Carol Rees Parrish, R.D., M.S., Series Editor

Enteral Feedings in Hospitalized Patients: Early versus Delayed Enteral Nutrition

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Nutrition support is a cornerstone in the treatment of malnourished and critically ill hospitalized patients where the clinician expects significant delays in the patient's ability to resume adequate oral intake of protein and calories. The existing literature supports the concept that enteral nutrition is preferred over parenteral, when possible, for its beneficial effects on intestinal and immunologic function. However, the question of "When to institute enteral feeding?" is unresolved. For general surgery and trauma patients, the literature supports starting nutrition as soon as possible since the benefit, usually measured by a reduction in infectious complications, is seen within a few days of injury. The issue is much less clear when treating with burn or medical intensive care patients. This article evaluates the evidence regarding the use of early enteral nutrition in hospitalized patients and provides general guidelines for clinicians involved in nutritional support.

EARLY ENTERAL FEEDING

The successful administration of parenteral nutrition (PN) in the late 1960s and 1970s provided clinicians a way to feed patients with significant loss of intestinal mass or function who would otherwise starve. In the 1980s and early 1990s, laboratory and clinical data demonstrated that there were benefits gained when nutrition is delivered via the gastrointestinal tract rather than parenterally (1–5). Simultaneously, clinicians noted that most of the "ileus" that occurs in patients remains limited to the colon and the stomach (6), while the intestine remains capable of absorbing and processing those nutrients if delivered into the small intestine (7,8). As a result, the concept of "resting the bowel" or to bypass the "ileus" through the use of PN has been replaced with the concept of providing enteral nutrition (EN) whenever the gastrointestinal tract is functional (1–2,4–5). "Starving the gut" is no longer a standard of practice in the critically ill or injured patient, or even in disease states such as pancreatitis. Many studies and meta-analyses address the "PN or EN?" issue and conclude that EN results in fewer infectious complications and possibly shorter hospital stays under some conditions (1–5,9). However, the question of "How early should (and can) we feed?" in order to gain these benefits remains controversial. Many of the meta-analyses analyzing this issue have compared patients receiving PN to those on early or late delivery of EN and have failed to answer the question of how soon feeding must be started in order to benefit the patient (2–5,9). This review attempts to address those issues.

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BASIC CONCEPTS FOR INTERPRETING NUTRITION SUPPORT LITERATURE

Several concepts and general principals should be recognized in the interpretation of the nutritional support literature. The first of these is the heterogeneity of the patient populations recruited into studies, as almost assuredly, the response to nutrition support will differ in various patient populations. For example, it is unlikely that comparable results (length of ICU stay, length of hospital stay, infectious complications, feeding tolerance, etc.) will occur in patients admitted with graft versus host disease following pulmonary transplant versus a patient with an 80% third-degree burn, versus a multiple trauma and a major hepatic laceration requiring an omental packing, versus another with spinal cord injury and a severe pulmonary contusion. Each of these would differ from patients admitted with diabetes mellitus, severe pneumonia and diabetic ketoacidosis, or a general surgery patient undergoing esophagectomy or a Whipple procedure or right hemicolectomy. Each problem carries its own risk of complications as well as potential responsiveness to nutrition therapy. A combination of all types of patient with heterogeneous problems makes it difficult to find significant effects of any therapy including nutritional therapy. Thus, most studies use homogenous populations of patients and the findings are often generalized to other patient populations which may or may not have the same response. This issue will be addressed in the evaluation of the specific studies sited in this article (10–19).

A second principal is that of risk stratification. Administration of a specific nutritional therapy to a patient who does not have the risk for which that specific therapy treats is unlikely to provide any benefit to that individual. Since nutritional therapy—both parenteral and enteral—carries some risk with its use, the risk-to-benefit ratio in this patient population would be fairly high. However, if investigators only recruit patients with the potential risk of a complication for which a specific therapy is treating into the study, then the results should reflect both the complications associated with that therapy as well as the benefit associated with that therapy. It is this benefit-to-risk ratio which addresses the when, what, and how nutrition should be provided. There are several examples of this:

