Do Data Support Nutrition Support? Part II. Enteral Artificial Nutrition
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ABSTRACT
Artificial nutrition is widely advocated as adjunctive care in patients with a variety of underlying diseases. In recent years more emphasis has been placed on delivering it directly into the gastrointestinal tract through tubes in the stomach or proximal small intestine (enteral nutrition). Because the efficacy of any therapeutic intervention is best established by demonstrating it in one or more randomized controlled trials, this review focuses on data from such studies. The specific issue to be assessed is the ability of enteral nutrition to influence the mortality and morbidity of various diseases, a question that was addressed in depth in a recent systematic review. This article presents the highlights of that systematic review and puts it in context with the perspective of a practicing food and nutrition professional. Using established search strategies, 30 randomized controlled trials were identified that compared enteral nutrition to no artificial nutrition. In addition, other randomized controlled trials were identified that did provide some insight into the clinical utility of enteral nutrition. The randomized controlled trials were stratified by the underlying disease state. No high-quality evidence indicated that enteral nutrition had any beneficial effect on clinical outcome. Low-quality evidence, which tends to overestimate the treatment effect, suggested that enteral nutrition may be useful in reducing the incidence of postoperative complications and infection rates in intensive care units, improving mortality in chronic liver disease, and reducing length of stay when provided as trophic feeding to low-birth-weight neonates who are also receiving intravenous artificial nutrition. Enteral nutrition was not helpful when given during the first week to patients with dysphagic strokes. Thus, the randomized controlled trials that have compared enteral nutrition to no artificial nutrition have only found benefit when the methodologic rigor of the studies is inadequate to prevent bias from interfering with the interpretation of the data. No high-quality data are available to prove that enteral nutrition is of benefit.


For more than 40 years, artificial nutrition has been advocated for patients who have underlying disease states that have caused, or threatened to cause, malnutrition (1). Although the original efforts emphasized the intravenous administration of the nutrient solution, over the years more emphasis has been placed on infusing the formulation directly into the gastrointestinal tract (through tubes placed in the stomach or proximal small intestine).

In a companion article that appeared in the June 2007 Journal, the data generated in an effort to establish utility of intravenous nutrition were examined (1). Because of the limitations of non-randomized clinical trials, that narrative review was restricted to data from the gold standard, namely randomized controlled trials. That review also focused on the intravenous infusion of nutrients. Although the rationale for employing artificial nutrition is usually the same when it is delivered enterally, the physiologic mechanisms are different. It would be inappropriate to extrapolate any conclusions from intravenous nutrition to enteral nutrition. The objective of this review is to assess the clinical efficacy of delivering nutrients directly into the gastrointestinal tract via a tube.

EVIDENCE
The reasons that randomized controlled trials are considered the gold standard for establishing clinical efficacy were discussed in the companion article (1). As was also noted in that work, even randomized controlled trials are subject to bias, particularly if strict methodologic rigor (eg, lack of blinding, inadequate generation of the randomization scheme or inadequate concealment with re-
garding the allocation into the treatment arms, or lack of an intent-to-treat analysis) is not employed. It has been shown that surrogate nutrition outcomes (e.g., body weight or nitrogen balance) do not correlate with morbidity or mortality (1), so only randomized controlled trials that assess clinical outcomes can be used.

A systematic in-depth review that addressed the use of enteral nutrition was recently published (2). That systematic review only considered randomized controlled trials. These trials were identified by using established search strategies (1, 2). The randomized controlled trials were stratified by the underlying disease state. The randomized controlled trials of interest were those that compared a group of patients receiving enteral nutrition to a group receiving no artificial nutrition or oral nutrient supplements. (The systematic review also considered trials of “sip diets” or orally consumed nutritional supplements, but that aspect of nutrient delivery will not be considered here.) When three or more randomized controlled trials provided data about a clinical outcome in a particular disease state, the data were combined with meta-analysis and the estimated effect was presented in the same manner as previously discussed (1). Subgroup analyses assessing specific factors (e.g., quality of trial or type of formulation employed) were also done. A high-quality randomized controlled trial was one that was either blinded for both subject and observer, or explicitly described an acceptable method to conceal allocation and could be analyzed on an intent-to-treat basis. Although only randomized controlled trials comparing treatment to no treatment were used in the meta-analyses, other randomized controlled trials were mentioned when appropriate.

