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**Does enteral nutrition affect clinical outcome?  
A systematic review of the randomized trials**

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## Study Highlights

### *Current knowledge:*

1. Because malnourished patients have poorer outcomes than do nourished ones, artificial nutrition is employed in order to improve the clinical outcome.
2. Randomized trials of parenteral nutrition have largely been unable to show that this therapy improves the clinical outcome, and have even suggested that the therapy is associated with net harm (especially in patients undergoing cancer chemo- or radiation therapy).

### *What is new:*

1. Randomized trials of low quality have indicated that nutritional supplements, taken orally, improve survival in malnourished geriatric patients who are in institutions (including hospitals). Two trials of high quality found effects in the same direction, but failed to achieve statistical significance.
2. Randomized trials of low quality have suggested that enteral nutrition may reduce infection rates in critically ill patients and improve outcome in low-birth-weight infants (when provided as “trophic feeding”).
3. Randomized trials of low quality have suggested that both enteral nutrition and oral supplements may be helpful in the postoperative situation and in patients with chronic liver disease.
4. Two large high quality randomized trials found that there is no benefit in providing enteral nutrition in the first week to patients with strokes associated with dysphagia or in providing supplements to stroke patients who do not have dysphagia.
5. Low quality randomized trials have failed to demonstrate any utility from EN in the non-surgical treatment of cancer patients, or in the treatment of patients with inflammatory bowel disease or hip fractures.

6. Low quality randomized trials have failed to demonstrate any utility from oral supplements in the non-surgical treatment of cancer patients or in patients with chronic pulmonary disease or hip fractures.
7. There are no or inadequate data from randomized trials to assess the use of enteral nutrition or oral supplements in any other diseases.

## Abstract

**Background:** Both parenteral nutrition (PN) and enteral nutrition (EN) are widely advocated as adjunctive care in patients with various diseases. A systematic review of 82 randomized controlled trials (RCTs) of PN published in 2001 found little, if any, effect on mortality, morbidity, or duration of hospital stay; in some situations, PN increased infectious complication rates. **Objective:** To assess the effect of EN or volitional nutrition support (VNS) in individual disease states from available randomized controlled trials (RCTs). **Design:** We conducted a systematic review. RCTs comparing EN or VNS to untreated controls, or comparing EN to PN, were identified and separated according to the underlying disease state. Meta-analysis was performed when at least 3 RCTs provided data. The evidence from the RCTs was summarized into one of five grades. A or B indicated the presence of strong or weak (low quality RCTs) evidence supporting the use of the intervention. C indicated a lack of adequate evidence to make any decision about efficacy. D indicated that limited data could not support the intervention. E indicated either that strong data found no effect, or that either strong or weak data suggested that the intervention caused harm. **Patients and settings:** RCTs could include either hospitalized or non-hospitalized patients. The EN or VNS had to be provided as part of a treatment plan for an underlying disease process. **Interventions:** The RCT had to compare recipients of either EN or VNS to controls not receiving any type of artificial nutrition or had to compare recipients of EN with recipients of PN. **Outcome measures:** Mortality, morbidity (disease-specific), duration of hospitalization, cost, or interventional complications. **Summary of grading:**

A – No indication was identified.

B – EN or VNS in the perioperative patient or in patients with chronic liver disease; EN in critically ill patients or low birth weight infants (trophic feeding); VNS in malnourished geriatric patients. (The low

quality trials found a significant difference in survival favoring the VNS recipients in the malnourished geriatric patient trials; two high quality trials found non-significant differences that favored VNS as well.)

C – EN or VNS in liver transplantation, cystic fibrosis, renal failure, pediatric conditions other than low birth weight infants, well-nourished geriatric patients, non-stroke neurologic conditions, AIDS; EN in acute pancreatitis, chronic obstructive pulmonary disease, non-malnourished geriatric patients; VNS in inflammatory bowel disease, arthritis, cardiac disease, pregnancy, allergic patients, preoperative bowel preparation

D – EN or VNS in patients receiving non-surgical cancer treatment or in patients with hip fractures; EN in patients with inflammatory bowel disease; VNS in patients with chronic obstructive pulmonary disease

E – EN in the first week in dysphagic, or VNS at any time in non-dysphagic, stroke patients who are not malnourished; dysphagia persisting for weeks will presumably ultimately require EN.

**Conclusions:** There is strong evidence for not using EN in the first week in dysphagic, and not using VNS at all in non-dysphagic, stroke patients who are not malnourished. There is reasonable evidence for using VNS in malnourished geriatric patients. The recommendations to consider EN/VNS in perioperative/liver/critically ill/low birth weight patients are limited by the low quality of the RCTs. No evidence could be identified to justify the use of EN/VNS in other disease states.

## **Introduction**

An association exists between malnutrition and a poor clinical outcome. Furthermore, deprivation of nutrient intake for a long enough period of time will have adverse clinical consequences. These two observations have led to the hypothesis that providing artificial nutrition to patients who are, or who are at risk of becoming, malnourished, would be beneficial. However, artificial nutrition is a medical intervention with associated risks and costs. As such, we need to know that it is efficacious. The best way to establish efficacy is to demonstrate it in a randomized controlled trial (RCT). In 2001, a systematic review of the RCTs of parenteral nutrition (PN) failed, with a few exceptions, to find outcome improvements (1).

That review considered the intravenous infusion of nutrients. While the rationale for artificial nutrition is usually the same when it is delivered directly into the gastrointestinal tract (consumed by mouth or infused through a tube), the physiologic mechanisms are different than when it is provided intravenously. It would be inappropriate to extrapolate any conclusions from PN to another form of artificial nutrition. The objective of this systematic review is to evaluate the clinical efficacy of medical interventions that deliver nutrient formulations directly into the gastrointestinal tract through defined orally consumed supplements (volitional nutritional support [VNS]) or via a tube (enteral nutrition [EN]). In doing so, we focus on RCTs that evaluate the ability of such interventions to alter one or more clinically important outcomes in specific disease states.

## **Methods**

A protocol was written in which *a priori* decisions were made regarding methodology. The terminologies used to describe study groups and the artificial nutrition formulations are defined in Table 1.

RCTs were identified employing previously reported strategies (1); the details are available electronically (“Literature Search Methodology”). This search was begun in 1975; in the intervening 3 decades, some efforts were made to contact authors to obtain more information about a particular study. However, no systematic effort was undertaken to contact all authors for this systematic review. No language restrictions were employed; when translation facilities were not available, the data from the English abstract, as well as any interpretable data from tables, were employed. Abstracts from meetings were included.