- The Veteran's Affairs Cooperative Study randomized patients to either early PN or to an ad libitum oral diet prior to a general surgical procedure (20). The populations recruited had varying degrees of malnutrition from mild to severe which affected the results of the trial. Parenteral feeding increased infectious complications in patients with mild or moderate malnutrition with no benefit seen in noninfectious complications (such as wound dehiscence or anastomotic failure). Complications from the therapy exceeded the benefit that nutrition could provide in these mildly malnourished patients who had little risk of nutrition-related complications. However, when the subpopulation of patients who were severely malnourished (and at risk of nutritional related complications) was analyzed separately, PN significantly reduced the incidence of healing complications with no increase in infectious complications. Similar results were noted in studies of trauma patients (21,22).
- Moore, et al demonstrated that early EN with an elemental diet administered via jejunostomy to patients with moderate to severe traumatic injuries significantly reduced infectious complications compared to patients who were either not fed during the first five days of their hospitalization, or trauma patients who were started on early PN (21).
- Subsequently, Kudsk, et al duplicated these results, but noted that almost all of the benefit of enteral feeding occurred in patients who were severely injured and at higher risk of developing infectious complications (23). Patients with only mild injuries (and therefore less susceptible to infectious complications) showed no difference between parenteral and enteral feeding in infectious complications. However, the more severely injured patient population (stratified by scoring systems that quantified either total body injury or intra-abdominal injury) who were fed parenterally had dramatic increases in infectious complications compared to those fed enterally.
- Kondrup, et al analyzed a series of clinical trials and validated this concept of stratification by severity and nutrition index by examining how severity of illness and nutritional risk affected results of the nutrition intervention trials (24). The degree of severity of disease and also pre-existing malnutrition in each trial

were defined as absent, mild, moderate, or severe, and converted to a validated numeric score. The higher the score, the greater was the nutrition risk. Each study was then analyzed, provided a numeric score dependent on the patient populations recruited into that trial, and examined for the trial results in response to the nutrition therapy. Trials which recruited populations with greater severity of injury and greater degrees of malnutrition had increasingly positive results with nutrition support. Of 75 studies with patients classified as nutritionally at-risk, 43 showed a positive effect of nutrition support on outcome. However, of 53 studies which included a high percentage of patients considered not to be at nutritional risk, only 14 showed any positive effect.

As a result, any analysis must take these issues into account. When this is done, basic concepts of early versus delayed EN begin to emerge. In general, the data appears fairly clear in the non-critically ill patient undergoing elective transplantation or gastrointestinal surgery (10,11,16,18). The issues become much more complex however when evaluating the critically ill patients since individual studies of burn patients, cervical spine injury patients, blunt trauma patients, mechanically ventilated patients, and adult critically ill patients admitted to a medical ICU have produced differing results (12–15,17,19).

EARLY VERSUS LATE ENTERAL FEEDING

Non-critically Ill Patients Undergoing Elective Surgery

As shown in Table 1, four studies have evaluated early versus late EN after major abdominal surgery, gastrointestinal resection, or liver transplantation (10,11,16,18). In the entire early-fed group, early feeding was instituted immediately after surgery with the latest being within 24 hours of surgery. Consistently, shorter hospital stays, fewer complications, or reduced infectious complications were noted in these trials. All patients were fed into the jejunum or the duodenum rather then intragastric due to the expected problems with gastroparesis. In conclusion, it appears that early EN instituted within 24 to 48 hours of major abdominal surgery provides benefits that are not gained when EN is delayed.

Critically Ill Patients

Studies comparing early versus delayed EN in the critically ill have recruited diverse patient populations including burns, cervical spine injuries, blunt trauma, mechanically ventilated patients with a head injury, and adult critically ill patients in the intensive care unit (12–15,17,19). Given the diversity of their risks, clinical problems, and outcome variables, it is not surprising that results are inconsistent among the various trials.