As was true in the companion article (1), the focus of this review will be on randomized controlled trials employing an untreated (with regard to artificial nutrition) control group. However, the randomized controlled trials with other study designs (also identified as part of the literature search) that did provide some insight into the issue will also be discussed. The definitions of types of enteral nutrition and formulations that were considered are available in Figure 1. When mortality data are provided in this review, it will refer to in-hospital events unless otherwise noted.

It should be appreciated that this article, as was the companion article, is a narrative review and does not represent original research. Its purpose is to provide food and nutrition professionals with an overview of the available data. It is presumed that such knowledge will assist in making recommendations about when, or when not, to recommend enteral nutrition.

**ENTERAL NUTRITION IN VARIOUS DISEASE STATES**

**Perioperative Trials**

Sixteen randomized controlled trials compared enteral nutrition to no treatment in surgical patients (3-18). No differences in mortality or duration of hospitalization were seen. There were scant data regarding cost; one randomized controlled trial (3) found no significant differences.

Enteral nutrition, when compared to no nutritional treatment, reduced the incidence of infections (estimated effect −11% [95% confidence interval −20%, −1%]) (2). The estimate was only significant in the trials that were of low quality (estimated effect −14%, 95% confidence interval [CI] −22%, −7%); by contrast, the high-quality randomized controlled trials found essentially no effect of enteral nutrition on infections (estimated effect −2%, 95% CI −25%, +21%) (2).

Several years ago, Lewis and colleagues (19) published a meta-analysis of 11 randomized controlled trials (3, 5, 7, 11, 18, 20-25) that assessed early postoperative enteral nutrient delivery in surgical patients. That analysis included interventions with enteral nutrition or with sip diets. Lewis and colleagues concluded that the treatment appeared to reduce the infection rate, but suggested that a large trial was still needed. The data from the more recent meta-analysis (2) suggest that such a trial is still needed.

Even if enteral nutrition does prevent postoperative infections, it should be appreciated that the number needed to treat to prevent one such event is nine. In fact, given the fact that the low-quality trials usually overestimate the effect (26, 27), that number is probably even higher. This does have implications with regard to resource use; it may be that more resources would be required to provide enteral nutrition to nine (or more) patients than to treat one infection.

Specialized formulations containing putative immunonutrients (n-3 fatty acids, arginine, ribonucleic acid, and/or glutamine) are being employed more widely. Only one trial (7) evaluated specialized enteral nutrition. Whereas that study failed to find any differences in outcomes, this is too limited a database to allow us to draw

![Figure 1. Definitions of terms used in discussions of enteral artificial nutrition.](image-url)
any meaningful conclusions. A meta-analysis of a number of surgical trials that compared standard to specialized enteral nutrition suggested that immunonutrition formulations result in fewer infections than do standard formulations (28).

Four studies each assessed the outcomes of diarrhea (5-7,9) and nausea and vomiting (4,5,7,9) in patients who did, or did not, receive enteral nutrition. No significant differences were seen. Also, no differences were observed in the incidences of postoperative ileus in three studies (7,9,15).

Critical Illness

Only three randomized controlled trials compared enteral nutrition to no artificial nutrition in critically ill patients (29-32) (Note: references 30 and 31 are separate abstracts of the same study). In addition, one of the enteral nutrition trials in liver transplantation provided data about the postoperative course of patients in an intensive care unit (33). No differences were seen with regard to mortality (29-31), length of stay in the hospital (30-32) or in the intensive care unit (33), duration of time on the respirator (29,33), or cost (32).

Infectious complications were more frequent in the control groups of all three enteral nutrition trials; when the data from these 126 patients were combined, enteral nutrition significantly reduced the rate of infections (estimated effect –17%, 95% CI –31%, –3%) (2). However, the largest trial, with 63 patients (32), provided parenteral nutrition to any controls who were not eating by the fifth day; about 30% of controls were so treated. As noted in the companion article (1), parenteral nutrition predisposes patients to develop infections. The low quality of the trials, as well as the confounding factor in the largest of them, undermines any enthusiasm that we might otherwise develop for advocating enteral nutrition in intensive care units.