The RCTs that compared EN to no treatment, EN to PN, or VNS to no treatment were so categorized within each disease state. We assessed the outcomes of mortality, total and/or infectious complications, lengths of hospitalization, costs, interventional complications (e.g., nausea/vomiting, diarrhea, hyperglycemia), or any of the disease-specific outcomes. A list of these specific diseases, as well as the disease-specific outcomes, is available electronically (“Disease States Considered”). Meta-analysis (Revman 4.2, Cochrane Collaboration) was performed when data were available from 3 or more RCTs. (If only one or two trials were available, we thought that there would be no more insight available from data combination by meta-analysis than could be gleaned by just assessing each trial individually.)

Any RCT meeting the following criteria was used in the respective meta-analysis:

- 1) The report explicitly stated that the groups were randomized; quasirandomized or cluster randomized trials were excluded.
- 2) The study compared treatment groups as defined above.
- 3) The study reported one or more of the outcomes being sought.
- 4) The therapeutic intervention was employed for at least five days, during which time the control group received only standard therapy (or PN in the comparative trials). (Since the hypothesis underlying

artificial nutrition is that the morbidity or mortality is due to malnutrition, it was assumed that it would require at least five days to begin to reverse that process; this same assumption was made previously [1].)

If a report included groups of patients randomized to an untreated control and to two or more forms of EN or VNS, all treated groups were combined and compared to the control. If a report included groups of patients assigned to EN and to VNS, the data from the EN group were included in the EN analysis and the data from the VNS group were included in the VNS analysis. (The same control group was used in both analyses in this latter case.)

If dichotomous outcomes were reported as a total number instead of the number of affected patients, it was assumed that there was one event per patient. (If the number of events was greater than the number of patients, each patient was assigned one event.) Numerical estimates were made from graphs when necessary.

Meta-analysis of continuous data requires knowledge of both the mean and standard deviation for both treatment arms. Thus, the initial analyses only included trials in which these numbers were reported. However, one of the peer reviewers of this paper pointed out a statistical method of converting the median and range into a mean and variance (2). Thus, post facto analyses were also performed employing continuous data from trials in which the medians and ranges were provided. Since none of those analyses materially changed any of the estimates or conclusions, they will not be subsequently reported.

Two reviewers independently abstracted the information from each RCT onto predesigned data summary forms. Discrepancies were resolved by consensus between the two abstractors.

Heterogeneity (i.e., adding apples and oranges) is a limitation of meta-analysis. It can be sought with statistical tests; the Revman software calculates both Cochran's Q (expressed as a p value) and  $I^2$  statistics (3). Statistical heterogeneity was defined as  $p \leq 0.10$  or  $I^2 > 25\%$ . A fixed (or random) effects model was employed when heterogeneity was absent (or present).

Dichotomous data are presented as an absolute risk difference (ARD), namely the difference between the incidence in the treated group and that in the control group. A 95% confidence interval (CI) that did not include 0% was considered “significant”. The term “tendency” was applied to an analysis in which one end of a confidence interval was 0% (i.e., the confidence interval included the possibility of no difference). A negative ARD indicates a beneficial effect associated with the treatment.

Continuous variables are reported as weighted mean differences and 95% CIs. The same rules for significance and tendency were applied to these calculations. A negative number represents a beneficial effect in the treated group.

RCTs with more methodologic rigor have demonstrated lower treatment effects (4, 5); this is presumed to represent the advertent or inadvertent introduction of bias into the less rigorous trials. “Quality” is a term that reflects the degree of rigor that was employed. Thus, each trial was graded for quality, with the expectation that all of the studies were randomized and the large majority of them were not blinded. A “high quality” (lower risk of bias) study was one in which either 1) the investigators/assessors and participants were blinded, or 2) the RCT contained both an explicit description of an adequate allocation concealment and data that were evaluable on an intent-to-treat basis. RCTs not meeting one or the other of these criteria were categorized as low quality.

In order to explore possible sources of heterogeneity, subgroup analyses were planned. These planned analyses are available electronically (“Analyses and subgroup analyses planned”). Those that are relevant will be discussed.

Our primary focus is the strength of the evidence that supports the use of EN or VNS in each disease state. These assessments (grades) are based only on data from RCTs. Nonrandomized controlled trials are less reliable because of potential bias (6). Expert opinion is often based on incomplete information (7-9) and/or influenced by conflicts of interest (10, 11).

The evidence was graded by the amount and quality of the RCTs that were available as well as what effects those trials did, or did not, demonstrate. The grades ranged from A to E, with A describing a situation in which there was a high likelihood of benefit and E indicating a high likelihood of no benefit, or even of harm. For some conditions, a limited amount of information was available, and that information failed to demonstrate any significant differences in outcomes. In such situations, it may be that a true difference was present, but the numbers were too small to establish it (i.e., a type II error), or it may be that the failure to observe a difference was due to the intervention not having an effect.

It was decided that, if at least three low quality RCTs had failed to show a difference, the intervention would be judged to be ineffective. If only one or two RCTs were available, the total number of patients were considered; if that total was less than 100, the evidence was classified as being inadequate to determine the presence or absence of a benefit.

If at least 100 patients were studied, the direction of the difference was then considered. (If two RCTs were available, the data were arithmetically combined.) If that direction was in favor of the control group, the intervention was judged to be ineffective. If it was in favor of the treated group, a p value for the difference was obtained. If that p value was  $\leq 0.20$ , it was concluded that a type II error might be present, so the data were considered as inadequate. (Employing a one-sided test [since only benefit was being sought] and an  $\alpha$  error of 0.20, there is approximately an 80% power of seeing an ARD of 15% between the two groups; since the trials were almost always of low quality, the real ARD would likely be lower. Given the resources required [both economic and time], such an ARD would be the lowest one that would be clinically meaningful.)

The evidence was thus divided into 5 grades:

A – One or more high quality RCTs demonstrated benefit.

B – The evidence of benefit was limited to low quality RCTs.

C – There were inadequate data to decide if benefit is present or absent. Three different scenarios could result in a C grade: 1) no RCTs were available; 2) only one or two RCTs containing fewer than 100 patients were available; 3) 100 or more patients were available but a type II error could not be ruled out.

D – Limited evidence was not able to define a benefit. Either at least three low quality RCTs failed to show a difference or a type II error was not likely to be present.

E – One or more high quality RCTs indicated that the intervention was not effective or that there was any evidence that it caused harm.

As will be noted, none of the RCTs included severely malnourished individuals. Thus, these grades will refer to studies in which the patients were not severely malnourished and would not be deprived of nutrient intake for > 2 weeks. Although there are only limited data to allow us to know with certainty the period of time for which such individuals can tolerate nutrient deprivation, it was previously concluded that waiting at least 2 weeks in the non-severely malnourished patient was reasonable (1).

## **Results**

### **Summary of RCTs identified**

The total number of assessed titles could not be determined; this information was not collected during the handsearch of Index Medicus. However, each identified RCT was stored, so the total number of RCTs from which those included in the meta-analyses were derived could be ascertained.