Burn Patients

Chiarelli examined 20 patients with 25% to 60% body surface area burns and noted a blunting of their hypermetabolism when EN was started early (12). This work supported earlier experimental work in guinea pigs showing that EN (compared to PN) significantly reduced the hypermetabolic response of the burned animals (25,26). However, these results were not substantiated in subsequent studies (12,27). The issue in burn patients is probably not reductions in infectious complications, hospital stay, metabolic rate or, in particular, mortality. A number of aspects including, the size and depth of the burn, the presence or absence of inhalation injury, age, preexisting medical illnesses, other comorbidities and other injuries influence mortality. However, one clear benefit of delivering early EN relates to subsequent management of individual patients. Chiarelli and colleagues showed that burn patients fed early (<5 hours from admission) results in earlier positive nitrogen balance (12). Thus, avoidance of nitrogen loss seems beneficial and a recommendation for early institution of EN advisable.

Head Injured Patients

Taylor, et al examined the effect of early enhanced EN on clinical outcome of head injured patients requiring mechanical ventilation in a randomized, controlled trial of 82 patients (19). Significant reductions in infectious complications as well as overall complications were noted in the early EN group and the metabolic response, measured by a blunted rise in levels of the acute phase protein, C reactive protein, seemed to indicate a beneficial outcome. Overall, they noted a slight improvement ($p = 0.08$) in neurologic outcome at three months in the patients fed early EN, but no difference in ultimate outcome at six months. They concluded that the improvement in infectious complications and the reduction in the inflammatory response noted with early EN justified its administration. One caveat, however, is that both groups required feeding fairly early in their course. The control patients started at 10 mL with intragastric feeding and were advanced as tolerated to goal rate using gastric residuals of 150 mL as a marker of intolerance. Patients fed early had tubes advanced into the intestine and were advanced at a much more rapid rate. Therefore, confounding variables of intragastric feeding with high residuals (with the potential for aspiration and potential infectious complications) versus direct small bowel feeding confounds the interpretation of these data for early versus delayed enteral feeding.

Acute Spinal Cord Injury

Dvorak, et al performed a pilot study of patients with acute spinal injury randomized to either early EN instituted within 72 hours of injury or late EN instituted ≥6 days after injury (14). While 23 patients met eligibility criteria, only a small population of 17 patients (seven in the early group and 10 in the late group) were included. Patients with major chest or abdominal injury were excluded and all patients were fed intragastrically. All but one patient (in the late group) received methylprednisolone during the trial. There were no differences in infectious complications between the two groups and no obvious benefit of early EN. In fact, length of stay increased in the early fed group and there was a higher rate of infectious complications, although these results did not reach significance. The difficulty with this trial is that all patients received intragastric feeding and the groups had similar incidences of intolerance (abdominal distention, tube feeds held, need for prokinetics). It is unknown whether tolerance in either the early or the late group could have been improved by the advancement of the feeding tube into the small bowel. In addition, almost all patients received steroids after the spinal injury. Although this approach was widely accepted as standard procedure in the 1990s after an earlier publication in the *New England Journal of Medicine* showed favorable results (28), steroids as routine therapy has fallen out of favor due to high rate of infectious complications with treatment (29). Thus, the immunosuppression induced by the steroids may render any immunoprotection induced by early EN mute. In summary, there is no evidence of benefit with early intragastric feeding in patients with spinal cord injuries treated with steroids.

Blunt Trauma Patients

Eyer, et al randomized blunt trauma patients to early EN within 24 hours of ICU admission or to late EN instituted >72 hours after ICU admission (15). All patients underwent nasoenteric tube feeding placement distal to the pylorus using fluoroscopy with administration of a peptide-based formula. One outcome variable in this trial was the measurement of the metabolic response, postulated to be reduced as discussed above. Of the 52 patients recruited, 14 were dropped due to: missed intra-abdominal injury (one patient), steroid administration (three patients), rapid recovery with advancement to a regular diet (3 patients), loss of, or failure to place a tube (four patients), or withdrawal from the study. A significant problem in the randomization occurred with the distribution of chest injuries. Since 11 out of 19 early-fed patients had significant pulmonary trauma compared to four out of 19 in the late group, there appeared to be significantly more infectious complications in the early-fed group. Many of these infections had never been demonstrated to be associated with a lack of nutrition, such as an eye infection, catheter sepsis, or urinary tract infections which accounted for 15 of the 29 infections in the early-fed group. However, the rate of pneumonia was twice as high in the early-fed group. At the time of this trial, the prevailing criteria to diagnose pneumonia at that time was fever, leukocytosis, and new or changing infiltrate. With these criteria, pneumonia is over-diagnosed by approximately 60% (30). With the significantly higher degree of blunt pulmonary trauma in the early-fed group and lack of confirmation with quantitative cultures, it is unclear whether the incidence of pneumonia was actually increased or merely reflected an inaccurate diagnosis due to pulmonary contusion from the blunt trauma. It was clear, however, that early