More favorable conclusions were reached by a group of Canadian intensivists who asked a variety of questions about artificial nutrition in an intensive care unit, particularly in mechanically ventilated patients (34). However, those conclusions rested on data from studies that did not clearly compare enteral nutrition to no treatment in an intensive care unit and on meta-analyses that only found statistically insignificant differences favoring the treated groups.

Only one of the trials that assessed enteral nutrition vs no treatment provided any data regarding treatment complications (29). Virtually all patients in the study appeared to develop one or more of them.

Acute Pancreatitis

Only two randomized controlled trials have compared enteral nutrition to no treatment in patients with pancreatitis (35,36), and only limited information is available. No significant differences in the length of stay were observed in either study (35,36), although there was a trend for that outcome to be shorter in the treated group in the first trial (35). In one trial, no difference was seen in an organ failure score (36). In one of the trials, the recipients of enteral nutrition had higher nausea scores than did those treated conventionally, although the investigators stated that this was not due to the enteral nutrition (36).

More information is available regarding the comparison of enteral nutrition (employing predigested formulations) to parenteral nutrition (37-41). No differences were seen in mortality. The recipients of the parenteral nutrition are more likely to become infected or have other major complications (42). The difficulty in interpreting such data is our lack of knowledge about the absolute utility of either intervention (eg, if parenteral nutrition is harmful, enteral nutrition may simply be less harmful).

Liver Disease

Five randomized controlled trials were identified that compared enteral nutrition to no nutrition support in patients with chronic liver disease (43-47). No differences were found with regards to infectious (42,44) or other liver-related complications (43,44), including hepatic encephalopathy (45-47) or the duration of hospitalization (43,44,46). No differences in the rates of diarrhea were appreciated (44,46).

Because enteral nutrition did not have any appreciable effect on morbidity, it is curious that, when the data from the three trials that provided information about mortality were combined (43,44,46), survival was significantly better in the enteral nutrition recipients (estimated effect –18%, 95% CI –35%, –1%) (2).

One small randomized controlled trial compared enteral nutrition to no nutrition therapy in liver transplant patients (33). The recipients of enteral nutrition had fewer infections, but the difference did not achieve statistical significance. No difference was seen in the duration or cost of hospitalization.

Cabre and colleagues (48) compared 4 weeks of inpatient enteral nutrition to steroid therapy in 71 patients with alcoholic hepatitis; steroids are generally considered to be effective in this disease (at least during the acute hospitalization). Although the initial mortality was similar in both groups (31% vs 25%), significantly more patients in the steroid group died (8% vs 37%) during the subsequent outpatient followup. Most of these late deaths in the steroid group were from infections, and the steroid therapy may have simply masked these conditions earlier. Thus, in the absence of a true control group (one receiving no therapy), we cannot know if the enteral nutrition prevented late deaths or if the steroids predisposed the patients to a late mortal outcome.

Inflammatory Bowel Disease

No trials have compared enteral nutrition to no nutrition treatment in inflammatory bowel disease (Crohn’s disease and/or ulcerative colitis). Four randomized controlled trials, enrolling a total of 121 patients, compared enteral nutrition to parenteral nutrition (49-52). No deaths were noted in the two trials that reported mortality data (50,51). No differences were observed with regard to remission rates.

The data for using enteral nutrition in inflammatory bowel disease are limited, but no profound effects or differences were observed (2). From these data, as well as
the data regarding parenteral nutrition (1), there is no reason to believe that patients with inflammatory bowel disease derive benefit from being kept in a fasting state. If enteral nutrition is indeed equivalent to parenteral nutrition, because parenteral nutrition was not shown to be effective in colitis (1), inferential reasoning suggests that enteral nutrition would not be effective either. It is known from several meta-analyses (53-55) that enteral nutrition is inferior to steroid therapy for treating Crohn's disease.