Only 33 of 376 RCTs of EN met our inclusion criteria (12-45); data for one of these trials were extracted from two different abstracts (25, 26). Similarly, we included 48 of 115 RCTs comparing EN to PN (19, 25, 26, 44, 46-92); data for three of these trials were extracted from two different papers (25, 26, 69, 70, 76, 77). Finally, 54 of 418 RCTs of VNS were included (30, 93-145).

Data from one of the EN versus PN RCTs (55) were published at least seven different times (55, 146-151). Different numbers of patients appear in each publication, and, in at least one instance, a portion

of the study was extended and additional patients were added (151). In order to avoid duplication, we used the most recent paper (55) and supplemented any missing categories of data with information from the other publications. The details of the 135 RCTs employed in the various meta-analyses (“Study Characteristics”), as well as the excluded trials and the reason(s) for exclusion (“References Excluded from Meta-analyses”), are available electronically.

### **Perioperative Trials**

The results of the meta-analyses of the perioperative RCTs (12, 13, 15, 19, 24, 27, 29, 32, 34, 36-40, 44, 45, 48, 50, 53-56, 64-66, 71, 74, 75, 78, 81, 82, 84-87, 95, 102, 109, 115, 122, 134, 136, 138, 141) are summarized in Table 2. No differences were seen with regard to mortality. EN, when compared to no artificial nutrition, was not shown to reduce the rate of total/major/wound complications or postoperative pneumonia. There were significantly fewer infections in the EN recipients as well as a tendency for fewer intraabdominal or intrathoracic complications. The heterogeneity resolved, and the significant differences persisted, in the low quality trials and in the trials of the patients without cancer.

EN produced better outcomes than PN. VNS provided across-the-board benefits. These conclusions must also be tempered by the fact that the data were largely derived from low quality studies.

Several years ago, Lewis et al (152) published a meta-analysis of 11 RCTs (12, 15, 24, 34, 45, 153-158) that assessed early postoperative enteral nutrient delivery in surgical patients. These trials utilized EN or VNS. Lewis et al noted that artificial nutrition reduced the infection rate, but suggested that a large trial needed to be conducted. Six of these RCTs were excluded from our analyses. While our analysis of 11 trials of mostly postoperative EN (12, 15, 24, 27, 29, 32, 34, 36, 38, 39, 45) demonstrated a similar effect, when only the four high quality trials were considered, this observation could not be confirmed (ARD -2% [95% CI -25%, + 21%]).

Specialized formulations containing putative immunonutrients ( $\omega$ -3 fatty acids, arginine, ribonucleic acid, and/or glutamine) are often employed. A limited database (24, 55, 109) precluded meaningful conclusions. Such specialized EN resulted in fewer infections than did standard EN (159).

The durations of therapy in the VNS trials were analogous to those in the EN trials (days or a few weeks). However, all of these patients were capable of orally consuming supplements. The beneficial effect was limited to the trials of postoperative VNS and VNS in malnourished patients.

VNS also appeared to shorten hospitalization. The subgroup analyses indicated that this benefit was limited to the trials of preoperative VNS and VNS provided to nourished patients. Given the data regarding complications, this observation seems counterintuitive. The quality of the trials was low and duration of hospitalization is a subjective outcome. Furthermore, one high quality (22) and four other low quality (115, 136, 141, 160) trials that did not provide adequate information to be included in the meta-analysis failed to find significant differences in the duration of hospitalization.

### **Non-surgical cancer treatment**

PN causes net harm to cancer patients undergoing chemotherapy or radiation therapy (1). There was no apparent positive or negative effect from the enteral provision of nutrients (either through a tube [35, 43] or by volitional consumption [93, 96, 103, 126, 135]). The trials of VNS provided mortality data; the estimated effect favored the control group (ADR +5%) but the CIs crossed 0% (-2%, +12%). Two of the VNS trials reported data regarding the incidences of gastrointestinal toxicity; in one the treated group had significantly more (96) and in the other the treated group had significantly fewer (135). No trials assessed EN or VNS in hematologic malignancies. A systematic review of artificial nutrition in bone marrow transplantation did not identify any data regarding the enteral delivery of nutrients (alone or in comparison to PN) (161).

## **Liver disease**

*Chronic liver disease:* The outcomes in patients with chronic liver disease that could be assessed with meta-analysis are summarized in Table 3 (97, 113, 125, 129, 137). VNS did not have any effect on survival. Survival was also not affected when VNS was provided with EN as a backup (162) or when given with an anabolic steroid (163). VNS did not have a significant effect on infectious complications or the development of hepatic encephalopathy. Although the data could not be combined, VNS did not appear to influence the length of hospitalization (97, 113, 129). Limited information was available from one or two trials about other outcomes. There was no effect on the subsequent development of hepatocellular carcinoma (125) or gastrointestinal bleeding (113, 129). The VNS recipients had significantly lower incidences of total complications in two trials (113, 129) and also may have been less likely to develop ascites (113, 129).

EN did not appear to have any impact on liver-disease-associated morbidity (14, 17, 21, 28, 164) nor on the length of hospitalization (14, 17, 28). Survival with EN was not different from that with PN (79). In light of these observations, it is curious that three low quality RCTs (14, 17, 28) of EN versus no therapy found improved survival in the treated recipients when the fixed effects model was employed. This model was used because the p value for heterogeneity was 0.21; however, the  $I^2$  statistic was 37% and when the random effects model was employed, this significant difference disappeared.

Branched-chain amino acids had a modest effect in treating hepatic encephalopathy but this effect disappeared if the analysis was limited to the high quality trials (165).

*Liver transplantation:* No significant differences were observed (23, 90, 120).

## **Pancreatic disease (acute pancreatitis)**

RCTs have evaluated the use of EN in acute pancreatitis, but not in pancreatic insufficiency. The meta-analyses of five RCTs (46, 49, 67, 72, 73) comparing EN to PN are displayed in Table 4.

Predigested formulations were delivered into post-pyloric sites. EN is safer and more effective than PN, a conclusion also reached in another systematic review (166).

There are only limited data about the absolute value of either modality. Two small studies compared EN to no treatment; no differences in duration of hospitalization (33) or an organ failure score (167) were seen. One RCT compared PN to no therapy in mild pancreatitis; the PN recipients had worse outcomes (longer duration of hospitalization and more infections) (168). If PN is harmful, a comparative trial cannot determine whether EN is better than doing nothing.

One other trial of PN should be noted (169), but it is difficult to fit these observations into the nutrition support picture because the results seem very unlikely. The dramatic differences in mortality (3/41 [7%] in two PN groups versus 10/23 [43%] in the controls) have not been described in any other PN RCT. Unfortunately, only limited methodologic details were available and efforts to contact the author in China have, to date, been unsuccessful. The term “randomization” in the Chinese literature may not have the same meaning as in western papers (170).