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EN failed to affect the metabolic response, a concept which is no longer accepted.

The final two trials failed to show any benefit of early EN (13,17). Doig, et al enrolled 1,118 critically ill patients who were expected to stay in the ICU for ≥2 days. They attempted to determine whether application of defined feeding guidelines would improve feeding practices and reduce mortality in ICU patients. Although they demonstrated that guidelines do improve administration of early EN while achieving caloric goals more successfully, they found no differences in discharge mortality, length of stay or ICU stay. Unfortunately, mortality is a relatively blunt indicator of improvement. In addition, the diversity and heterogeneity of the patient population does not allow identification of who might or might not benefit from early EN. However, it is clear that attention to guidelines do improve the successful administration of EN.

Finally, in an observational study, Ibrahim et al evaluated early versus late EN in mechanically ventilated patients randomizing them to intragastric feeding either at day one or day five. However, the day five patients received 20% of their estimated enteral requirements during the first four days of mechanical ventilation resulting in a study that investigates early aggressive institution of EN versus a slow rate of enteral administration. All patients were fed enterally using bolus feedings run in by gravity, which certainly raises the issue of gastroesophageal reflux and early aspiration. Although the head of the bed was elevated to 30 degrees in most patients most contemporary units use a continuous infusion of feeding or advance the tube into the duodenum or proximal small intestine. Total intake of calories and protein were significantly greater for the early EN group; however, there were significant increases in ventilator associated pneumonia, gastroparesis and gastroesophageal reflux due to bolus feeding, as well as increased incidence of positive *Clostridium difficile* infections. Of note, the incidence of *Clostridium difficile* was found using rectal swabs instead of the usual practice of testing for the presence of toxin in collected stool. This could explain the high incidence of *Clostridium difficile* "infection." In addition, ICU stay and hospital stay were significantly greater for the early EN group. Mortality rate, while higher in the late-fed group failed to approach statistical significance $p = 0.334$. Given the method used for EN in this patient population, it seems advisable not to use intragastric bolus feeding in ICU patients. The issue of early versus late delayed EN cannot be determined from this trial.

As the trials listed in Table 1 have small N's, a meta-analysis has tried to answer the question, "is early EN better?" (3). The authors of this meta-analysis define early EN as "the initiation of EN within 36 hours of admission to the hospital or within 36 hours of injury." Late EN was defined as EN initiated after 36 hours of admission or surgery. The authors specifically excluded studies from analysis if "patients in the treatment group received PN in addition to EN." Results showed that EN was associated with a lower risk of infectious complications and a shorter length of hospital stay. These results should be interpreted with caution, as there was significant heterogenicity among the trials, and patients in control groups often received PN. This means that many of these trials compare early EN (experimental group) versus early PN with late EN (control groups). The inclusion of PN patients in the control groups could account for lower infectious rates among the early EN patients, as many studies show that PN feeding results in higher infectious complications and higher levels of inflammatory cytokines (20–23). Also, giving PN in the absence of EN deprives the intestines of intraluminal nutrients, which, in animal studies, results in mucosal atrophy and a decreased immune response (31–34).