**Oncologic Therapy**

Only two randomized controlled trials assessed the use of enteral nutrition in patients receiving radiation therapy or chemotherapy for treatment of cancer (56,57). Neither showed any difference in survival. One trial suggested that the treatment reduced the incidence of stomatitis (57). The other found that the incidence of mucositis was lower in the patients receiving a standard formulation, but that the use of an immunonutrient-containing one did not afford such protection (56). No difference in tumor response was observed in one trial (57).

**Acquired Immunodeficiency Syndrome**

No randomized controlled trials assessing enteral nutrition were identified.

**Pulmonary Disease, Including Cystic Fibrosis**

One small randomized controlled trial (58) compared enteral nutrition to no treatment in patients with cystic fibrosis. None of the 11 patients in the trial died.

A systematic review concluded that there is no evidence that nutrition interventions are of benefit in chronic obstructive pulmonary disease (59). A systematic review by Jalalian and colleagues (60) concluded that almost any type of intervention would achieve weight gain in patients with cystic fibrosis, be it behavioral therapy or nutrition support; only one of the included studies was a randomized controlled trial. However, these authors note that it is unknown if weight gain translates into any meaningful improvements in cystic fibrosis (60). Two other systematic reviews noted the lack of good outcome data regarding the use of enteral nutrition in cystic fibrosis (61,62).

**Renal Failure**

No randomized controlled trials were identified that assessed the utility of enteral nutrition in patients with acute or chronic renal failure.

**Pediatrics**

Low-birth-weight infants are often given only parenteral nutrition because of a fear of enteral nutrition-induced necrotizing enterocolitis. The hypothesis that small amounts of enteral nutrient delivery would facilitate an ultimate transition to full enteral feeding (so-called trophic feeding) was addressed in a systematic review (63). The recipients of the minimal feedings had an overall reduction in the time to full feeding (2.7 days) and a 15.6-day reduction in length of hospitalization. There was no increased or decreased risk of necrotizing enterocolitis from this intervention. Whereas this analysis seemed to show a benefit from the trophic feeding, the reviewers were concerned about methodologic problems in the individual trials. They finally concluded that it was unclear if this intervention was helpful.

Artificial nutrition is often advocated for children with a variety of underlying conditions who are failing to grow normally. Although anecdotal reports suggest that this is useful, no randomized controlled trials were identified.

**Geriatric Conditions**

Three randomized controlled trials compared enteral nutrition to no treatment in patients with hip fractures (64-66). Enteral nutrition had no effect on survival (estimated effect +2%, 95% CI –10%, +16%) (2) or the total complication rate (65). The length of hospitalization tended to be longer in the enteral nutrition group (38 days vs 24 days) (65). One of these studies also assessed the use of enteral nutrition for preventing pressure ulcers (64). No difference was seen.

Another small trial compared “nutritional support” (ranging from sip diets to enteral nutrition to parenteral nutrition) to standard care in patients who already had developed pressure ulcers (67). No differences in healing were observed.

One randomized controlled trial of enteral nutrition in dysphagic stroke patients (68) is the largest trial identified. Gastric infusions of nutrient solutions were either begun on admission or withheld for at least 7 days in 859 patients. The primary endpoint of this high-quality Feed or Ordinary Diet trial was long-term survival; no difference was seen. There were also no differences with regard to complications or long-term neurologic function.

Placing percutaneous endoscopic gastrostomies in patients with end-stage dementia has become a common occurrence in today’s hospitals. The rationale for placing these tubes is that nursing homes will not take the patients otherwise. No randomized controlled trials have addressed the issue of efficacy.

**Summary of the Evidence**

The evidence that is available to assess the utility of enteral nutrition, based on the data from the randomized controlled trials, is summarized in Figure 2. The classification of that evidence employs the same system that was used for intravenous nutrition (1). Again, only randomized controlled trials were considered. A few potential benefits were identified (reduction in postoperative infectious complications, reduced infection rates in intensive care units, improved mortality in chronic liver disease, and reduced lengths of hospitalization when trophic feedings were given to low-birth-weight infants), but these conclusions rely on data from low-quality randomized controlled trials.