No differences were observed in the durations of hospitalization between those provided with PN and those given EN (46, 67, 72). If PN causes more complications, especially major ones, the durations of hospitalization should not be equivalent.

### **Inflammatory Bowel Disease**

Four RCTs compared EN to PN (59, 61, 62, 68). A meta-analysis of the three RCTs comparing these therapies in active Crohn’s disease (59, 62, 68) found no difference in remission rates (ARD -12% [95% CI -32%, +9%]). No differences in remission rates were seen in two RCTs that compared VNS to PN (171, 172). No RCTs were identified comparing EN to no therapy. In the only VNS trial (173), the data were presented as a series of subgroup analyses; the treated subgroups had fewer surgeries and days

of hospitalization, and, while the differences were not significant, a type II error may have been present. Keeping patients with inflammatory bowel disease in a fasting state is of no benefit (1).

PN did not confer any benefit in colitis (1). Since data from the only trial comparing PN and EN found no difference (61), it could be inferred that EN would also be ineffective. Three systematic reviews concluded that EN is inferior to steroid therapy for treating Crohn's disease (174-176).

If predigested formulations are less antigenic, they might be useful in Crohn's disease. However, no differences were seen in comparisons with formulas containing undigested protein (174, 175).

### **Critical Illness**

The few RCTs comparing EN to no treatment in the critically ill do not provide compelling evidence to employ this intervention. No differences in mortality (25, 31), duration of time on the respirator (18, 23), or length of stay in the intensive care unit (23) or hospital (25, 31) were observed.

When 3 RCTs (126 patients) were combined (18, 25, 31), EN reduced the infection rate (ARD - 17% [95% CI -31%, -3%]). However, 30% of the control patients, who were not eating by day five, were given PN, a source of potential infection, in the largest of these trials (63 patients) (31). Another systematic review, employing a different set of RCTs, failed to demonstrate a reduction in the infection rate (relative risk 0.66 [95% CI 0.36, 1.22]) (177).

That same systematic review also considered early versus later intervention with artificial nutrition and concluded that those treated within 1-2 days of admission may have had a better survival, although the difference was not statistically significant (relative risk 0.52 [95% CI 0.25, 1.08]) (177). Most of the RCTs included in that meta-analysis were excluded from ours because 1) the control group received the intervention before 5 days, 2) PN was being evaluated, and/or 3) we judged the RCT not to be randomized.

Burn patients who had EN initiated at the time of admission may have had fewer episodes of sepsis (3/10 vs 7/10,  $p > 0.10$ ) (178). Those who had the EN continued during surgery had fewer wound infections (2/40 vs 9/40,  $p < 0.05$ ) (179). However, the descriptions of the randomization process were confusing. We are told that the patients “were randomly assigned by a case-control method” (178) and that “randomly assigned” patients were “matched” to patients whose infusions were withheld (179).

One short term (72 hours) trial assessed the ability of EN to prevent stress bleeding in ventilated patients (180). While blood-stained nasogastric aspirates were more common in the controls, no patient had a significant hemorrhage. A systematic review concluded that EN should not be used for this purpose until RCTs establish efficacy (181).

Many intensivists, believing that artificial nutrition is important, have compared different interventions. Since the trials lack an untreated control arm, it is again difficult to determine the absolute utility of either.

RCTs comparing EN to PN (25, 26, 47, 51, 52, 57, 58, 63, 69, 70, 76, 77, 83, 88, 92) did not find any differences in the duration of time on the respirator (47, 69, 70) or in the long-term sequelae of head-injured patients (83, 92). The outcomes that could be assessed with meta-analysis are summarized in Table 5. No differences were seen with regard to survival. Another systematic review, employing different trials, made the same observation (177). However, a third one, restricted to trials with at least a 95% followup of the enrolled patients and including studies of patients not in intensive care units, estimated that PN, compared to EN, was associated with a reduced mortality rate (182).

Should specialized formulations be employed? Two systematic reviews of RCTs comparing them to standard formulations failed to find any difference in mortality in the critically ill (159, 183). However, significantly fewer infectious complications were seen when specialized formulations were used.

### **Pulmonary disease (including cystic fibrosis)**

EN had no effect on the pulmonary outcome in patients with cystic fibrosis in one RCT (16).

While non-randomized trials have suggested that nutritional interventions produce weight gain in this disease (187), three RCTs of VNS were unable to prove this (184-186). Furthermore, we do not know if this would translate into improved clinical outcomes (188, 189).

Ten VNS trials assessed patients with lung disease (predominantly chronic obstructive pulmonary disease) (98, 101, 106, 121, 127, 140, 142, 190-192). One RCT reported improvements in an activity of daily living score (192) and another described benefits in one aspect of respiratory muscle strength (191). Otherwise, no differences were seen in exercise capacity (98, 106, 191), handgrip strength (121), pulmonary function (98, 101, 106, 121, 127, 190), respiratory muscle strength (101, 121, 190), or quality of life (101). Only one death was reported in all of these trials (140) and no differences were seen in the two trials that provided data regarding total complications (140, 142). Another systematic review also failed to find evidence supporting artificial nutrition in chronic obstructive pulmonary disease (193).

### **Renal Failure**

One trial of VNS (ten patients on chronic hemodialysis) reported no deaths and two patients in each group had some complication (132).

### **Acquired Immunodeficiency Syndrome**

Two RCTs (165 patients) compared VNS to no therapy (116, 133). No significant differences were seen in mortality (116), infectious complications (116), CD4 counts (116), or overall quality of life (133). However, the possibility of a type II error could not be excluded.

No trials have assessed EN. One RCT comparing VNS to PN found no differences in median survival, CD4 counts, or overall quality of life (194). The VNS recipients had better physical functioning

in this unblinded trial. Since one RCT of protracted (2 months) PN failed to show any benefit (195), it might be inferred that VNS also would not be useful.

### **Pediatrics**

No RCTs addressed the use of EN or VNS for children who are failing to grow normally. Two small RCTs comparing EN to PN in low birth weight infants found no difference in mortality (80) or infection rates (80, 89). A systematic review (of non-randomized trials) addressing the use of gastrostomy or jejunostomy tubes versus oral feeding in children with cerebral palsy concluded that the available evidence did not show that EN provided any benefit (196).

PN is often employed in low birth weight infants. A systematic review of low quality trials of trophic feeding (providing small amounts of enteral nutrients) indicated that this intervention reduced the time to full feeding by 2.7 days and the duration of hospitalization by 15.6 days without altering the risk of necrotizing enterocolitis (197). However, those reviewers were concerned about methodologic problems (absence of blinding, lack of details about the randomization processes, inability to perform intent to treat analyses, and publication bias).

