lengths of mechanical ventilation and ICU stay, and mortality are less clear. This distinction may be best explained by the fact that VAP may be more closely linked to aspiration of bacteria-laden oropharyngeal secretions than to aspiration of contaminated gastric contents. Since they are easier and cheaper to administer, it is reasonable to consider gastric feedings initially for delivery of early EN. All efforts should be made to enhance the tolerance of gastric feeding (elevate head of the bed, promotility agents, strict glucose control [< 180 mg/dL], and bowel opiate antagonists). Small-bowel feeding can reasonably be reserved for patients with intolerance to gastric feedings, high risk of aspiration, and those with gastric/duodenal obstruction.

Conclusion and Summary

Patients with moderate to severe critical illness admitted to the ICU should be started as soon as possible on early enteral feeding as tolerated. Providing at least 25% of goal calories may be sufficient to obtain the nonnutritional benefits for maintaining gut integrity, commensal bacteria, and attenuating the systemic inflammatory response syndrome. An assessment for nutritional risk should be performed within 24 to 48 h. In those patients determined to be at high nutrition risk (either because of evidence of malnutrition or higher disease severity), consideration should be made for advancing enteral feedings to as close to full caloric and protein goals as tolerated. Immune-modulating formulas with arginine and fish oil are likely appropriate for the elective surgery patient undergoing a major operation. However, the role of fish oils in patients with ALI is controversial, and immunonutrition and antioxidant supplementation can no longer be recommended for the heterogenous group of critically ill patients in a medical ICU. GRVs, although routinely measured as standard of care in many ICUs, do not appear to convey increased safety for enteral feedings and should not be used as the sole criterion on which decisions on altering enteral feeding rates are made. Enteral feedings can be initiated into the stomach in most patients, and routine placement of feeding tubes into the small bowel is not necessary. However, in patients intolerant to gastric feedings, moving the tube distally to a postpyloric position may reduce the incidence of aspiration and vomiting, although it has not demonstrated benefit in other clinical outcomes.

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