CLINICAL INTERPRETATION OF EARLY VERSUS LATE ENTERAL TRIALS

The most consistent data is found in non-critically ill patients undergoing major abdominal surgery where early EN clearly appears to benefit this patient population in each of the trials (10,11,16,18). However, in the critically ill patients, no such conclusion is supported by the data. Intragastric bolus feeding is probably inadvisable and is not recommended (17). Intragastric continuous feedings are more appropriate, and small bowel feedings should be used when there is evidence of intolerance to gastric feeds. Early EN reduces infectious complications in moderate to severely injured trauma patients compared to PN or starvation for five days

Table 1

Reference/ Study type	*N/ completed*	*Study population*	*Early EN defined*	*Route*	*Outcomes*	*Stratified by nutritional risk?*	*Comments*
CRITICALLY ILL PATIENTS							
Chiarelli, et al (12) Observational	20 early = 10 late =10	Burn patients with 25–60% body surface area burns	<5 hours from admission	Nasogastric	Early may be beneficial	No	• Early nutrition significantly reduces catecholamine and glucagon secretion. • Earlier positive nitrogen balance.
Dvorak, et al (14) Prospective, randomized controlled	17 early = 7 late = 10	Cervical spinal cord injury	<72 hours after injury	Nasogastric	No difference	No	• No significant differences in incidence of: infection, nutritional status, feeding complications, number of ventilator hours, or length of stay.
Eyer, et al (15) Prospective, randomized, controlled	38 early = 19 late = 19	Blunt trauma	<24 hours from admission	Naso-duodenal	Early may be harmful	Patients with pre-existing malnutrition were excluded	• Significantly increased incidence of infection in the early EN group.
Ibrahim, et al (17) Observational	150 early = 75 late = 75	Medical ICU	<24 hours from intubation	Orogastric	Early may be harmful	Patients with pre-existing malnutrition were excluded	• Significantly increased incidence of ventilator-associated pneumonia and *C. Difficile* infections, longer ICU and hospital stays for early EN patients.
Taylor, et al (19) Prospective, randomized, controlled trial	82 early = 41 late = 41	Mechanically ventilated patients with head injury	<24 hours	Early patients fed via nasointestinal if possible, all late fed via nasogatric or orogastric tubes	Early may be beneficial	No	• Early EN had fewer infectious complications.
Doig, G, et al (13) Cluster-randomized controlled trial	Prospective, 1118 early = 561 late = 557	Adult critically ill patients	Per protocol	Variety	No difference	No	• No significant difference in mortality and mean ICU length of stay.
NON-CRITICALLY ILL PATIENTS							
Sagar S, et al (18) Prospective, randomized, controlled	30 early = 15 control = 15	Post-major abdominal surgery patients	Within 24 hours from surgery	ND	Early may be beneficial	No	• Significantly shorter hospital stay and significantly less weight loss.
Hasse JM, et al (16) Prospective, randomized, controlled	31 early = 14 late = 17	Post-liver transplant patients	≤12 hours from transplantation	Post-pyloric	Early may be beneficial	No	• Significantly less time to positive nitrogen balance in early EN and significantly fewer post-operative viral infections. • No difference in hospital length of stay or total complications.
Beier-Holgersen R, et al (10) Prospective, randomized, controlled	Prospective 60 early = 30 late = 30	Post-gastro-intestinal resection patients	≤4 hours from surgery	ND	Early may be beneficial	Yes	• Significantly lower number of postoperative complications and infectious complications in patients who were fed early.
Carr, et al (11) Prospective, randomized, controlled	Prospective 28 early = 14 late = 14	Post-gastro-intestinal resection patients	Immediately after surgery	NJ	Early may be beneficial	No	• No difference in complications or hospital stay. • Significantly lower gut permeability in patients fed early.

(21,23), but how long the EN can be delayed and still receive benefit is unknown. The issue has yet to be determined in medical ICUs; however, subsequent trials should be designed to use continuous rather than bolus feeding, and to stratify patients by severity of illness.

SUMMARY

Several trials and one meta-analysis compare early EN to late EN. In interpreting all trials, it is important to stratify patients based on nutritional risk and type and severity of illness. Early EN can decrease gut permeability, improve nitrogen balance and potentially decrease hospital stay and incidence of infectious complications for non-critically ill patients undergoing major abdominal surgery. In moderate to severely injured trauma patients, early EN reduces infectious complications compared to PN. In medical intensive care units, evidence supporting early EN is less robust. Future trials with adequate study design are needed before the clinician can routinely justify early EN in all populations. ■

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