### **Geriatrics**

The data from meta-analyses of 16 RCTs of VNS (30, 94, 100, 104, 108, 110, 111, 117-119, 124, 128, 130, 131, 144, 145) are summarized in Table 6; these patients were almost always malnourished and/or institutionalized (including being in hospitals). The VNS recipients had a significantly better survival. Two of these trials (130, 131) were high quality; while the mortality rates in both of them (11% vs 17%, 381 patients [130] and 5% vs 7%, 136 patients [131]) also favored the treatment group, neither difference was statistically significant. No significant effect of VNS on infectious complications (the only other outcome reported) was observed.

From study to study, some individual measures of functional status may have been improved by the VNS. Different measures improved in different studies, and those that improved in one trial did not necessarily improve in another. Quality of life scores were not affected.

Neither of two trials of VNS (114, 117) nor one of EN (22) found any significant differences with regard to the development or severity of pressure ulcers. One small study of VNS (198), and another of generic artificial nutrition (VNS, EN, or PN) (199), found no differences in healing in patients who already had developed pressure ulcers. (In one of these trials [198], the further addition of arginine, vitamin C, and zinc did improve healing as assessed by a numerical score.)

No RCTs were found addressing the use of EN in demented patients nor for providing VNS to healthy elderly individuals.

### **Hip fractures**

In three trials of EN (22, 41, 42), and in six trials of VNS (99, 112, 114, 123, 139, 200) (meta-analyses results summarized in Table 7), mortality rates, the incidences of various complications, and various functional or quality-of-life measures were not altered. A systematic review that included quasirandomized and unpublished trials as well as other types of supplements concluded that, while the evidence was weak (low quality trials), these supplements may have reduced “unfavorable outcomes” (a combination of mortality and survivors with complications) (201).

### **Neurologic conditions**

The RCTs from the “Feed Or Ordinary Diet” (FOOD) consortium represent the largest trials in this review (20, 105). These were high quality studies that assessed patients shortly after a stroke. In one, gastric infusions of nutrient solutions were either begun on admission or withheld for at least 7 days in 859 dysphagic patients (20). The primary outcome was long-term survival; no difference was seen. The intervention also did not alter complication rates or duration of hospitalization.

The other one assessed VNS in 4023 nondysphagic stroke patients (105). No differences were seen when death alone or death and poor neurologic outcome were the end-points. In a separate smaller VNS trial, survival was no better at the time of discharge or at 3 months (107).

### **Allergic disorders**

No specific RCTs of EN or VNS were identified.

### **Arthritis**

No specific RCTs of EN or VNS were identified.

### **Cardiac disease**

One RCT compared the use of a high-calorie VNS formulation to a “placebo” (a 1:10 dilution of the VNS formulation) in patients with congestive heart failure (202). No differences were seen in intermediate outcomes.

### **Pregnancy**

One systematic review assessed various interventions to increase energy and/or protein intake in pregnant women (203). Based on observational data, no benefits or harms could be attributed to the various nutritional interventions.

### **Bowel preparation**

One small RCT (26 patients) of VNS in surgical patients also provided data regarding the efficacy of the bowel preparation (141). No difference was seen compared to standard mechanical preparation with a low residue diet.

## **Discussion**

We use artificial nutrition, with its associated morbidity and cost, as a therapeutic intervention to accomplish some clinical objective. We should not think about it as “eating” or “feeding” (204),

particularly because these words have an inherent emotional value. It is appropriate to use RCTs to help us make clinical decisions about employing, or not employing, these treatments.

A summary of the graded evidence of EN or VNS in the various disease states is presented in Table 8. There is strong evidence for not using VNS in non-dysphagic stroke patients and for not employing EN in the first week in patients who have strokes resulting in dysphagia. (It is likely, although there is no evidence from RCTs, that, if the dysphagia persists for weeks, EN will ultimately be required.)

There is not quite strong evidence for providing VNS to malnourished geriatric patients. We were unable to assign an A grade because the high quality trials did not show a statistically significant improvement in survival. However, this was seen in the low quality trials and both high quality trials found an effect in a favorable direction. A recent meta-analysis that was less restrictive in its definition of supplements also found that oral supplements improved survival and reduced complication rates (205). To be noted, these data cannot be extrapolated to healthy elderly individuals; there are no data for providing dietary supplements to such people. Similarly, no data were identified to support the use of EN in patients with end-stage dementia.

Data from low quality RCTs suggest that there is potential benefit for providing EN or VNS to surgical patients who can tolerate these interventions or to patients with chronic liver disease. There was similar low quality evidence for using EN as trophic feeding in low-birth-weight neonates or in critically ill patients. However, the grades for the critically ill patients or those with chronic liver disease rest on even more problematic data.

The grading in the critically ill is based on a study that was confounded by giving PN to some control patients after 5 days (31); PN predisposes patients to infections (1). EN did not improve any parameters of morbidity in patients with chronic liver disease, so it is unclear why it would improve

survival; furthermore, this significant difference in mortality was only demonstrable when the less conservative model (fixed effects) was employed.

For the remaining disease states, there are no data to support the use of EN or VNS. Either there were no (or an insufficient number of) RCTs available or the RCTs indicated that there was no benefit.

These data, as well as those for PN, are disappointing. Since malnutrition is accompanied by adverse clinical consequences, why should its prevention or correction of malnutrition not improve outcome? There are a number of possible reasons.

We may be providing the wrong formulations. Important nutrients may be absent, deficient, or even excessive. However, since we do not know what to correct, we can only note that currently available EN and VNS formulas lack established efficacy.

It does not appear to be a problem of inadequate delivery of artificial nutrition. The EN recipients usually received more nutrients than did the controls; in only one RCT were the intakes comparable (20) and no data were available in three others (33, 35, 36). We know that artificial nutrition does improve nutritional outcomes (e.g. body weight or nitrogen balance), but improving these surrogate markers does not translate into improved clinical outcome (206).

Many of the RCTs were small, and it would be unlikely that a limited benefit could be demonstrated (perhaps even with data combination). We considered the problem of type II errors earlier. Moreover, if only a small benefit exists, the clinician would have to weigh it against the resource expenditures that would be required.

There may be patient subgroups for whom artificial nutrition would be beneficial; for example, severely malnourished patients were usually excluded from the RCTs. However, if such subgroups do exist, we have not yet identified them. Making a decision to treat everybody in order not to miss an appropriate few will not accomplish any good.

There are shortcomings of the systematic review process. It may be that important RCTs were not found. The search process did identify a large number of RCTs of artificial nutrition. Of course, if investigators performing RCTs selectively avoided publishing the beneficial outcomes of the interventions, the search process would have missed those data. However, the opposite phenomenon is more likely to occur (207).