**Discussion**

Evidence allows the clinician to formulate decisions about patient care. When a proposed therapeutic intervention has established effectiveness and does not entail the ex-
<table>
<thead>
<tr>
<th>Clinical condition</th>
<th>Benefit</th>
<th>Effect not likely</th>
<th>Harm</th>
<th>No or inadequate RCTs</th>
<th>Summary assessment</th>
</tr>
</thead>
</table>
| Perioperative                            | +, c    |                  |      |                       | B
| Critical illness                         | +, ce   |                  |      |                       | B
| Acute pancreatitis                       | +, f    |                  |      |                       | C
| Chronic liver disease                    | +, g    |                  |      |                       | B
| Liver transplant                         | +, h    |                  |      |                       | C
| Inflammatory bowel disease               | +       |                  |      |                       | C
| Chemo/radiation therapy for cancer       | +, i    |                  |      |                       | D
| Acquired immunodeficiency syndrome       | +, m    |                  |      |                       | C
| Cystic fibrosis                          | +       |                  |      |                       | C
| Chronic obstructive pulmonary disease    | +       |                  |      |                       | C
| Renal disease                            | +       |                  |      |                       | C
| Low birth weight infant                  | +, n    |                  |      |                       | B
| Pediatric conditions ^a                   |         |                  |      |                       | B
| Hip fracture                             | +       |                  |      |                       | D
| Dysphagic stroke patients                | +       |                  |      |                       | E
| Other neurologic conditions              | +       |                  |      |                       | C

^aRCTs—randomized controlled trials.  
^bA—Therapy supported by high-quality evidence; B—therapy supported by low-quality evidence; C—therapy is untested, or inadequately tested; D—low-quality evidence suggesting therapy ineffective; E—high-quality evidence indicating that the therapy is ineffective or any evidence indicating that the therapy is harmful.  
^cBenefits that were observed were limited to studies of lower quality.  
^dSpecialized EN containing putative immunonutrients appears to be more effective than standard EN, but there was inadequate information comparing these specialized formulations to untreated controls to justify a categorization; the only available study (7) found no difference between the treated and control groups.  
^eAlthough meta-analyses have suggested that EN is associated with fewer infections, the summary estimate depends on a trial in which about 30% of control group received delayed parenteral nutrition (PN) (32); PN is associated with infections (1).  
^fTwo RCTs, enrolling 55 patients and comparing EN to no nutritional therapy (34,35) failed to find a difference; although EN is superior to PN, PN may be harmful (42).  
^gSummary analysis of three low-quality trials found improved survival in EN recipients; the reason for this finding is unclear because no differences in any of the morbidity rates were observed.  
^hOne RCT enrolling 31 patients (33) found an arithmetic difference in the incidence of posttransplantation viral infections in the recipients of EN.  
^iAlthough no RCTs have directly compared EN to no nutritional therapy, EN is inferior to steroid treatment for acute exacerbations of Crohn’s disease. EN is comparable to PN (49-52), and PN was not better than no nutritional therapy in two small trials in patients with colitis (1).  
^jTwo RCTs, enrolling a total of 162 patients (56,57), failed to find any significant, or even trends for, benefit.  
^kData are available only for solid tumors; effect on hematologic cancers is unknown.  
^lEvidence from nonrandomized trials suggests that weight gain is not associated with beneficial clinical effects.  
^mOne low-quality trial in 11 patients with cystic fibrosis (58) did not demonstrate any benefit from EN.  
^nTrophic feeding (provision of small amounts of enteral nutrients to low-birth-weight infants whose nutrition is otherwise being provided by intravenous infusions) may be beneficial, although the poor quality of the trials limits the reliability of this conclusion.  
^oCystic fibrosis and inflammatory bowel disease considered elsewhere.  
^pEN not indicated for at least 1 week after stroke (68); if dysphagia persists for weeks (or is permanent), some type of gastric infusion of nutrients will be necessary.

Figure 2. Summary of evidence available for the use of enteral nutrition (EN) in various clinical conditions. (Recommendations may not be appropriate for severely malnourished patients [1].)

As has been noted repeatedly, most of these studies were of low quality. However, the temptation to use this excessive use of resources, it should be employed. On the other hand, when a proposed intervention is shown not to be effective (or even harmful), it should not be used. Unfortunately, most of the tests and treatments that are available to us in clinical medicine are inadequately studied to permit such black-and-white conclusions.

There are randomized controlled trials available from which to begin the decision-making process about the provision of enteral nutrition. Although these data are probably still disappointing to many proponents of artificial nutrition, there are several areas where low-quality randomized controlled trials do suggest that a benefit may exist. These include the perioperative period, critical illness, chronic liver disease, and trophic feedings for low-birth-weight neonates. However, even in these conditions, the evidence is certainly not compelling.

Were there problems with the randomized controlled trials that we reviewed here (or in the previous discussion of intravenous nutrition)? First, concern might be raised that not all of the randomized controlled trials were found. This would be the case particularly if the more favorable studies were not published (publication bias). However, publication bias usually occurs in the opposite direction, namely favorable studies are more likely to be submitted to journals (69). Thus, if randomized controlled trials were missing because they were unpublished, the actual effect of artificial nutrition would probably be even less favorable than what was demonstrated.

The focus of these reviews was on the clinical endpoints related to mortality and morbidity, not on surrogate end points such as body weight or nitrogen balance. Whereas these latter endpoints are easier to study (and usually improve), it cannot be assumed that making such tests better will make patients better. In fact, making such tests better does not translate into improved clinical outcomes (70).
as an excuse to dismiss the data should be avoided. Because low-quality trials tend to show larger treatment effects (26,27), artificial nutrition may be even less effective than what the data have suggested.

Type II errors occur when true differences are not demonstrated because the sample size studied is inadequate to make that difference statistically apparent. It may be that, especially in the disease states for which only limited amounts of data were available, a benefit was missed.

The most obvious reason for the failure of randomized controlled trials to demonstrate efficacy is that the intervention is not effective. If the association between malnutrition and a poor outcome is not causative, improving the former would not be expected to improve the latter. Even if malnutrition were partly responsible for the poor outcome, the side effects of the interventions might equal the benefits they provided, so no net effect would result.

Food and nutrition professionals and other health care workers should stop using the words “feeding” or “eating” to refer to artificial nutrition, as these terms elicit instinctive emotional responses that do not reflect the reality of the treatments. Artificial nutrition is a medical intervention. It has defined costs and morbidities. As such, it should not be employed where they are known to do no good. Any future policy that promotes interventions with artificial nutrition with few exceptions, there is no evidence base to justify ordering it. Current guidelines need to be rewritten to take the best data into account; for the most part, these guidelines would recommend a much more conservative approach. Any future policy that promotes interventions with artificial nutrition must be based on clearly established proof of efficacy, namely data from large, well-designed, high-quality randomized controlled trials.

CONCLUSIONS

Because medical resources are constrained, these resources have to be employed where they are known to do the most good. Data are available regarding artificial nutrition; unfortunately, those data do not provide a compelling argument for its use. These data cannot be disregarded. Rather, food and nutrition professionals and other health care workers should limit their enthusiasm for employing artificial nutrition. With few exceptions, there is no evidence base to justify ordering it. Current guidelines need to be rewritten to take the best data into account; for the most part, these guidelines would recommend a much more conservative approach. Any future policy that promotes interventions with artificial nutrition must be based on clearly established proof of efficacy, namely data from large, well-designed, high-quality randomized controlled trials.

References

24. Schroeder D, Gillanders L, Mahr K, Hill GL. Effects of immediate and delayed feeding on outcome, the side effects of the interventions might equal the benefits they provided, so no net effect would result. Food and nutrition professionals and other health care workers should stop using the words “feeding” or “eating” to refer to artificial nutrition, as these terms elicit instinctive emotional responses that do not reflect the reality of the treatments. Artificial nutrition is a medical intervention. It has defined costs and morbidities. As such, it should not be employed where they are known to do no good. Any future policy that promotes interventions with artificial nutrition must be based on clearly established proof of efficacy, namely data from large, well-designed, high-quality randomized controlled trials.

References