The methodologic quality of most of the studies included in this review was low. Some might argue that we should disregard any data derived from such trials, as the data are unreliable. However, since RCTs of low quality tend to produce an overestimation of a treatment benefit, a more realistic concern is that the true treatment benefit is not as good as this current analysis has suggested.

Heterogeneity is always a problem in meta-analysis. We did limit these analyses to a similar intervention in a similar disease state, and we also used statistical tests to decide which combining model to employ. The random effects model, which tends to weigh smaller trials more heavily, could be postulated to be susceptible to greater risk of bias, since small trials may be more influenced by bias. On the other hand, the fixed effects model usually results in a smaller CI, so “significance” would be more likely to be seen. In either event, with the single exception regarding the ability of EN to improve survival in patients with chronic liver disease, no substantially different conclusions would have been made if the alternative model was employed.

Finally, it may be that the interventions simply are not effective. The observed association between malnutrition and poor outcome need not be causative; since sicker patients are likely to have both, the malnutrition may only be an epiphenomenon. Also, while the duration of starvation or semi-starvation that can be tolerated by a patient before the adverse effects of malnutrition occur is not clearly defined, it is probably measured in weeks, not days.

Most of these observations were limited to patients who were not severely malnourished and who would be without oral or enteral nutrients for no more than 14 days. There is no substantive information from which to make conclusions about how or when to treat severely malnourished individuals or to decide about the period of time beyond two weeks when it would be appropriate to employ artificial nutrition. In such situations, or in those disease states for which data from RCTs are limited or non-existent, the clinician will not have any evidence upon which to base a decision. Instead, he or she will have to rely on an understanding of the patient's clinical condition and anticipated outcome, a judgment as to the patient's ability to tolerate undernutrition, and an appreciation of the desires and needs of the patient and his or her family.

For many of the clinical conditions, the evidence grades were based on a limited number of studies. Future large trials could demonstrate effects that would change them. However, a recommendation for implementation of this, or any other, therapy must be preceded by proof of efficacy.

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## Table 1. Definitions

### Study group terminology:

**Enteral nutrition (EN)** – The infusion of a putative complete (including essential micronutrients if given in caloric sufficiency) nutrient liquid formulation through a tube placed in the upper gastrointestinal tract. (It will have been the intent of the investigator to provide a source of nitrogen [intact protein, protein hydrolysate, and/or free amino acids] and >10 kcal/kg/day of non-nitrogenous calories.)

**Parenteral nutrition (PN)** – The intravenous provision of nitrogen (as amino acids or protein hydrolysate) and > 10 kcal/kg/day of non-nitrogenous calories via either a central or peripheral venous catheter.

**Volitional nutritional support (VNS)** – A liquid formulation containing at least a non-protein source of calories (carbohydrate and/or fat) and nitrogen (as intact protein, digested protein, and/or amino acids) that is taken orally by the patient, with specific instructions regarding its consumption on a scheduled basis. This formulation may be provided as a supplement to the ad-lib intake of standard food. These formulations differ from supplemental “snacks” prepared from real food (e.g., milk shakes, sandwiches, etc.) (Note: VNS requires the patient to consume the nutrient solution him- or herself rather than having medical personnel infuse the liquid.)

**No treatment** – No receipt of EN, VNS, or PN. (These patients may have received ad-lib feeding of standard food, nutritional counseling, and intravenous fluids containing 5% dextrose.) Studies that allowed for these patients to “fall back” to EN or PN after a proscribed period of time (that was at least 5 days) are included in the analysis.

**Randomized controlled trial (RCT)** – Any study in which patients were assigned by chance to one of the above interventions, and then prospectively followed to ascertain the incidence or magnitude of one or more clinical outcomes in each group.

**Malnourished patient** – A patient satisfying whatever criterion for malnutrition that the investigator employed. (A study including “malnourished” patients is one in which  $\geq 50\%$  of the study patients met the investigator’s criterion.)

**Artificial nutrition formulation terminology:**

**Specialized enteral nutrition** – A nutrient formulation enriched with nutrients that are believed to have specific favorable pharmacologic properties (including but not limited to branched chain amino acids, essential amino acids,  $\omega$ -3 fatty acids, arginine, ribonucleic acid [RNA], and glutamine).

**Immunonutrients** – Substances (including but not limited to  $\omega$ -3 fatty acids, arginine, RNA, and glutamine) that are believed to have metabolic activities that alter the intestinal and/or systemic immune response in a clinically beneficial way.

**Predigested formulation** – Nitrogen source in the liquid formulation consists predominantly of amino acids or protein hydrolysates. (The non-nitrogenous energy sources include carbohydrate [which may range from simple sugars to complex carbohydrates] and fat [including medium chain triglycerides]; these formulations tend to contain simple sugars and limited or no fat [often as medium chain triglycerides when present].)

**Undigested formulation** – Nitrogen content in the liquid formulation consists of unhydrolyzed protein. (The non-nitrogenous energy sources tend to be more complex carbohydrates [rather than simple sugars] and higher amounts of fat, usually as long-chain triglycerides.)

**Table 2. Meta-analyses of perioperative trials**

<u>Outcome</u>	<u>Absolute Risk Difference*</u>	<u>95% Confidence Intervals</u>	<u>Number of Studies (Patients) Included</u>	<u>Tests for heterogeneity p value</u>	<u>I<sup>2</sup></u>
<b>EN vs no nutrition treatment:</b>					
Mortality	-2% <sup>1</sup>	-5%, +1%	13 (1032)	0.78	0%
Total complications	-10% <sup>2</sup>	-22%, +2%	12 (941)	<0.00001	85%
Infectious complications	-11% <sup>2</sup>	-20%, -1%	10 (911)	0.0005	68%
Major complications	-5% <sup>2</sup>	-13%, +3%	11 (911)	0.02	54%
Wound complications	-5% <sup>2</sup>	-11%, +1%	12 (1053)	0.05	45%
Intra-abdominal/thoracic complications	-5% <sup>1</sup>	-9%, 0%	11 (871)	0.42	3%
Postoperative pneumonia	-4% <sup>1</sup>	-9%, +1%	9 (854)	0.64	0%
Nausea/vomiting	-4% <sup>2</sup>	-20%, +12%	4 (483)	0.01	73%
Diarrhea	+4% <sup>1</sup>	-3%, +11%	4 (441)	0.64	0%
Postoperative ileus	0% <sup>1</sup>	-5%, +6%	3 (445)	0.83	0%
Duration hospitalization	+ 0.34 days <sup>2,3</sup>	-1.93 days, +2.61 days	8 (459)	0.007	64%

**EN vs PN:**

Mortality	-1% <sup>1</sup>	-3%, +2%	16 (1391)	0.92	0%
Total complication rate	-8% <sup>1</sup>	-13%, -3%	15 (1368)	0.10	34% <sup>4</sup>
Infectious complication rate	-11% <sup>1</sup>	-15%, -6%	17 (1404)	0.87	0%
Major complications	-6% <sup>1</sup>	-10%, -1%	9 (941)	0.32	14%
Wound complications	-3% <sup>1</sup>	-6%, +1%	9 (901)	0.81	0%
Intra-abdominal/thoracic complications	-4% <sup>1</sup>	-8%, 0%	9 (944)	0.72	0%
Postoperative pneumonia	-5% <sup>1</sup>	-9%, -1%	9 (948)	0.18	30% <sup>5</sup>
Deep vein thrombosis	-1% <sup>1</sup>	-3%, +2%	5 (569)	0.56	0%
Postoperative ileus	+5% <sup>1</sup>	0%, +9%	6 (394)	0.20	32% <sup>6</sup>
Total interventional complications	+8% <sup>2</sup>	-2%, +17%	7 (671)	0.03	57%
Nausea/vomiting	+3% <sup>1</sup>	-1%, +6%	4 (461)	0.29	21%
Diarrhea	+7% <sup>2</sup>	+1%, +13%	10 (1161)	0.0001	73%
Metabolic complications <sup>7</sup>	-3% <sup>1</sup>	-7%, +2%	3 (374)	0.22	81%
Duration hospitalization	-1.70 days <sup>1,3</sup>	-2.64 days, -0.75 days	5 (699)	0.93	0%

**VNS vs no nutrition treatment:**

Mortality	0% <sup>1</sup>	-2%, +2%	8 (792)	1.00	0%
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Total complication rate	-13% <sup>2</sup>	-23%, -3%	9 (789)	0.006	63%
Infectious complication rate	-10% <sup>2</sup>	-18%, -1%	8 (637)	0.01	61%
Major complications	-11% <sup>2</sup>	-20%, -2%	6 (568)	0.08	50%
Wound complications	-11% <sup>2</sup>	-22%, 0%	6 (477)	0.003	73%
Intra-abdominal/thoracic complications	-11% <sup>1</sup>	-17%, -4%	4 (376)	0.25	28% <sup>8</sup>
Postoperative pneumonia	-4% <sup>1</sup>	-8%, +1%	5 (451)	0.55	0%
Gastrointestinal side effects	+6% <sup>1</sup>	-1%, +13%	4 (384)	0.33	13%
Duration hospitalization	-2.04 days <sup>1,3</sup>	-3.37 days, -0.72 days	5 (517)	0.98	0%

EN = Enteral Nutrition; VNS = Volitional Nutrition Support; PN = Parenteral Nutrition

\* This represents the difference between the outcome in the treated group and the control group; a negative number represents a benefit for the treated group.

<sup>1</sup> Fixed effects model

<sup>2</sup> Random effects model

<sup>3</sup> Weighted mean difference

<sup>4</sup> Estimated effect (95% confidence interval) by random effects model = -7% (-13%, 0%)

<sup>5</sup> Estimated effect (95% confidence interval) by random effects model = -4% (-8%, +1%)

<sup>6</sup> Estimated effect (95% confidence interval) by random effects model = +3% (-1%, +8%)

<sup>7</sup> Largely hyperglycemia

<sup>8</sup> Estimated effect (95% confidence interval) by random effects model = -10% (-18%, -2%)

**Table 3. Meta-analyses of trials in chronic liver disease**

<u>Outcome</u>	<u>Absolute Risk Difference*</u>	<u>95% Confidence Intervals</u>	<u>Number of Studies (Patients) Included</u>	<u>Tests for heterogeneity p value</u>	<u>I<sup>2</sup></u>
<b>EN vs no nutrition treatment:</b>					
Mortality	-18% <sup>1</sup>	-35%, -1%	3 (88)	0.21	37% <sup>2</sup>
<b>VNS vs no nutrition treatment:</b>					
Mortality	-6% <sup>1</sup>	-16%, +4%	5 (318)	0.46	0%
Infectious complication rate	-5% <sup>3</sup>	-15%, +4%	3 (281)	0.009	79%
Development of encephalopathy	0% <sup>1</sup>	-7%, +7%	4 (171)	0.79	0%

EN = Enteral Nutrition; VNS = Volitional Nutrition Support

\* This represents the difference between the outcome in the treated group and the control group; a negative number represents a benefit for the treated group.

<sup>1</sup> Fixed effects model

<sup>2</sup> Estimated effect (95% confidence interval) by random effects model = -17% (-38%, +5%)

<sup>3</sup> Random effects model

**Table 4. Meta-analyses of trials comparing EN to PN in acute pancreatitis**

<u>Outcome</u>	<u>Absolute Risk Difference*</u>	<u>95% Confidence Intervals</u>	<u>Number of Studies (Patients) Included</u>	<u>Tests for heterogeneity</u> p value	<u>I<sup>2</sup></u>
Mortality	-1% <sup>1</sup>	-12%, +10%	4 (151) <sup>2</sup>	0.41	0%
Total complication rate	-16% <sup>3</sup>	-35%, +10%	3 (119)	0.06	65%
Infectious complication rate	-15% <sup>1</sup>	-26%, -4%	4 (187)	0.53	0%
Pseudocysts/abscesses/phlegmons	-12% <sup>1</sup>	-24%, 0%	3 (170)	0.55	0%
Metabolic complications <sup>4</sup>	-21% <sup>1</sup>	-36%, -6%	3 (123)	0.21	35% <sup>5</sup>

EN = Enteral Nutrition; PN = Parenteral Nutrition

\* This represents the difference between the outcome in the treated group and the control group; a negative number represents a benefit for the treated group.

<sup>1</sup> Fixed effects model

<sup>2</sup> Mortality data in one of the studies (49) were only available in a subgroup of patients, and this trial not included in the analysis

<sup>3</sup> Random effects model

<sup>4</sup> Hyperglycemia

<sup>5</sup> Estimated effect (95% confidence interval) by random effects model = -20% (-38%, -1%)

**Table 5. Meta-analyses of trials comparing EN to PN in critically ill patients**

<u>Outcome</u>	<u>Absolute Risk Difference*</u>	<u>95% Confidence Intervals</u>	<u>Number of Studies (Patients) Included</u>	<u>Tests for heterogeneity p value</u>	<u>I<sup>2</sup></u>
Mortality	0% <sup>1</sup>	-9%, +8%	9 (427)	0.008	62%
Infectious complication rate	-9% <sup>1</sup>	-22%, +5%	7 (374)	0.008	65%
Metabolic complications <sup>2</sup>	-30% <sup>1</sup>	-57%, -3%	3 (170)	0.005	81%
Diarrhea	-4% <sup>1</sup>	-26%, +18%	4 (252)	0.01	73%
Duration of hospitalization	-0.40 days <sup>3,4</sup>	-4.10, +3.31	4 (236)	0.92	0%

EN = Enteral Nutrition; PN = Parenteral Nutrition

\* This represents the difference between the outcome in the treated group and the control group; a negative number represents a benefit for the treated group.

<sup>1</sup> Random effects model

<sup>2</sup> Hyperglycemia

<sup>3</sup> Fixed effects model

<sup>4</sup> Weighted mean difference

**Table 6. Meta-analyses of VNS in geriatric populations<sup>1</sup>**

<u>Outcome</u>	<u>Absolute Risk Difference*</u>	<u>95% Confidence Intervals</u>	<u>Number of Studies (Patients) Included</u>	<u>Tests of heterogeneity p value</u>	<u>I<sup>2</sup></u>
Mortality	-4% <sup>2</sup>	-7%, -1%	15 (1733)	0.35	10%
Infectious complication rate	-5% <sup>2</sup>	-13%, +3%	3 (503)	0.43	0%
Gastrointestinal side effects	+8% <sup>3</sup>	-8%, +24%	6 (677)	<0.00001	96%

<sup>1</sup> Patients malnourished and/or institutionalized

<sup>2</sup> Fixed effects model

<sup>3</sup> Random effects model

**Table 7. Meta-analyses of hip fracture trials**

<u>Outcome</u>	<u>Absolute Risk Difference*</u>	<u>95% Confidence Intervals</u>	<u>Number of Studies (Patients) Included</u>	<u>Tests of heterogeneity p value</u>	<u>I<sup>2</sup></u>
<b>EN vs no nutrition treatment:</b>					
Mortality	+2% <sup>1</sup>	-11%, +16%	3 (204)	0.03	71%
<b>VNS vs no nutrition treatment:</b>					
Mortality	-3% <sup>2</sup>	-13%, +7%	4 (179)	0.15	44% <sup>3</sup>
Total complication rate	-9% <sup>2</sup>	-22%, +3%	4 (216)	0.67	0%
Infectious complication rate	+2% <sup>2</sup>	-7%, +11%	3 (113)	0.42	0%

<sup>1</sup> Random effects model

<sup>2</sup> Fixed effects model

<sup>3</sup> Estimated effect (95% confidence interval) by random effects model = 0% (-12%, +11%)

**Table 8. Evidence grades regarding utility of EN or VNS in specific disease states**

Disease state	Route of artificial nutrition	Grade	Comments
Perioperative	EN	B	EN reduced the incidence of postoperative infectious and there was also a tendency for there to be a reduced incidence of intra-abdominal or intra-thoracic complications in meta-analyses of low quality trials.
	VNS	B	VNS reduced postoperative complications in meta-analyses of low quality trials. It is unclear if this translated into shorter hospital stay.
Non-surgical cancer treatment <sup>1</sup>	EN	D	Two RCTs (162 patients) failed to find any significant, or even trends for, benefit.
	VNS	D	Meta-analysis of four RCTs found no difference in mortality.
Chronic liver disease	EN	B	Mortality may have been improved, but the trials were of low quality. Branched-chain amino acids may improve hepatic encephalopathy (possibly a pharmacologic effect).
	VNS	B	Two trials each found a significant reduction in the development of ascites and suggested that there may be a reduction in total complications. No other

			significant benefits were identified.
Liver transplantation	EN	C	One RCT (31 patients) failed to find any significant benefit.
	VNS	C	One RCT (80 patients) failed to find any significant benefit.
Acute pancreatitis	EN	C	Two RCTs (55 patients) failed to find any significant, or even trends for, benefit..
Inflammatory bowel disease	EN	D	EN is comparable to PN. PN is not better than standard therapy in patients with inflammatory bowel disease. EN is less effective than steroids in Crohn's disease.
	VNS	C	One RCT enrolling 125 patients available, but statistical evaluation was not possible from the data presented; some differences favored VNS and some of those p values were probably $\leq 0.20$ .
Critical illness	EN	B	Meta-analyses suggest that EN is associated with fewer infections, but the estimate depends on low quality trials, particularly one in which 30% of the control patients received delayed PN.
Chronic pulmonary disease	EN	C	No RCTs available.
	VNS	D	Ten RCTs failed to demonstrate any benefit in a variety of outcomes.
Cystic fibrosis	EN	C	One RCT (22 patients) failed to find any significant, or even trends for, benefit.
	VNS	C	No RCTs available.

Renal disease	EN	C	No RCTs available.
	VNS	C	One small trial (10 patients on hemodialysis) did not find any differences.
Acquired immuno-	EN	C	No RCTs available.
deficiency syndrome	VNS	C	Two RCTs (165 patients) failed to demonstrate a benefit but the presence of a type II error could not be excluded. VNS was comparable to PN, but PN was no better than no artificial nutrition.
Low birth weight	EN	B	Trophic feeding may be of benefit, but the trial quality is low.
infants			
Other pediatric	EN	C	No RCTs available.
conditions	VNS	C	No RCTs available.
Malnourished geriatric	EN	C <sup>2</sup>	One RCT (129 patients) failed to find any benefit from EN with regard to mortality or the prevention of pressure ulcers in elderly patients with hip fractures.
patients			
	VNS	B	VNS improves survival in the low quality RCTs of malnourished (usually hospitalized/institutionalized) geriatric patients who are able to consume the supplements. Neither of the two high quality trials found a significant difference, although in both the direction of the effect was in favor of the treated groups.

Nourished geriatric patients	EN	C	No RCTs available.
Hip fractures	VNS	C	No RCTs available.
	EN	D	Three RCTs failed to find any benefit.
	VNS	D	Six RCTs failed to demonstrate any benefit.
Stroke patients	EN	E	High quality evidence exists indicating that early (at the time of admission versus waiting at least one week) EN in dysphagic stroke patients is not of any benefit. If dysphagia persists for weeks (or is permanent), some type of gastric infusion of nutrients will be necessary.
	VNS	E	High quality evidence exists indicating that long term VNS in non-dysphagic patients is not of benefit.
Other neurologic conditions	EN	C	No RCTs have assessed EN (specifically through gastrostomies) in patients with end-stage dementia.
	VNS	C	No RCTs available.
Allergic disorders	VNS	C	No RCTs available.
Arthritis	VNS	C	No RCTs available
Cardiac disease	VNS	C	No RCTs available.
Pregnancy	VNS	C	No RCTs available.

Bowel preparation      VNS      C      One RCT (26 patients) in surgical patients failed to find any difference between low residue diets and commercial liquid diets.

<sup>1</sup> Grade for both EN and VNS only applies to non-hematologic malignancies; no RCTs identified for hematologic malignancies (Grade C)

<sup>2</sup> Grade of C because population studied was only a limited sample of all malnourished geriatric patients (i.e., those with hip fractures).